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Cover page of the integrated protocol

A randomized, double-blind Phase III study of copanlisib versus placebo in patients with rituximab-refractory indolent non-Hodgkin's lymphoma (iNHL) – CHRONOS-2

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

- **Original protocol,** Version 1.0, dated 20 MAY 2014
- **Amendment 01** (global amendment described in Section 13.1) forming integrated protocol Version 2.0, dated 25 NOV 2014
- **Amendment 03** (global amendment described in Section 13.2) forming integrated protocol Version 3.0, dated 16 FEB 2016
- **Amendment 04** (global amendment described in Section 13.3) forming integrated protocol Version 4.0, dated 21 JUL 2016
- **Amendment 05** (global amendment described in Section 13.4) forming integrated protocol Version 5.0, dated 31 MAR 2017
- **Amendment 06** (global amendment described in Section 13.5) forming integrated protocol Version 6.0, dated 01 DEC 2017

Amendments not included in the consecutive numbering of amendments are local amendments not forming part of this integrated global protocol. This currently includes:

- **Amendment 02**, dated 10 JUN 2015 (local amendment valid for Ireland only)

Title page

A randomized, double-blind Phase III study of copanlisib versus placebo in patients with rituximab-refractory indolent non-Hodgkin's lymphoma (iNHL) – CHRONOS-2

Phase III copanlisib in rituximab-refractory iNHL

Test drug:	BAY 80-6946 / copanlisib		
Study purpose:	Assess the efficacy and safety of copanlisib		
Clinical study phase:	III	Date:	01 DEC 2017
EudraCT no.:	2014-000925-19	Version no.:	6.0
Study no.:	BAY 80-6946 / 17322		
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 PPD :	PPD MD, PhD Rua Domingos Jorge, 1100 – Bloco 301 - 2º andar 04779-900, São Paulo, SP Brasil Telephone: PPD (*modified by amendment 4, 5 and 6*)		

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

Signature of the sponsor's medically responsible person

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

Responsible person changed by amendment 1 and 5.

Name: PPD MD Role: PPD

Date: PPD Signature: PPD

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 randomized, double-blind Phase III study of copanlisib versus placebo in patients with rituximab-refractory indolent non-Hodgkin's lymphoma (iNHL) – CHRONOS-2**
Short title	Phase III copanlisib in rituximab-refractory iNHL
Clinical study phase	III
Study objectives *(modified by amendment 1, 5 and 6)*	The primary objective of this study is: • To assess the safety of copanlisib.
Test drug	Copanlisib
Name of active ingredient	Copanlisib / BAY 80-6946 / phosphatidylinositol 3-kinase (PI3K) inhibitor
Dose	Starting dose: 60 mg. Dose reductions due to toxicities to 45 mg and further to 30 mg are allowed. To be administered on Days 1, 8 and 15 of each 28-day treatment cycle.
Route of administration	Intravenous (IV) infusion.
Duration of treatment *(modified by amendment 1, 5 and 6)*	Treatment will be continued until disease progression (PD) by radiological assessments or clinical progression (tumor evaluations will be made at intervals that comply with the institution's standard of care [per investigator's assessment]), unacceptable toxicity, or until another criterion is met for withdrawal from the study treatment.
Reference drug *(modified by amendment 5)*	Not applicable.
Indication	Rituximab-refractory iNHL ("*asymptomatic" removed by amendment 1*).
Diagnosis and main criteria for inclusion	Histologically confirmed diagnosis of indolent B-cell NHL, with histological subtype limited to the following: • Follicular lymphoma (FL) grade 1-2-3a. • Small lymphocytic lymphoma (SLL) with absolute lymphocyte count < 5 x 10^9/L at the time of diagnosis and at study entry. • Lymphoplasmacytoid lymphoma/Waldenström macroglobulinemia (LPL/WM). • Marginal zone lymphoma (MZL) (splenic, nodal, or extra-nodal). Patients must have received two or more prior lines of treatment (*changed by amendment 1*). A previous regimen is defined as one of the following: at least two months of single-agent therapy, at least two consecutive cycles

	of polychemotherapy, autologous transplant, radioimmunotherapy. Prior therapy must include rituximab and alkylating agent(s). Prior exposure to idelalisib or other PI3K inhibitors is acceptable (except to copanlisib) provided that there is no resistance (*modified by amendment 1 and 3*). Patients must be refractory to the last rituximab-based treatment, defined as no response or response lasting < 6 months after completion of treatment. Time interval to assess refractoriness will be calculated between the end date (last day) of the last rituximab-containing regimen and the day of diagnosis confirmation of the subsequent relapse (*modified by amendment 3*). Patients must have at least one bi-dimensionally measurable lesion (which 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 (*changed by amendment 1*). 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 (*changed by amendment 1 and 3*). Male or female patients ≥ 18 years of age. ECOG (Eastern Cooperative Oncology Group) performance status ≤ 1. Life expectancy of at least 3 months. Availability of fresh (preferred) and/or archival tumor tissue at Screening. Adequate bone marrow, liver and renal function as assessed within 7 days before start of study treatment. Left ventricular ejection fraction (LVEF) ≥ the lower limit of normal (LLN) for the Institution.
Main criteria for exclusion	Histologically confirmed diagnosis of FL grade 3b. Chronic lymphocytic leukemia (CLL). Transformed disease (assessed by investigator): • histological confirmation of transformation, or • clinical and laboratory signs: rapid disease progression, high standardized uptake value (> 12) by positron emission tomography (PET) at baseline if PET scans are performed (optional). Bulky disease (*criterion changed by amendment 1*): • Lymph nodes or tumor mass (except spleen) ≥ 7 cm LDi (longest diameter). Known lymphomatous involvement of the central nervous system. Uncontrolled arterial hypertension despite optimal medical management (per investigator's assessment) (*modified and added to synopsis by*

	amendment 3). Type I or II diabetes mellitus with HbA1c > 8.5% at Screening (*modified by amendment 3*). 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. Patients positive for HCV immunoglobulin G (IgG) will be eligible if they are negative for HCV-RNA. History or concurrent condition of interstitial lung disease of any severity and/or severely impaired lung function (*clarified by amendment 1*). Documented evidence of resistance to a prior treatment with idelalisib or other PI3K inhibitors defined as (*exclusion criterion added by amendment 1*): • 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 (SD) within 6 months from the start of the therapy with a PI3K inhibitor (*modified by amendment 3*). Patients who discontinued treatment due to other reason than disease progression, and did not exhibit any signs of PD, will be allowed to enroll in this study after discussion with the sponsor. Prior treatment with copanlisib (*added by amendment 3*).
Study design *(modified by amendment 1, 5 and 6)*	Initially this was a randomized, double-blind, two-arm Phase III study to evaluate the efficacy and safety of copanlisib as monotherapy in comparison to placebo in patients with rituximab-refractory iNHL. Following sponsor's decision to stop enrollment due to lack of feasibility to complete this study in reasonable time frame, the study design is modified. All patients will be given an opportunity to continue treatment with copanlisib. Patients who are on copanlisib treatment at the time of unblinding will continue copanlisib treatment. Patients who are on placebo at the time of unblinding will be offered to switch to copanlisib treatment after unblinding procedures are completed. After individual patient unblinding, patients receiving placebo, who switch to copanlisib will have all study assessments reset to the initial schedule of study evaluations (i.e. as if the patient was restarted the study at Cycle 1 Day 1).
Methodology *(modified by amendment 1, 3, 4, 5 and 6)*	The study is composed of the following periods: Screening, Treatment, and Safety-follow-up. By the time the protocol amendment 6 becomes effective, screening procedures are no longer applicable as screening for the study ended on 03 MAR 2017. All screened eligible patients have started treatment. Patients will receive 60 mg copanlisib IV infusion on Days 1, 8 and 15 of each 28-day treatment cycle. Treatment will be continued until PD, unacceptable toxicity, or until

	another criterion is met for withdrawal from the study treatment. An End-of-treatment (EOT) visit will be performed within 7 days after the decision is made to discontinue study treatment. Following completion of the EOT visit, patients will enter the Safety follow-up. The Safety follow-up (SFU) visit will take place 30 days (window of +5 days allowed) after the last administration of study drug. Safety evaluations will be done at Screening, on the first day of study drug administration (Cycle 1 Day 1), at each clinic visit during the treatment, and at the SFU visit. Tumor assessments (and laboratory/clinical tests for WM patients) will be made according to the institution's standard of care. Bone marrow biopsy may be performed at the investigator discretion if there is clinical suspicion of bone marrow infiltration. Bone marrow biopsy will be performed per local standard of care.
Type of control *(modified by amendment 5)*	Not applicable.
Number of patients *(modified by amendment 5)*	Following sponsor's decision to stop the study no further patients will be enrolled. All patients enrolled in the study by the time the protocol amendment 5 is approved will be unblinded.
Primary variable *(modified by amendment 5 and 6)*	The primary analysis is safety, which includes treatment-emergent AEs (TEAEs) and serious adverse events (SAEs), laboratory parameters, and vital signs.
Plan for statistical analysis *(modified by amendment 5 and 6)*	Due to the decision of stopping enrollment as protocol amendment 5 becomes effective, limited number of patients will be included in the analyses. Therefore, the statistical analyses included in this study will be focused on descriptive statistics on safety variables only. Two sets of analyses will be performed at the timing when all patients have completed the study treatment and Safety follow-up period (if applicable): 1) unblinding cutoff: analyze all data available before the unblinding (details in section 6.5); 2) final analysis: analyze all data available until all patients have completed the copanlisib study treatment and Safety follow-up period.

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List of abbreviations

List of abbreviations was updated by amendment 1, 3, 4 and 5.

^{131}I	Iodine-131
^{90}Y	Yttrium-90
β-hCG	β-human chorionic gonadotropin
AE	Adverse event
AG	Joint stock company, *Aktiengesellschaft*
AKT	Protein kinase B
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
$AUC_{(0-25)}$	AUC from time zero to 25 hours
BP	Blood pressure
BTK	Bruton's tyrosine kinase
BUN	Blood urea nitrogen
CBC	Complete blood count
CD4	Cluster of differentiation 4
CD8	Cluster of differentiation 8
CD20	B lymphocyte antigen CD20
CHOP	Cyclophosphamide, hydroxydaunorubicin, vincristine, prednisolone
c-KIT	Proto-oncogene cKIT (CD117)
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
CSP	Clinical study protocol
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CVP	Cyclophosphamide, vincristine, prednisolone
CYP3A4	Cytochrome P450 isoenzyme 3A4
CxDy	Cycle x Day y
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)
e.g.	For example, *exempli gratia*

ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EOT	End of treatment
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
g	Gram
GCL	Global Clinical Leader
GCP	Good Clinical Practice
GEF	Guanine nucleotide exchange factor
GFR	Glomerular filtration rate
GI	Glycemic index
GMP	Good Manufacturing Practice
GPV	Global Pharmacovigilance
h	Hour(s)
HbA1c	Glycated hemoglobin
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HER	Human epidermal growth factor receptor
HIV	Human immunodeficiency virus
i.e.	That is, *id est*
IB	Investigator's Brochure
IC_{50}	Half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonization
IDMS	Isotope dilution mass spectrometry
IEC	Independent Ethics Committee
IGF-1R	Insulin-like growth factor 1 receptor
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHC	Immunohistochemistry
iNHL	Indolent non-Hodgkin's lymphoma
INR	International normalized ratio
IRB	Institutional Review Board
ISO	International Organization for Standardization

ITT	Intent to treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
kg	Kilogram
LDi	Longest diameter
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LLN	Lower limit normal
LPL	Lymphoplasmacytoid lymphoma
LVEF	Left ventricular ejection fraction
M-1	Metabolite 1
MALT	Marginal-zone lymphoma of mucosa-associated lymphoid tissue
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
Met	Mesenchymal epithelial transition factor
mg	Milligram
min	Minute(s)
mL	Milliliter
mmHg	Millimeter of mercury
MN	Minnesota
MR	Minor response
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
mTOR	Mammalian target of rapamycin
MUGA	Multiple gated acquisition
MZL	Marginal zone lymphoma
NCCN-FACT	National Comprehensive Cancer Network – Functional Assessment of Cancer Therapy
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NHL	Non-Hodgkin's lymphoma
NIP	Non-infectious pneumonitis
NJ	New Jersey
NK	Natural killer
nM	Nanomolar
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	Progressive disease
PDGFR	Platelet-derived growth factor receptor
PDK-1	3-phosphoinositide-dependent protein kinase-1
PET	Positron emission tomography

PFS	Progression-free survival
PFS2	Secondary progression-free survival
PH	Pleckstrin homology
PID	Patient identification number
PI3K	Phosphatidylinositol 3-kinase
PI-4,5-P2	Phosphatidylinositol-4,5-bisphosphate
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha
PIP3	Phosphatidylinositol-3,4,5-trisphosphate
PK	Pharmacokinetic(s)
PPD	Product of perpendicular diameters
PR	Partial response
PRO	Patient-reported outcome
PT	Prothrombin time
PTEN	Phosphatase and tensin homolog
PTT	Partial thromboplastin time
QA	Quality assurance
QoL	Quality of life
QTcB	QT interval corrected for heart rate – Bazett
QTcF	QT interval corrected for heart rate – Fridericia
RBC	Red blood cell count
RNA	Ribonucleic acid
RR	Response rate
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical analysis system
SCR	Serum creatinine
SD	Stable disease
SDi	Shortest diameter
SFU	Safety follow-up
SGLT-2	Sodium/glucose co-transporter 2
SLL	Small lymphocytic lymphoma
SMZL	Splenic marginal-zone lymphoma
SPD	Sum of the product of the diameters
SOC	Standard of care
SUSAR	Suspected, unexpected, serious adverse reaction
TEAE	Treatment-emergent adverse events
ULN	Upper limit of normal
UPCR	Urine protein to creatinine ratio
US, USA	United States (of America)
vs.	As opposed to, *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
WorseDRSP	Worsening of disease-related symptoms – physical

Definitions of terms

Section changed by amendment 1.

The tumor response assessment will be done according to the Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification (21), henceforth referred to as the Lugano classification.

For patients with WM, response assessment will be done according to the Response Assessment in Waldenström macroglobulinemia: update from the VIth International Workshop (22), henceforth referred to as the Owen criteria.

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 in two main prognostic groups: indolent NHL (iNHL) 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, finally evolving into a refractory disease or in 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 World Health Organization (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 immunoglobulin M (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 with 25% of newly diagnosed cases (4), followed by MALT lymphoma with 7% of all NHLs, 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 iNHL is controversial because of low cure rates with the current therapeutic options. The first line standard therapy usually includes rituximab (anti-CD20 monoclonal antibody), either alone or in combination with purine nucleoside analogs such as fludarabine or 2-chlorodeoxyadenosine, alkylating agents (with or without steroids), or combination chemotherapy (CVP, CHOP, FND). The recent rediscovery of the 'old' alkylating agent bendamustine has added a new effective and well-tolerated therapeutic option in iNHL, both as first line and in relapsed patients.

As patients invariably relapse, further active and well-tolerated agents are needed. In general, treatment with standard agents rarely produces a cure in patients whose disease has relapsed. Sustained remissions after relapse can often be obtained in patients with indolent lymphomas, but relapse will usually ensue. Relapsed patients can often have their disease controlled with single agent or combination chemotherapy, rituximab, radiolabeled anti-CD20 monoclonal antibodies, or palliative radiation therapy. In recent years a large number of new agents have been developed and are under extensive clinical investigations in FL and indolent non-follicular lymphomas, including new monoclonal antibodies binding CD20 or other surface antigens, immunoconjugates, immunomodulatory agents such as lenalidomide and novel agents inhibiting intracellular cancer key pathways such as proteasome inhibitors, mammalian target of rapamycin (mTOR)/phosphatidylinositol 3-kinase (PI3K) inhibitors and Bruton's tyrosine kinase (BTK) inhibitors (5).

The emergence of refractoriness to rituximab-based therapy represents a turning point in the course of disease, as the number of available treatment options sharply decreases. The most recent chemotherapeutic agent that has been approved for use in patients with rituximab-refractory iNHL is the alkylating agent bendamustine, which has become an important therapeutic option, although it is not curative (6). Nevertheless, bendamustine is nowadays mostly used in combination with rituximab in first or second line, and it is therefore less available in later lines of treatment. In addition, chemotherapy-containing regimens are associated with long-term toxic effects, including cumulative myelosuppression, neuropathy, cardiac toxicity, and secondary cancers (7-10). Radioimmunotherapies (11) such as iodine-131 (^{131}I)–labeled tositumomab (12) and yttrium-90 (^{90}Y)–labeled ibritumomab (13) are also active, but owing to the potential for hematologic toxic effects, their use has been limited to patients with adequate marrow function and limited marrow involvement by tumor. The use of these agents is further constrained by the complex procedures for their administration. For these reasons, ^{90}Y-ibritumomab is used infrequently, and ^{131}I-tositumomab has been withdrawn from the market (14). Very recently, idelalisib (Zydelig) was approved for the treatment of patients with double-refractory FL after two prior lines of therapy (15) (*sentence added by amendment 1*).

There is a continuing need for additional, active and safe drugs that can be used in the refractory setting.

1.1.1 Copanlisib (BAY 80-6946)

The PI3K/AKT/mTOR pathway is one of the prominent pathways that promote cellular survival and constitutively is activated in many types of cancers (16, 17). 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 (GEF) by generation of phosphatidylinositol-3,4,5-trisphosphate (PIP3). The tumor suppressor phosphatase and tensin homolog (PTEN) antagonizes PI3K by dephosphorylating PIP3, and its activity is frequently lost in cancer cells (18). 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 (17), and radiation (17, 19).

Four of 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 PIP3. Elevated PIP3 in cellular membranes drives several hallmarks of the cancer phenotype: cell proliferation, survival, metabolic reprogramming, and migration. PI3Kα and PI3Kβ are ubiquitous; PI3Kγ and PI3Kδ 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 (20).

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 further details, see Investigator's Brochure (IB) for copanlisib).

1.1.2 Clinical experience

Section updated by amendment 3, 4 and 6.

Copanlisib is currently under investigation in various trials enrolling cancer patients. As of 21 JUN 2017, approximately 772 patients with advanced cancer have been treated with copanlisib in Phase 1, Phase 2, and Phase 3 clinical trials (please refer to IB) 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 given 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 MTD 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 (*modified by amendment 1*). 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 iNHL, 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 (*paragraph updated by amendment 1 and 3*).

The most frequent TEAEs, regardless of relationship to study drug, occurring in > 20% of the whole study population were hyperglycemia (59.3%), hypertension (56.8%), diarrhea (40.7%), fatigue (35.8%), nausea (32.1%), neutropenia (28.4%) and anemia (27.2%). The two most common study drug-related TEAEs were hyperglycemia (56.8%) and hypertension (53.1%). At the time of the cut-off, a total of 75 patients (92.6%), 30 with indolent, and 45 with aggressive lymphomas, had discontinued the study treatment. Altogether 20 patients (24.7%) stopped treatment because of AEs. No conspicuous cluster of AEs causing treatment discontinuation emerged. Overall 17 out of 81 patients received treatment with short-acting insulin (*paragraph updated by amendment 1 and 3*).

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

1.2 Rationale of the study

Section modified by amendment 1, 5 and 6.

The natural history of patients with progressive iNHL refractory to rituximab as per protocol is not known. Copanlisib is a targeted agent that works by controlling the signaling pathway relevant for the survival and proliferation of iNHL cells. In addition to objective responses, copanlisib appears to induce, in a number of patients, tumor regressions that are below response level, but can nevertheless have a positive effect on the course of the disease. The evaluation of copanlisib's anticancer activity via a clinical trial design that controls for the natural history of tumor growth minimizes investigator bias in assessing treatment outcomes.

Following sponsor's decision to stop enrollment due to lack of feasibility to complete this study in reasonable time frame, the study design is modified. All patients on study treatment will be offered to continue treatment with copanlisib after unblinding procedures are completed.

1.3 Benefit-risk assessment

Section modified by amendment 1, 3 and 5.

The proposed indication is a serious and, in the long-term, life-threatening disease. Advanced iNHL can be controlled with current treatments for a relatively long time, but remains an incurable disease of which the patient will 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, and increasing residual toxicity. There are no guideline recommendations or widely accepted standards of care for patients beyond first relapse. The treatment given depends on the patient's condition, physician's preference, and availability of drugs not already used in previous lines of treatment. 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 has showed activity in patients with iNHL. In the Phase I study 12871 all 6 patients with FL responded (please see Section 1.1.2). In the Phase II study 16349 (part A), response rates in patients with iNHL of various histologies were: 40% in FL, 67% in MZL, and 100% in SLL. Responses included complete remissions. Patients with iNHL were heavily pretreated, with 82% having received ≥ 3, and 36% ≥ 5 lines of treatment prior to study start.

Hyperglycemia and hypertension, the most frequently observed and expected toxicities with copanlisib, have been manageable. Toxicities will be carefully monitored during the course of the study with a detailed and tailored program of management.

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

Section modified by amendment 1, 5 and 6.

The primary objective of this study is:

- To assess the safety of copanlisib.

3. Investigator and other study personnel

Sponsor's PPD (*changed by amendment 4, 5 and 6*)

Name:
PPD MD, PhD
Rua Domingos Jorge, 1100 – Bloco 301 - 2º andar
04779-900, São Paulo, SP Brasil
Telephone: PPD

Coordinating Investigator (*added by amendment 1*)

Name: Grzegorz S. Nowakowski, MD
Address: Division of Hematology
Mayo Clinic
200 First Street SW
Rochester, MN 55905, USA

All other study personnel not included in this section are identified in a separate personnel list (not part of this clinical study protocol [CSP]) 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

Section modified by amendment 3 and 5.

A Data Monitoring Committee (DMC) will be established for this study (according to a separate DMC charter) in order to ensure ongoing safety of study patients.

The DMC will include at least three members, including an independent Statistician and Oncologist. Safety review meetings will be held as per separate DMC charter.

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

Central radiological evaluation

Section modified by amendment 5.

After study stopped for enrollment and all patients will be unblinded and offered an open label study treatment, there will be no central radiological evaluation.

Central pathology review

The confirmation of histopathological diagnosis will be performed centrally.

4. Study design

Section modified by amendment 1, 3, 4, 5 and 6.

Design overview

Following sponsor’s decision to stop enrollment due to lack of feasibility to complete this study in reasonable time frame, the study design is modified. All patients on study treatment will be offered to continue treatment with copanlisib after unblinding procedures are completed (see Section 6.5).

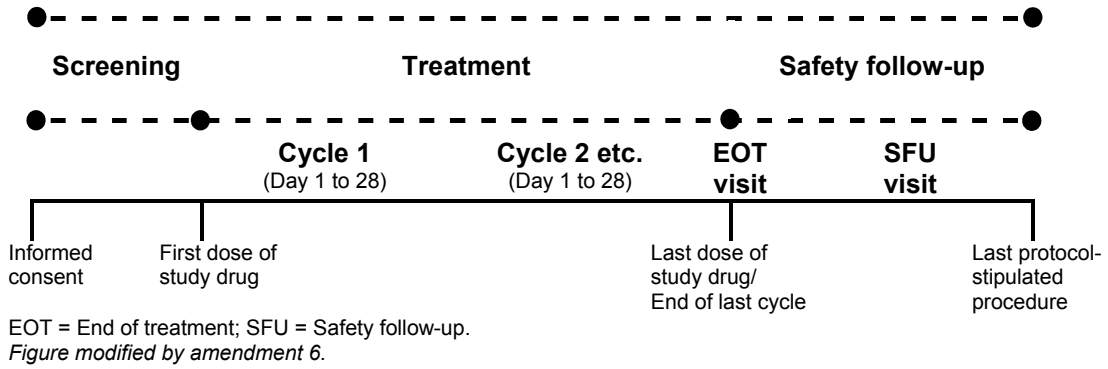
By the time the protocol amendment 6 becomes effective, screening procedures are no longer applicable as screening for the study ended on 03 MAR 2017. All screened eligible patients have started treatment.

Initially this was a randomized, double-blind, two-arm Phase III study to evaluate the efficacy and safety of copanlisib as monotherapy in comparison to placebo in patients with rituximab-refractory iNHL.

The patients have failed at least two previous lines of therapy. Previous treatments must have included rituximab and alkylating agent(s); and the patients must have progressed within six months of the end of the last previous rituximab-containing regimen.

The overview of study periods updated by amendment 6 is presented in Figure 4–1.

Figure 4–1 Study periods as of amendment 6



EOT = End of treatment; SFU = Safety follow-up.
Figure modified by amendment 6.

The start of the study period is defined by signing of the informed consent form (ICF).

A graphical presentation of the study design valid as of amendment 5 is shown in Figure 4–2.

Figure 4–2 Overall study design as of amendment 5

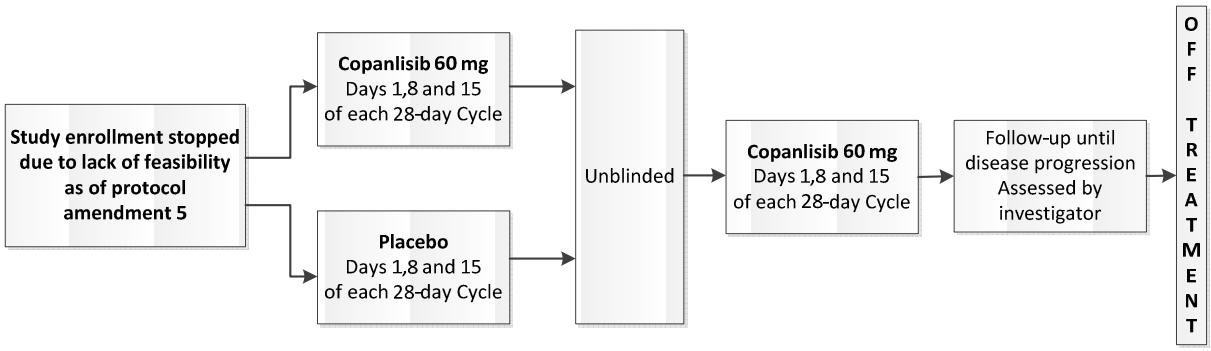


Figure modified by amendment 1 and replaced by amendment 5.

The start of the treatment period is defined by first administration of study drug (copanlisib). Copanlisib will be administered IV over approximately 1 h at starting dose of 60 mg on Days 1, 8 and 15 of each 28-day treatment cycle. Treatment will be continued until PD by radiological assessments or clinical progression (tumor evaluations will be made at intervals that comply with the institution's standard of care [per investigator's assessment]), unacceptable toxicity, or until another criterion is met for withdrawal from the study treatment (see Section 5.2).

All patients, after unblinding procedures are completed, will be offered an opportunity to continue this clinical study and receive active treatment with copanlisib. Patients who are on copanlisib treatment at the time of unblinding will continue copanlisib treatment. Patients who are on placebo at the time of unblinding will switch to copanlisib treatment after unblinding procedures are completed. After individual patient unblinding, patients receiving placebo, who switch to copanlisib will have all study assessments reset to the initial schedule of study evaluations (i.e. as if the patient was restarted the study at Cycle 1 Day 1). Patients will be treated until disease progression (per investigator's assessment), unacceptable toxicity, or until another criterion is met for withdrawal from the study treatment (see Section 5.2).

An End-of-treatment (EOT) visit will be performed within 7 days after the decision is made to discontinue study treatment. Following completion of the EOT visit, patients will enter the Safety follow-up. The Safety follow-up (SFU) visit will take place 30 days (window of +5 days allowed) after the last administration of study drug.

Safety evaluations will be done at Screening, on the first day of study drug administration (Cycle 1 Day 1), at each clinic visit during the treatment, and at the SFU visit. The National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 will be used to grade toxicities/AEs. Doses may be delayed or reduced in the event of clinically significant hematological or other toxicities (see Section 6.4.1.1 and Section 6.4.1.2) that are possibly, probably or definitely related to study treatment. The dose modification levels of study drug will follow the pre-defined dose levels outlined in Section 6.4.1.

Tumor assessments (and laboratory/clinical tests for WM patients) will be made according to the institution's standard of care.

The response assessment will be done according to the Lugano Classification (21), and for patients with WM, according to the Owen criteria (22). Detailed instructions on tumor assessment are provided in Appendix 14.1.

Bone marrow biopsy may be performed at the investigator discretion if there is clinical suspicion of bone marrow infiltration. Bone marrow biopsy will be performed as per local standard of care.

All collected blood, plasma and tumor tissue samples may be utilized for biomarker analysis to contribute to better understanding the mechanism of action and the disease (see Section 7.6.1).

Primary variable

Due to the decision of stopping enrollment, limited number of patients will be included in the analyses. Therefore, the statistical analyses included in this study will be focused on descriptive statistics for safety only.

Justification of the design

The pre-clinical profile of copanlisib and preliminary efficacy data from Phase I study 12871 and Phase II study 16349 suggest that copanlisib may improve PFS in patients with rituximab-refractory iNHL who have received two or more prior lines of treatment and have been exposed to rituximab and alkylating agent(s). The purpose of this study is to evaluate the safety of copanlisib treatment.

End of study

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

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

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] (*footnote added by amendment 1*).
2. Histologically confirmed diagnosis of indolent B-cell NHL, with histological subtype limited to the following:
   - Follicular lymphoma (FL) grade 1-2-3a.
   - Small lymphocytic lymphoma (SLL) with absolute lymphocyte count $< 5 \times 10^9$/L at the time of diagnosis and at study entry.
   - Lymphoplasmacytoid lymphoma/Waldenström macroglobulinemia (LPL/WM).
   - Marginal zone lymphoma (MZL) (splenic, nodal, or extra-nodal).
3. Patients must have received two or more prior lines of treatment (*changed by amendment 1*). A previous regimen is defined as one of the following: at least two months of single-agent therapy, at least two consecutive cycles of polychemotherapy, autologous transplant, radioimmunotherapy.
4. Prior therapy must include rituximab and alkylating agent(s). Prior exposure to idelalisib or other PI3K inhibitors is acceptable (except to copanlisib) provided that there is no resistance (*modified by amendment 1 and 3*).
5. Patients must be refractory to the last rituximab-based treatment, defined as no response or response lasting < 6 months after completion of treatment. Time interval to assess refractoriness will be calculated between the end date (last day) of the last rituximab-containing regimen and the day of diagnosis confirmation of the subsequent relapse (*modified by amendment 3*).
6. Patients must have at least one bi-dimensionally measurable lesion (which 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 (21) (*changed by amendment 1*).

[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 as noted in the protocol as well as results from CT/MRI scans, bone marrow sample, MUGA/echocardiogram and hepatitis testing which may also be used provided that they fall into the protocol-specified time window. Archival tissue obtained from the patients at any time during the course of their iNHL may also be used prior to the informed consent date and time if performed as part of the standard of practice. CT/MRI must also meet the quality standards of the Imaging Manual (*added by amendment 1*).

7. 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 (*changed by amendment 1 and 3*).
8. Male or female patients ≥ 18 years of age.
9. ECOG performance status ≤ 1.
10. Life expectancy of at least 3 months.
11. Availability of fresh (preferred) and/or archival tumor tissue at Screening.
12. 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 ICF and 3 months 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 (*criterion 12 modified by amendment 3*).
13. Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements conducted within 7 days before start of study treatment:
    - Total bilirubin ≤ 1.5 x ULN
      (≤ 5 x ULN for patients with proven Gilbert-Meulengracht syndrome or
      ≤ 3 x ULN for patients with cholestasis due to compressive adenopathies of the hepatic hilum) (*modified by amendment 3*).
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST)
      ≤ 2.5 x ULN
      (≤ 5 x ULN for patients with liver involvement of their lymphoma).
    - Lipase ≤ 1.5 x the ULN (*modified by amendment 3*).
    - Glomerular filtration rate (GFR) ≥ 30 ml/min/1.73 m^2 according to the Modification of Diet in Renal Disease (MDRD) abbreviated formula.

- International normalized ratio (INR) ≤ 1.5 and
  partial thromboplastin time (PTT) ≤ 1.5 x ULN (*modified by amendment 3*)
  Patients who are therapeutically treated with an agent such as warfarin or heparin will be allowed to participate provided that no prior evidence of underlying abnormality in coagulation parameters exists. Close monitoring is recommended according to the local standard of care.
- Platelet count ≥ 75,000/mm3. For patients with confirmed lymphomatous bone marrow infiltration, platelet count ≥ 50,000 /mm3. Platelet transfusion should not be given less than 7 days before the exam collection (modified by amendment 4).
- Hemoglobin (Hb) ≥ 10 g/dL.
- Absolute neutrophil count (ANC) ≥ 1500/mm^3.
- *Requirements related to serum creatinine* (*SCR*)*, serum lactate dehydrogenase* (*LDH*) *and serum beta-2-microglobulin levels removed by amendment 1.*

14. Left ventricular ejection fraction (LVEF) ≥ the lower limit of normal (LLN) for the Institution.

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, previous therapies and medications (*modified by amendment 4*)

3. Histologically confirmed diagnosis of FL grade 3b.
4. Chronic lymphocytic leukemia (CLL).
5. Transformed disease (assessed by investigator):
   - histological confirmation of transformation, **or**
   - clinical and laboratory signs: rapid disease progression, high standardized uptake value (> 12) by positron emission tomography (PET) at baseline if PET scans are performed (optional).
6. Previous or concurrent cancer that is distinct in primary site or histology from indolent B-cell NHL (*clarified by amendment 1*) within 5 years before start of study treatment **except** for curatively treated cervical cancer *in situ*, non-melanoma skin cancer and superficial bladder tumors [Ta (non-invasive tumor), Tis (carcinoma *in situ*) and T1 (tumor invades lamina propria)].

7. *Criterion 7 removed by amendment 1.*
8. Bulky disease (*criterion changed by amendment 1*):
    - Lymph nodes or tumor mass (except spleen) ≥ 7 cm LDi (longest diameter).
9. *Criterion 9 removed by amendment 1.*
10. *Criterion 10 removed by amendment 1.*
11. Known lymphomatous involvement of the central nervous system.
12. Congestive heart failure > New York Heart Association (NYHA) class 2.
13. Unstable angina (angina symptoms at rest), new-onset angina (begun within the last 3 months). Myocardial infarction less than 6 months before start of study treatment.
14. Uncontrolled arterial hypertension despite optimal medical management (per investigator's assessment) (*modified by amendment 3*).
15. Type I or II diabetes mellitus with HbA1c > 8.5% at Screening (*modified by amendment 3*).
16. Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis or pulmonary embolism within 6 months before start of study treatment.
17. Non-healing wound, ulcer, or bone fracture.
18. Active clinically serious infections > CTCAE Grade 2.
19. Known history of human immunodeficiency virus (HIV) infection.
20. Hepatitis B (HBV) or hepatitis C (HCV). All patients must be screened for HBV and HCV up to 28 days before start of study treatment using the routine hepatitis virus laboratory panel. Patients positive for HBsAg or HBcAb will be eligible if they are negative for HBV-DNA. Patients positive for HCV immunoglobulin G (IgG) will be eligible if they are negative for HCV-RNA.
21. Patients with seizure disorder requiring medication.
22. Patients with evidence or history of bleeding diathesis. Any hemorrhage or bleeding event ≥ CTCAE Grade 3 within 4 weeks before start of study treatment.
23. Renal failure requiring hemo- or peritoneal dialysis.
24. 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 (*modified by amendment 3*).
25. History or concurrent condition of interstitial lung disease of any severity and/or severely impaired lung function (as judged by the investigator) (*clarified by amendment 1*).
26. Concurrent diagnosis of phaeochromocytoma.

27. Pregnant or breast-feeding patients. Women of childbearing potential must have a serum pregnancy test performed a maximum of 7 days before start of study treatment, and a negative result must be documented before start of study treatment.
28. Unresolved toxicity > CTCAE Grade 1 attributed to any prior therapy/procedure excluding alopecia and ≤ CTCAE Grade 2 peripheral neuropathy.
29. Known hypersensitivity to any of the study drugs, study drug classes, or excipients in the formulation.
30. Substance abuse, medical, psychological or social conditions that may interfere with the patient's participation in the study or evaluation of the study results.
31. Any illness or medical conditions that are unstable or could jeopardize the safety of the patient and his/her compliance in the study.
32. *Criterion 32 removed by amendment 1.*
33. Treatment with investigational drugs within 28 days before start of study treatment (*criterion changed by amendment 1*).
34. Ongoing immunosuppressive therapy.
35. Radiotherapy or immuno/chemotherapy within 4 weeks before start of study treatment.
36. Radioimmunotherapy or autologous transplant within 3 months before start of study treatment.
37. Myeloid growth factors within 14 days before start of study treatment.
38. Blood or platelet transfusion within 14 days before start of study treatment.
39. 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 (*modified by amendment 3*). 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.
40. History of having received an allogeneic bone marrow or organ transplant.
41. Major surgical procedure, or significant traumatic injury (as judged by the investigator) within 28 days before start of study treatment; open biopsy within 7 days before start of study treatment.
42. Anti-arrhythmic therapy (beta blockers or digoxin are permitted).
43. Use of strong inhibitors of CYP3A4 is prohibited from Day -14 of Cycle 1 until the SFU visit.
44. Use of strong inducers of CYP3A4 is prohibited from Day -14 of Cycle 1 until the SFU visit.

45. Documented evidence of resistance to a prior treatment with idelalisib or other PI3K inhibitors defined as (*exclusion criterion added by amendment 1*):
    - No response (response defined as PR or CR) at any time during therapy, **or**
    - Progression (PD) after any response (PR/CR) or after stable disease (SD) within 6 months from the start of the therapy with a PI3K inhibitor (*modified by amendment 3*).

      Patients who discontinued treatment due to other reason than disease progression, and did not exhibit any signs of PD, will be allowed to enroll in this study after discussion with the sponsor.
46. Prior treatment with copanlisib (*criterion 46 added by amendment 3*).
47. Positive cytomegalovirus (CMV) PCR test at baseline (*criterion 47 added by amendment 4*).

For prohibited concomitant therapy please refer to 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.

5.2 Withdrawal of patients from study

5.2.1 Withdrawal

Section modified by amendment 1 and 5.

A patient who, for any reason (e.g. failure to satisfy the selection criteria), terminates the study before randomization is regarded a “screening failure”.

A patient who discontinues study participation prematurely for any reason is defined as a “dropout” if the patient has already entered treatment.

5.2.1.1 Withdrawal from 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. (See Section 11.2) (*modified by amendment 3 and 6*).
- If, in the investigator’s opinion, continuation of the study treatment would be harmful to the patient’s well-being.
- Disease progression (PD) as defined in the Lugano Classification (21), and for patients with WM, according to the Owen criteria (22) (*changed by amendment 1*). Detailed

instructions on tumor assessment are provided in Appendix 14.1 (*modified by amendment 5*).

- *The reason related to AEs due to disease-related complications removed by amendment 1.*
- 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 study drug 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 (*criterion changed by amendment 3 and 6*).
- CTCAE Grade 4 dermatologic toxicity.
- CTCAE Grade 4 non-infectious pneumonitis (NIP).
- Drug-induced pancreatitis.
- Development of a malignancy other than indolent B-cell NHL (*clarified by amendment 1*). New malignancy will be reported as a SAE.
- Start of a new anticancer regimen.
- Patient does not tolerate study drug dose of at least 30 mg.
- Severe allergic reaction to study drug (such as CTCAE Grade 3 or Grade 4 hypersensitivity reaction).
- Patient lost to follow-up.
- Substantial non-compliance with the requirements of the study.
- Delay in study drug administration due to toxicities for > 21 days (this does not include the required 1 week break), a delay of study drug dosing due to reasons other than toxicity is not included in this definition (*clarified by amendment 1*). Except in case of delays due to reactivation of CMV where delay could be up to 2 cycles (*modified by amendment 4*).
- 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 (β-hCG) test or any other sign consistent with pregnancy. Pregnancy will be reported within the same timelines as a SAE via the Pregnancy Monitoring Form.

Patients *may* 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).
- Clinical progression per investigator assessment (*added by amendment 6*).

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

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.

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.

For all patients who discontinue due to radiological PD or clinical PD, only date of PD will be collected and recorded in eCRF (*added by amendment 6*).

For patients who withdraw consent and object to follow-up data collection, no further study-related procedures will be allowed, and no further data will be collected. The patients will not suffer any disadvantage as a result (*modified by amendment 6*).

Details for the premature termination of the study as a whole (or components thereof [e.g. centers, treatment arms, dose steps]) are provided in Section 10.

5.2.1.2 Withdrawal from follow-up period

Section modified by amendment 1, 5 and 6.

Following completion of the EOT visit, patients will enter the Safety-follow up period.

Reasons for not performing the Safety 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 Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS) for unambiguous identification. The PID will be constructed as follows:

a. Digits 1 to 2: Unique country code (*clarified by amendment 1*).
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 17322 (this study) have a '2' as the 6th digit. As an example, PIDs in this study have the structure 'aabbb2ccc'.

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

6. Treatments

6.1 Treatments to be administered

Section modified by amendment 1 and 5.

The following treatments will be administered in this study:

- Copanlisib (BAY 80-6946) solution for IV infusion (study drug/investigational medicinal product)
- *Placebo solution for IV infusion removed by amendment 5*

Eligible patients will receive copanlisib IV infusion at a starting dose of 60 mg as single agent on Days 1, 8 and 15 of each 28-day treatment cycle.

In the event of toxicities, dose reductions to 45 mg and further to 30 mg are allowed. The dose modifications will follow the pre-defined dose levels outlined in Section 6.4.1. After full recovery from toxicity and in the absence of any criteria for further dose reduction or study treatment discontinuation, re-escalation will be allowed at the investigator's discretion. At no time should the administered dose exceed the starting dose of 60 mg. Patients who do not tolerate the dose of at least 30 mg must discontinue study treatment permanently (see Section 5.2).

See Pharmacy Manual for additional details.

6.2 Identity of study treatment

Section modified by amendment 1, 3 and 5.

The study drug will be labeled according to the requirements of local law and legislation. 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 the study drug, 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 ware of the ingredients. Lists linking all numbering levels will be maintained by the sponsor's clinical supplies QA group.

A complete record of batch numbers and expiry dates of study treatment as well as the label will be maintained in the sponsor study file.

Copanlisib

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.

6.3 Treatment assignment

Section modified by amendment 1 and 5.

With protocol amendment 5 there will be no randomization. All patients who are on study will be offered the opportunity to continue treatment with copanlisib.

The IXRS/IWRS will remain open in order to manage study drug.

6.4 Dosage and administration

Section modified by amendment 1, 3, 5 and 6.

Study drug (copanlisib) is administered 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 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)
Day 1 of cycle 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 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.
Table added by amendment 1 and modified by amendment 3 and 6.

- 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 using a handheld glucose meter. If handheld glucose meters are chosen, the appropriate calibration of glucose meters will be documented.

Recommendations on meal timing on infusion days

Because of inhibitory effect on PI3K α-isoform, which is implicated in insulin metabolism, copanlisib infusions could be associated with temporarily increase in blood glucose. Addition of meal in close proximity to study drug infusion may exacerbate glucose increase.

It is recommended on infusion days that timing of meal intake and additional glucose testing (if applicable) are managed and monitored by the investigators. Consultation with treating physician or diabetes specialist (e.g. 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.

- **On infusion days at any cycle:**

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

- **Cycle 1 Day 1:**

  Fasting is required before start of infusion.

- **Subsequent visits after C1D1 visit:**

  Fasting is not required before start of infusion.

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 day of infusion, with the exception of blood glucose, which must be performed on the day of infusion. All laboratory results must be assessed by the investigator and/or appropriate site personnel prior to administration of planned dose. On Day 1 of each subsequent cycle, the dose of study drug will be given only if the laboratory test 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
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

ANC = Absolute neutrophil count; ALT = Alanine aminotransferase; 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 on schedule 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 the source documentation and in the eCRF.

Table modified by amendment 1.

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

- CTCAE Grade ≥ 3 neutrophil count decreased (ANC < 1,000/mm^3)
- CTCAE Grade ≥ 3 platelet count decreased (platelets < 50,000/mm^3)
- CTCAE Grade ≥ 3 anemia (hemoglobin < 8 g/dL)

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 on schedule 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 the source documentation and in the eCRF.

Doses scheduled for Days 1 (after Cycle 1 Day 1), 8 and 15 may be delayed by up to 2 days. A delay of more than 2 days will be considered a missed dose. Missed doses will not be replaced. The minimum interval needed between two infusions of study drugs is 5 days.

6.4.1 Dose modification

Section modified by amendment 1, 3 and 6.

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 trials: e.g., transient increases in glucose and blood pressure. Based on this knowledge the investigator may decide on the necessary dose modifications. If the dose is reduced or interrupted, the investigator's decision is to be clearly documented in the patient's records and in the eCRF.

Dose modifications must be done according to the guidelines given in Section 6.4.1.1 and Section 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 study treatment (copanlisib) will follow the pre-defined dose levels shown in Table 6–3.

Table 6–3 Dose levels of study treatment

Dose level 1 (starting dose):	60 mg
Dose level -1:	45 mg
Dose level -2:	30 mg

After having fully recovered from toxicity and in the absence of any criteria for further dose reduction or study treatment 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 NIP.

Patients who do not tolerate the dose of at least 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. The guidelines for dose modifications in case of hematological toxicity are given in Table 6–4 (*changed by amendment 1 and modified by amendment 3*).

Table 6–4 Dose modification of study treatment for hematological toxicity

Note: This table should not be used to determine patient eligibility for infusion on days 1, 8 and 15. Please follow specific guidance given for laboratory test criteria on days 1, 8 and 15 (*note added by amendment 1*)

Hematological toxicity of CTCAE Grade (any of the following)	Study drug action (for all toxicities)
• Grade 4 thrombocytopenia (platelet < 25,000/mm^3) or Grade 3 (platelet < 50,000/mm^3) with bleeding. • Febrile neutropenia. • Grade 4 neutropenia (ANC < 500/mm^3).[a] • INR or PTT of Grade ≥ 3 with bleeding. • Grade ≥ 3 anemia (Hb < 8 g/dL).	Delay infusion until criteria displayed in Table 6–2 are met.[c] 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 study treatment permanently. The lowest dose level is 30 mg.

ANC = Absolute neutrophil count; CBC = Complete blood count; CTCAE = Common Terminology Criteria of Adverse Events; Hb = Hemoglobin; INR = International normalized ratio, PTT = Partial thromboplastin time.
a: For patients who develop CTCAE Grade 4 neutropenia, a CBC after 3 days is recommended.
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: Treatment with transfusion or growth factors is allowed at the investigator's discretion.
(*Table modified by amendment 3*)

6.4.1.2 Non-hematological toxicity

Dose modifications for non-hematologic toxicities except glucose increases, dermatologic toxicity, NIP and arterial hypertension are outlined in Table 6–5 (*table modified by amendment 1 and 3*).

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

		Study drug action	
Toxicity (CTCAE)	**Occurrence**	**For current course of therapy**	**For next course of therapy**
Grade 1-2	Any appearance	No change	No change
Grade 3[a]	1st appearance	Interruption until Grade ≤ 2	No change
	2nd appearance	Interruption until Grade ≤ 2	Decrease by one dose level[b]
	3rd appearance	Interruption until Grade ≤ 2	Decrease by one dose level[b]
	4th appearance	Permanent discontinuation	–
Grade 4	Any appearance	Permanent discontinuation	–
Toxicity requiring delay for > 21 days		Permanent discontinuation	–

CTCAE = Common Terminology Criteria of Adverse Events.
a: Despite maximum supportive therapy.
b: Not applicable for 30 mg dose level.
A delay > 21 days in study drug administration due to toxicities will cause permanent discontinuation of study treatment.
Study treatment 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.
Table modified by amendment 1 and 3.

Dermatologic toxicity

The guidelines for dose modifications in case of dermatologic toxicity are given in Table 6–6 (*changed by amendment 1*).

Table 6–6 Dose modification of study treatment for dermatologic toxicity

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

CTCAE = Common Terminology Criteria of Adverse Events. Toxicities according to CTCAE version 4.03.
a: Despite maximum supportive therapy.
b: Not applicable for 30 mg dose level.
The lowest dose level is 30 mg; if a patient is already on the 30 mg dose level and meets criteria for further dose decrease, study treatment will be discontinued permanently.
Table modified by amendment 1.

Non-infectious pneumonitis

In the event of NIP, an adjustment as described in Table 6–7 must be applied (*table modified by amendment 3*).

Table 6–7 Dose modification of study treatment for non-infectious pneumonitis (NIP)

	Study drug action	
Suspected or confirmed NIP of CTCAE	**For current course of therapy**	**Re-initiation of study drug (if recovered within 14 days)**
Grade 1	No change	Not applicable
Grade 2	Interruption	Decrease by one dose level[a]
Grade 2 re-occurrence	Permanent discontinuation	No
Grade 3	Interruption	Case by case decision (after consulting the sponsor)
Grade 3 re-occurrence	Permanent discontinuation	No
Grade 4	Permanent discontinuation	No

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 meets criteria for further dose decrease, study treatment will be discontinued permanently.
Table modified by amendment 3.

Pneumonitis is to be reported as such only in the event of NIP.

The investigator is requested to differentiate between NIP and infectious pneumonitis (viral, bacterial, fungal), aspiration pneumonitis, or other pneumonitis clearly not due to a potential hypersensitivity reaction to the copanlisib infusion; and provide the basis for his/her

assessment that it is infectious or other, as appropriate. The investigator is requested to report with the most specific clinical terms to describe the condition, not simple "pneumonitis" (*paragraph added by amendment 3*).

Glucose increases and arterial hypertension

a) Glucose increases

Section modified by amendment 1 and further revised by amendment 3 and 6.

Patients who develop transient post-infusion glucose > 250 mg/dL after study drug 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 study drug 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 study drug dose level despite optimal glucose lowering therapy (after at least one cycle of treatment) with consultation of a diabetes specialist requires permanent discontinuation of the study treatment (see Section 5.2.1.1).

b) Arterial hypertension

The guidelines for dose modifications of study drug in case of arterial hypertension are given in Table 6–8 (*table added by amendment 3*).

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 study drug 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 blood pressure of CTCAE Grade 4 must permanently discontinue the study drug (see Section 5.2.1.1) (*paragraph modified by amendment 3*).

Table 6–8 Dose modification of study treatment 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 skipped otherwise. 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.
Table added by amendment 3 and modified by amendment 4.

6.4.2 Treatment of toxicities

Recommendations for the treatment of toxicities described below apply to study treatment.

6.4.2.1 Management of transient post-infusion glucose increases that can occur with study treatment

Management of transient post-infusion glucose increases on infusion days

Section modified by amendment 1 and further revised by amendment 3 and 6.

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 added by amendment 3*).

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 diabetes specialist is recommended	• Hydration if appropriate • When planning next infusion consider prophylaxis with oral glucose lowering medication
Symptomatic or persisting glucose increases > 250 mg/dL	• Hydration status should be clinically assessed • If clinical assessment is consistent with dehydration, fluids should be given as clinically appropriate (orally or IV). • Laboratory test confirming increase should be repeated. If the repeated glucose value is > 250 mg/dL and/or patient is symptomatic and/or the hydration status indicate the need for hydration, glucose lowering medication should be administered • Prompt input from a diabetes specialist 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 diabetes specialist 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
Table added by amendment 3.

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

Section clarified by amendment 1 and modified by amendment 3 and 6.

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 (23). 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 (*changed by amendment 3*).

6.4.2.3 Treatment of blood pressure increases associated with study treatment

Heading modified by amendment 3.

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 study treatment 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). Topical nitrates should also be considered. Verapamil and diltiazem (non-dihydropyridine calcium channel blockers and moderate inhibitors of CYP3A4) should be used with caution due to a potential CYP3A4 interaction (*modified by amendment 3*). 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 study drug on 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 study drug, 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 h until diarrhea-free for 12 h; a maximum daily dose of 16 mg is not to be exceeded. If clinically indicated, diphenoxylate or Lomotil, which contains diphenoxylate plus atropine might also be used. In the event of CTCAE Grade 3 diarrhea with maximal pharmacological support, the administration of the study 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 min 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
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

CTCAE = Common Terminology Criteria for Adverse Events; bid = Twice daily; min = Minute(s)
Source: (24).

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

S*ection added by amendment 4*

6.4.2.6.1 Monitoring guidelines for OI

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

- Evaluation of any new onset or worsening of pulmonary symptoms (i.e. cough, dyspnea or fever) that includes an examination at each visit prior to infusion.
- Laboratory tests: cluster of differentiation 4 (CD4) for patients with signs of infection i.e. cough, dyspnea or fever, blood cultures when low ANC of CTCAE Grade 4, PCR for CMV (monthly for the first 6 months of study treatment and every 3 months thereafter).
    - 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 myelosuppressive cytotoxic therapy)
- History of CMV, herpes
- History of lower respiratory tract infection, history of immunodeficiency 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 will include:

- CD4 and cluster of differentiation 8 (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 scan)
    - Note: Treatment of opportunistic infections should be based on local SOC.

6.4.2.6.2 Prophylaxis of OI

Mandatory prophylactic therapy is not recommended in all patients:

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

Although not mandated in all patients, OI prophylaxis may be initiated at the discretion of the treating investigator's judgment of the benefit/risk ratio in any patient, irrespective of whether a high-risk feature is present, per local SOC. If so, drug name, indication, 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 local SOC in patients when high risk factors are identified (see protocol Section 6.4.2.6.1). For example: Bactrim or equivalent, Acyclovir or equivalent.

6.5 Blinding

Section modified by amendment 5.

Not applicable.

After individual patient unblinding, patients receiving active study drug will continue copanlisib treatment as scheduled. Patients receiving placebo will be offered to switch to copanlisib upon discretion of the investigator and patient's consent.

6.6 Drug logistics and accountability

Section modified by amendment 5.

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.

Study drug supply and predictive re-supply will be managed through the IVRS/IWRS. After a patient is assigned to treatment, the amount of study drug supply needed at the study site for each patient will be calculated. Re-supply of study drug will be performed automatically at regular intervals through the IVRS/IWRS based on the expected dosing of the study drug.

After closure of the study enrollment, the IxRS will continue to supply copanlisib treatment for all patients who remain in the study. When a patient is permanently withdrawn from treatment, the study site must notify the Sponsor through the IVRS/IWRS.

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

6.7 Treatment compliance

Section modified by amendment 5.

The administration of IV copanlisib will be performed in the clinic on a weekly basis and must be recorded in the eCRF.

6.8 Post-study therapy

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

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 inducers of CYP3A4 (e.g., rifampin, phenytoin, carbamazepine, phenobarbital, St. John's Wort) is not permitted from Day -14 of Cycle 1 until the SFU visit.
- Grapefruit and grapefruit juice (CYP3A4 inhibitor) consumption is not permitted during the study.
- 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 (*modified by amendment 3*). If a patient is on chronic corticosteroid therapy, corticosteroids should be de-escalated to the maximum allowed dose before the Screening. Patients may use topical or inhaled corticosteroids. Short term systemic corticosteroids above 15 mg prednisolone or equivalent will be allowed for the management of acute conditions (e.g. treatment of NIP) (*changed by amendment 1*). The use of corticosteroids as antiemetics prior to study drug administration will not be allowed.
- Myeloid growth factors within 14 days before start of study treatment.
- 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 treatment anyway).

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, including 5-HT3 blockers, such as granisetron, ondansetron, or an equivalent agent, is allowed as needed. The use of corticosteroids as antiemetics prior to study drug administration will be not allowed.
- Palliative and supportive care for the other disease-related symptoms (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 (*modified by amendment 3*).

7. Procedures and variables

7.1 Schedule of procedures

7.1.1 Tabulated overview

Schedule of procedures is presented in Table 7–1.

Table 7–1 Study flow chart

	Screening			Treatment *						EOT	SFU
	maximum days before C1D1			Cycle 1			Cycle 2 and higher			Within (days) after	
Days	**-28**	**-14**	**-7**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**7**	**30 + 5** days window[z]
Acceptable deviation (in days)				-1 to +2 days			-1 to +2 days			Decision to stop	Last dose
Screening and enrollment											
Patient informed consent (including genetic) [jj]	X[cc,dd]										
Check in- and exclusion criteria		X	X	X							
Medical history [a]		X									
IVRS/IWRS transaction [b, dd]	X			X[b]			X			X	
HBsAg, HBcAb, HCV IgG	X										
CMV PCR test [ff,ii]	X			X[ff]			X[ff]				
Serum pregnancy test (if applicable) [c]			X				X[c]			X[c, ee]	
UPCR / 24 h total urine protein quantification [ee]			X								
GFR [dd]			X				X				
Safety											
Toxicity / AE assessment [d]		X		X	X	X	X	X	X	X	X
Concomitant medication [d]		X		X	X	X	X	X	X	X	X
Complete physical examination [e]		X		X			X			X	
Brief physical examination [f, dd]					X	X		X	X		(X)
12-lead ECG [g, dd]	X									X[g]	
MUGA scan or echocardiogram [h, dd]	X[h]									X[h]	
HbA1c [i]			X							X	
Complete blood count [j]			X		X[x]	X[x]	X[x]	C2 only[x]	C2 only[x]	X	(X)
Hemoglobin, ANC and platelet counts (C3→)								X[x]	X[x]		
Chemistry panel [k]			X[k]		X[x]	X[x]	X[k,x]	C2 only[x]	C2 only[x]	X[k]	(X)
Coagulation panel: PT, INR and PTT			X			X[x]	X[x]			X	(X)

Table 7–1 Study flow chart

	Screening			Treatment *						EOT	SFU
	maximum days before C1D1			Cycle 1			Cycle 2 and higher			Within (days) after	
Days	**-28**	**-14**	**-7**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**7**	**30 + 5** days window[z]
Acceptable deviation (in days)				-1 to +2 days			-1 to +2 days			Decision to stop	Last dose
CD4 (for patients with signs of infection) and blood cultures when low ANC of CTCAE Grade 4 [gg, hh,ii]											
Urinalysis (dipstick)			X				X			X	
Glucose [l]				X	X	X	X	X	X		
Blood pressure [n]				X	X	X	X	X	X		
Bone marrow biopsy [o]	X										
CT/MRI and tumor evaluations and laboratory/clinical tests for LPL/WM patients[p]	X[p]									X[p]	
Study drug administration											
Copanlisib IV infusion				X	X	X	X	X	X		

AE = Adverse event; ALP = Alkaline phosphatase; ALT = Alanine aminotransferase; ANC = Absolute neutrophil count; AST = Aspartate aminotransferase; BUN = Blood urea nitrogen; CBC = Complete blood count; CD4 = Cluster of differentiation 4; CMV = cytomegalovirus; CT = Computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; D = Day; ECG = Electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = End of treatment; eCRF= Electronic case report form; FL = Follicular lymphoma; FLIPI = Follicular Lymphoma International Prognostic Index; FLymSI-18 = NCCN-FACT Lymphoma Symptom Index-18; GFR = Glomerular filtration rate; h = Hour(s); HbA1c = Glycated hemoglobin; HBcAb = Hepatitis B core antibody; HBsAg = Hepatitis B surface antigen; HCV = Hepatitis C virus; IgG = Immunoglobulin G; iNHL = Indolent non-Hodgkin's lymphoma; 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; min = Minute(s); MRI = Magnetic resonance imaging; MUGA = Multiple gated acquisition; NYHA = New York Heart Association; OI = Opportunistic infection; PCR = polymerase chain reaction; PT = Prothrombin time; PTT = Partial thromboplastin time; RBC = Red blood cell count; SCR = Serum creatinine; SFU = Safety follow-up; UPCR = Urine protein to creatinine ratio; WBC = White blood cell count (*list updated by amendment 1 and 5*).

* **NOTE**: After individual patient unblinding, patients receiving placebo who switch to copanlisib will have all study assessments reset to the initial schedule of study evaluations (i.e. as if the patient was restarting the study at Cycle 1 Day 1). For further information on laboratory requirements for patients who switch to open-label treatment, please see Section 7.1.2.2 (*clarified by amendment 1 and modified by amendment 3 and 5*).

a Demographics, relevant medical history findings, concomitant illnesses, allergy history, prior surgeries, most recent histology of tumor, most recent staging and grading of tumor, FLIPI score (for patients with FL), history of anticancer treatments (including type of treatment, type of response, date and duration of response and date of subsequent relapse), assessment of baseline toxicity and smoking history (*modified by amendment 1*).

b IVRS/IWRS transaction to register the patient in the system will be at Screening (*modified by amendment 1*). IVRS/IWRS transaction will take place within 48 h before the first dose of study drug. 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 *(modified by amendment 5)*.

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 (*changed by amendment 3*).

d After Screening: AE assessment and concomitant medication review must be updated before each dose and all AEs starting within 30 days after the last dose of study drug should be collected and recorded in eCRF (*modified by amendment 4*). 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. Contrast media does not need to be recorded as concomitant medication unless there is an AE related to its administration (e.g. allergic reaction) (*footnote modified by amendment 6*).

e Complete physical examination to include: ECOG performance status, NYHA classification, height (only at Screening), weight, vital signs (temperature, pulse and blood pressure), and a complete review of body systems (*changed by amendment 1*), including lung examination (*added by amendment 4*).

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 (*added by amendment 4*).

g 12-lead ECG (including QTcB and QTcF evaluation) will be performed at Screening (within 28 days before Cycle 1 Day 1), EOT and as clinically indicated. At the EOT visit, a 12-lead ECG is necessary only if not recorded within the previous 4 weeks. (*modified by amendment 5*)

h MUGA scan or echocardiogram to measure LVEF at Screening (within 28 days before Cycle 1 Day 1), EOT and as clinically indicated (if not previously done within 4 weeks). The method chosen at Screening must be the same throughout the whole study. (*modified by amendment 1 and 5*)

i HbA1c at Screening and at the EOT visit. The testing is not required if the previous test was performed within 4 weeks preceding EOT visit (*modified by amendment 3 and 5*).

j CBC: Hemoglobin, hematocrit, RBC, WBC (with differential to include absolute neutrophil, lymphocyte, monocyte, basophil and eosinophil counts and platelet count). From Cycle 2 onwards, only hemoglobin, platelet and ANC counts will be performed on Day 8 and Day 15 prior to each infusion. Differential blood count in percentage can be provided when absolute count is not available per standard of care of the local lab (*modified by amendment 4 and 5*).

k 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), SCR, uric acid, total bilirubin, creatine phosphokinase, ALT, AST, LDH, ALP, lipase, amylase (or pancreatic amylase, if total amylase is not routinely measured at the site), cholesterol (total and LDL) and triglycerides. Total cholesterol, LDL and triglycerides will be tested only at Screening and at the EOT visit. On these dates patients must be fasting prior to sampling according to local standards. If a patient can't adhere to fasting requirements, the evaluation of lipid-panels including triglycerides is considered not feasible (*modified by amendment 1, 3 and 5*).

l On Cycle 1 Day 1, glucose will be measured at pre-dose and post-dose after the end of study drug infusion (0), 1 h and 2 h. Additional measurements to be performed at the clinic as clinically indicated. On subsequent infusions, glucose will be measured prior to and 1 h after the end of infusion. Deviation of ± 10 min is allowed for glucose measurements, except for the pre-dose measurement. For details on fasting requirements and pre-dose glucose levels, see Section 6.4. Glucose is also measured as part of the chemistry panel (*footnote changed by amendment 1, 3 and 6*).

m *Footnote removed by amendment 6.*

n Blood pressure will be measured every 5-10 min prior to infusion of study drug (no more than 4 measurements) until there are 2 consecutive results < 150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. On infusion days, blood pressure will be measured at 0 h (pre-dose), 30 min (mid-infusion), 60 min (end of infusion); and 1 h and 2 h after the end of infusion. Time window of ± 10 min is allowed for all blood pressure measurements except for 0 h (pre-dose). The patient should rest for 5-10 min before blood pressure is recorded (*footnote modified by amendment 1 and 3*).

o Bone marrow biopsy may be performed at the investigator discretion if there is clinical suspicion of bone marrow infiltration. Bone marrow biopsy will be performed as per local standard of care (*clarified by amendment 1 and modified by amendment 4, 5 and 6*).

p Tumor assessments and their frequency as well as laboratory/clinical tests for WM patients will follow the institution's standard of care (*footnote changed by amendment 1, 3, 5 and 6*).

q *Footnote removed by amendment 5.*

r *Footnote removed by amendment 6.*

s *Footnote removed by amendment 6.*

t *Footnote removed by amendment 6.*

u *Footnote removed by amendment 6.*

v *Footnote removed by amendment 5.*

w *Footnote removed by amendment 6.*

x Laboratory tests prior to each infusion may be performed either the day before or on the planned date of infusion, with the exception of blood glucose (or capillary glucose sampling via glucose meter), which must be performed on the day of infusion (*modified by amendment 1*). For dosing criteria, see Section 6.4.

y *Footnote removed by amendment 5.*

z The post-treatment follow-up 30 days (window of +5 days allowed) after the last administration of study drug can be conducted via telephone if the patient is no longer being actively seen at the clinic or has started another therapy. Procedures marked with "(X)" are only to be performed, if clinically indicated *(modified by amendment 5)*.

aa *Footnote removed by amendment 6.*

bb *Footnote removed by amendment 6.*

cc Written informed consent must be obtained prior to any study-specific procedures. Certain results from diagnostic testing performed as part of the standard of practice prior to the informed consent date and time may be used to fulfill screening criteria. This includes fresh tissue as noted in the protocol as well as results from CT/MRI scans, bone marrow sample, MUGA/echocardiogram and hepatitis testing which may also be used provided that they fall into the protocol-specified time window. Archival tissue obtained from the patients at any time during the course of their iNHL may also be used prior to the informed consent date and time if performed as part of the standard of practice. 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) (*footnote added by amendment 1 and modified by amendment 6*).

dd *Modified by amendment 1.*

ee *Modified by amendment 3.*

ff Blood test for CMV. Should be performed in all patients prior to IV infusion of copanlisib. Every month for the first 6 months of treatment and every 3 months 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 (*footnote added by amendment 4*).

gg For patients with identified risk factors and those who developed OI on study treatment, 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 should be 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) (*footnote added by amendment 4*).

hh Blood cultures should be performed as per local SOC if the patient develops low ANC of CTCAE Grade 4. CD4 count should be performed for patients with signs of infection (*footnote added by amendment 4*).

ii *Modified by amendment 4.*

jj As of amendment 5, all patients will be reconsented and need to voluntarily agree to sign the ICF and have to do so, to continue in the study (*added by amendment 5*).

7.1.2 Timing of assessments

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 CSP. For assessments during the treatment period, deviations of -1 day and +2 days are acceptable unless otherwise specified in the protocol (*modified by amendment 1 and 3*).

7.1.2.1 Screening period

By the time the protocol amendment 6 becomes effective, screening procedures are no longer applicable as screening for the study ended on 03 MAR 2017. All screened eligible patients have started treatment (*paragraph added by amendment 6)*.

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 as noted in the protocol as well as results from CT/MRI scans, bone marrow sample, MUGA/echocardiogram and hepatitis testing which may also be used provided that they fall into the protocol-specified time window. Archival tissue obtained from the patients at any time during the course of their iNHL may also be used prior to the informed consent date and time if performed as part of the standard of practice. 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) (*paragraph modified by amendment 1 and 6*).

Within 28 days before the first administration of study drug (*clarified by amendment 3*):

- IVRS/IWRS transaction to register the patient in the system.
- Blood test for HBV and HCV: HBsAg, HBcAb and HCV IgG.
  (If HBsAg or HBcAb positive also HBV DNA; if HCV IgG positive also HCV RNA).
- Blood test for CMV infection per local SOC. Patients who are CMV testpositive at baseline will not be eligible (*added by amendment 4 and modified by amendment 5*).
- 12-lead ECG including QTcB and QTcF evaluation (*added by amendment 1*) (see Section 7.5.3.4).
- Multiple gated acquisition (MUGA) scan or echocardiogram to measure LVEF. The method chosen at Screening must be the same throughout the whole study (*added by amendment 1*) (see Section 7.5.3.5).
- Bone marrow biopsy: mandatory at Screening. A bone marrow biopsy may be performed at the investigator discretion if there is clinical suspicion of bone marrow infiltration. Bone marrow biopsy will be performed as per local standard of care (*clarified by amendment 1and modified by amendment 4, 5 and 6*).

- IV (and oral, if indicated) contrast-enhanced CT/MRI of neck, chest, abdomen and pelvis (including WM patients). Corticosteroids must be stopped or reduced to the allowed dose (less than 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 the baseline must be the same throughout the study (see Section 7.3.2) (*paragraph modified by amendment 1 and 6*).

- *Tumor tissue collection removed by amendment 6.*

Within 14 days before the first administration of study drug (*clarified by amendment 3*):

- Check inclusion and exclusion criteria (see Section 5.1).
- Complete medical and surgical history including demographics, relevant medical history findings, concomitant illnesses, allergy history, prior surgeries, most recent histology of tumor, most recent staging and grading of tumor, FLIPI score (for patients with FL), history of anticancer treatments (including type of treatment, type of response, date and duration of response and date of subsequent relapse), assessment of baseline toxicity and smoking history (*modified by amendment 1*) (see Section 7.2).
- *Serum beta-2-microglobulin was changed to be performed only in patients with LPL/WM by amendment 1* (*see below*).
- 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 AEs (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 grading definitions in Appendix 14.3), NYHA classification (see Appendix 14.4), height, weight, vital signs (temperature, pulse and blood pressure), and a complete review of body systems (*changed by amendment 1*) (see Section 7.5.3.2).
- *12-lead ECG and MUGA scan/echocardiogram measurements moved to previous section* (*less than 28 days before start of treatment*) *by amendment 1*.
- *Laboratory/clinical tests for LPL/WM patients removed by amendment 6.*

Within 7 days before the first administration of study drug (*clarified by amendment 3*):

- 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 (*modified by amendment 3*) (see Section 7.5.3.1).

- GFR measurement (see Section 7.5.3.1 and Appendix 14.5).
- Blood tests for HbA1c, CBC, chemistry and coagulation panels (see Section 7.5.3.1). Patients must be fasting prior to sampling according to local standards (*changed by amendment 3*). If a patient can't adhere to fasting requirements, the evaluation of lipid-panels including triglycerides is considered not feasible.
- Urinalysis (dipstick). Microscopy as clinically indicated (see Section 7.5.3.1).
- *Training on glucose self-monitoring removed by amendment 6.*

7.1.2.2 Treatment period

Section modified by amendment 1, 3 and 5.

After all screening assessments have been completed and the patient's eligibility has been confirmed and documented, the patient will be assigned to treatment via IVRS/IWRS. The randomization will take place within 48 h before the first dose of study drug.

After individual patient unblinding, patients receiving placebo, who switch to copanlisib will have all study assessments reset to the initial schedule of study evaluations (i.e. as if the patient was restarted the study at Cycle 1 Day 1). For Day 1 of subsequent cycles, dosing criteria outlined in Table 6–2 will apply for patients receiving open-label treatment.

The following assessments should be performed at each visit before receiving study treatment (*added by amendment 4*)

- Monitoring for OI (see Section 6.4.2.6):

  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:

  - 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, PCR for CMV (monthly for first 6 months of treatment and every 3 months thereafter)

    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 (*fasting requirements changed by amendment 1 and 3*).

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

- *QoL questionnaire removed by amendment 5.*
- 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 transaction will take place within 48 h before the first dose of study drug *(modified by amendment 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 AEs (see Section 7.5.1.3).
- Monitoring for OI (see Section 6.4.2.6) (*added by amendment 4*).
- 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 (*changed by amendment 1*) (see Section 7.5.3.2).
- *12-lead ECG removed by amendment 5.*
- Glucose will be measured at pre-dose and post-dose after the end of study drug infusion (0), 1 h and 2 h (deviation of ± 10 min is allowed, except for the pre-dose measurement). Additional measurements to be performed at the clinic as clinically indicated (see Section 6.4 and Section 7.5.3.6) (*changed by amendment 1, 3 and 6*).
- *Home blood glucose monitoring removed by amendment 6.*
- Blood pressure will be measured every 5-10 min prior to infusion of study drug (no more than 4 measurements) until there are 2 consecutive results < 150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. Blood pressure will be measured at 0 h (pre-dose), 30 min (mid-infusion), 60 min (end of infusion); and 1 h and 2 h after the end of infusion. Time window of ± 10 min is allowed for all measurements except for 0 h (pre-dose). The patient should rest for 5-10 min before blood pressure is recorded (*modified by amendment 1 and 3*).
- *PK sampling associated with 12-lead ECG removed by amendment 1.*
- *Biomarker sampling removed by amendment 6.*
    - *Whole blood for genetic biomarker analysis removed by amendment 5.*
- Study drug IV infusion.

Cycle 1 Day 4 removed by amendment 5

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).
- Monitoring for OI (see Section 6.4.2.6) (*added by amendment 4*).
- Blood tests for CBC and chemistry panel (excluding total cholesterol, LDL and triglycerides) (see Section 6.4 and Section 7.5.3.1).
- Glucose test prior to study drug infusion and 1 h after the end of study drug infusion (deviation of ± 10 min is allowed, except for the pre-dose measurement) (see Section 6.4 and Section 7.5.3.6) (*changed by amendment 1, 3 and 6*).
- Review of the blood glucose measurements/meal timing/oral glucose lowering medication/insulin administration, if applicable (*changed by amendment 1, 3 and 6*) (see Section 6.4.2.1).
- *Home blood glucose monitoring removed by amendment 6.*
- Blood pressure will be measured every 5-10 min prior to infusion of study drug (no more than 4 measurements) until there are 2 consecutive results < 150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. Blood pressure will be measured at 0 h (pre-dose), 30 min (mid-infusion), 60 min (end of infusion); and 1 h and 2 h after the end of infusion. Time window of ± 10 min is allowed for all measurements except for 0 h (pre-dose). The patient should rest for 5-10 min before blood pressure is recorded (*modified by amendment 1 and 3*).
- *PK sampling removed by amendment 6.*
- *Biomarker sampling removed by amendment 6.*
- Study drug 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).
- Monitoring for OI (see Section 6.4.2.6) (*added by amendment 4*).
- Blood tests for CBC, chemistry and coagulation panels (excluding total cholesterol, LDL and triglycerides) (see Section 6.4 and Section 7.5.3.1).
- Glucose test prior to study drug infusion and 1 h after the end of study drug infusion (deviation of ± 10 min is allowed, except for the pre-dose measurement) (see Section 6.4 and Section 7.5.3.6) (*changed by amendment 1, 3 and 6*).
- Review of the blood glucose measurements/meal timing/oral glucose lowering medication/insulin administration, if applicable (*changed by amendment 1, 3 and 6*) (see Section 6.4.2.1).
- *Home blood glucose monitoring removed by amendment 6.*
- Blood pressure will be measured every 5-10 min prior to infusion of study drug (no more than 4 measurements) until there are 2 consecutive results < 150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. Blood pressure will be measured at 0 h (pre-dose), 30 min (mid-infusion), 60 min (end of infusion); and 1 h and 2 h after the end of infusion. Time window of ± 10 min is allowed for all measurements except for 0 h (pre-dose). The patient should rest for 5-10 min before blood pressure is recorded (*modified by amendment 1 and 3*).
- *Biomarker sampling removed by amendment 6.*
- Study drug IV infusion.

Cycle 1 Day 22 removed by amendment 5

7.1.2.2.2 Treatment – Cycle 2 and higher

Cycle 2 and higher, Day 1

Fasting requirement removed by amendment 6.

- *QoL questionnaire removed by amendment 5.*
- 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 (*modified by amendment 3*).
- GFR measurement (see Section 7.5.3.1 and Appendix 14.5) (*added by amendment 1*).
- Toxicity/AE assessment (see Section 7.5.1.3).

- Monitoring for OI (see Section 6.4.2.6) (*added by amendment 4*).
- 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 (*changed by amendment 1*) (see Section 7.5.3.2).
- *12-lead ECG removed by amendment 5.*
- *MUGA scan or echocardiogram removed by amendment 5.*
- *Blood test for HbA1c removed by amendment 5.*
- Blood tests for CBC, chemistry and coagulation panels (see Section 6.4 and Section 7.5.3.1) (*modified by amendment 5*).
- Urinalysis (dipstick). Microscopy as clinically indicated (see Section 7.5.3.1).
- Glucose test prior to study drug infusion and 1 h after the end of study drug infusion (deviation of ± 10 min is allowed, except for the pre-dose measurement) (see Section 6.4 and Section 7.5.3.6) (*changed by amendment 1, 3 and 6*).
- Review of the blood glucose measurements/meal timing/oral glucose lowering medication/insulin administration, if applicable (*changed by amendment 1, 3 and 6*) (see Section 6.4.2.1).
- *Home blood glucose monitoring removed by amendment 6.*
- Blood pressure will be measured every 5-10 min prior to infusion of study drug (no more than 4 measurements) until there are 2 consecutive results < 150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. Blood pressure will be measured at 0 h (pre-dose), 30 min (mid-infusion), 60 min (end of infusion); and 1 h and 2 h after the end of infusion. Time window of ± 10 min is allowed for all measurements except for 0 h (pre-dose). The patient should rest for 5-10 min before blood pressure is recorded (*modified by amendment 1 and 3*).
- *Biomarker sampling removed by amendment 6.*
- Study drug IV infusion.
- *Laboratory/clinical tests for LPL/WM patients removed by amendment 6.*

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).
- Monitoring for OI (see Section 6.4.2.6) (*added by amendment 4*).
- On Cycle 2, blood tests for CBC and chemistry panel (excluding total cholesterol, LDL and triglycerides) will be performed. From Cycle 2 onwards, only hemoglobin, platelet and ANC counts will be performed prior to each infusion (see Section 6.4 and Section 7.5.3.1) (*modified by amendment 5*).
- Glucose test prior to study drug infusion and 1 h after the end of study drug infusion (deviation of ± 10 min is allowed, except for the pre-dose measurement) (see Section 6.4 and Section 7.5.3.6) (*changed by amendment 1, 3 and 6*).
- Review of the blood glucose measurements/meal timing/oral glucose lowering medication/insulin administration, if applicable (*changed by amendment 1, 3 and 6*) (see Section 6.4.2.1).
- *Home blood glucose monitoring removed by amendment 6.*
- Blood pressure will be measured every 5-10 min prior to infusion of study drug (no more than 4 measurements) until there are 2 consecutive results < 150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. Blood pressure will be measured at 0 h (pre-dose), 30 min (mid-infusion), 60 min (end of infusion); and 1 h and 2 h after the end of infusion. Time window of ± 10 min is allowed for all measurements except for 0 h (pre-dose). The patient should rest for 5-10 min before blood pressure is recorded (*modified by amendment 1 and 3*).
- *Biomarker sampling removed by amendment 6.*
- Study drug 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).
- Monitoring for OI (see Section 6.4.2.6) (*added by amendment 4*).
- *12-lead ECG removed by amendment 1.*
- On Cycle 2, blood tests for CBC and chemistry panel (excluding total cholesterol, LDL and triglycerides) will be performed. From Cycle 2 onwards, only hemoglobin, platelet and ANC counts will be performed prior to each infusion (see Section 6.4 and Section 7.5.3.1) (*modified by amendment 5*).
- Glucose test prior to study drug infusion and 1 h after the end of study drug infusion (deviation of ± 10 min is allowed, except for the pre-dose measurement) (see Section 6.4 and Section 7.5.3.6) (*changed by amendment 1, 3 and 6*).
- Review of the blood glucose measurements/meal timing/oral glucose lowering medication/insulin administration, if applicable (*changed by amendment 1, 3 and 6*) (see Section 6.4.2.1).
- *Home blood glucose monitoring removed by amendment 6.*
- Blood pressure will be measured every 5-10 min prior to infusion of study drug (no more than 4 measurements) until there are 2 consecutive results < 150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. Blood pressure will be measured at 0 h (pre-dose), 30 min (mid-infusion), 60 min (end of infusion); and 1 h and 2 h after the end of infusion. Time window of ± 10 min is allowed for all measurements except for 0 h (pre-dose). The patient should rest for 5-10 min before blood pressure is recorded (*modified by amendment 1 and 3*).
- *PK sampling associated with 12-lead ECG removed by amendment 1.*
- *Biomarker sampling removed by amendment 6.*
- Study drug IV infusion.

Cycle 2 and higher, Day 22 removed by amendment 5

7.1.2.3 Tumor assessments

Section modified by amendment 1, 4, 5 and 6.

After amendment 6 is effective, tumor assessments and their frequency as well as laboratory/clinical tests for WM patients will follow the institution's standard of care.

Bone marrow biopsy may be performed at the investigator discretion if there is clinical suspicion of bone marrow infiltration. Biopsy will be performed as per local standard of care.

Physical examination for lymphadenopathy, abdominal masses or organomegaly, and collection of B symptoms removed by amendment 1.

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:

- *QoL questionnaire removed by amendment 5.*
- 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) (*added by amendment 3*).
- 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, NYHA classification, weight, vital signs (temperature, pulse and blood pressure), and complete review of body systems (*changed by amendment 1*) (see Section 7.5.3.2).
- 12-lead ECG including QTcB and QTcF evaluation if not previously done within 4 weeks (see Section 7.5.3.4).
- MUGA scan or echocardiogram to measure LVEF if not previously done within 4 weeks (*clarified by amendment 1*). The method chosen at Screening must be the same throughout the whole study (see Section 7.5.3.5).
- Blood tests for HbA1c, CBC, chemistry and coagulation panels (see Section 7.5.3.1). Patients must be fasting prior to sampling according to local standards. If a patient can't 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 (*bullet point modified by amendment 3*).
- Urinalysis (dipstick). Microscopy as clinically indicated (see Section 7.5.3.1).

- Review of the blood glucose measurements/meal timing/oral glucose lowering medication/insulin administration, if applicable (*modified by amendment 1, 3 and 6*) (see Section 6.4.2.1).
- *CT/MRI removed by amendment 6.*
- *Tumor biopsy removed by amendment 6.*
- *Biomarker sampling removed by amendment 6.*
- *Laboratory/clinical tests for LPL/WM patients removed by amendment 6.*

7.1.2.5 Follow-up periods

Section removed by amendment 6.

7.1.2.5.1 Safety follow-up

Section modified by amendment 4 and 5.

If a patient discontinues study treatment at any time during the study for any reason (except death or lost to follow-up) SFU visit will take place 30 days (window of +5 days allowed) after the last administration of study drug. This visit includes:

- *QoL questionnaire removed by amendment 5.*
- 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).
- CBC (see Section 7.5.3.1).
- Chemistry and coagulation panels (see Section 7.5.3.1).

If a patient has begun treatment with another anticancer agent and is no longer being seen in the clinic, the post-treatment safety assessment can be conducted via telephone.

7.1.2.5.2 Active follow-up

Section modified by amendment 6.

As the study design is modified, patients will be followed for safety only. All patients who have already completed the safety follow-up visit at the time the amendment 6 becomes effective will discontinue the study.

7.1.2.5.3 Survival follow-up

Section modified by amendment 1, 5 and 6.

As the study design is modified, patients will be followed for safety only. All patients who have already completed the safety follow-up visit at the time the amendment 6 becomes effective will discontinue the study.

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 (where legally allowed)
- 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
- Considered relevant to the study

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

Disease history of the study indication will be recorded:

- Most recent histology of tumor
- Most recent staging and grading of tumor
- FLIPI score for patients affected by FL (FLIPI: Follicular Lymphoma International Prognostic Index [25])
- History of anticancer treatments (including type of treatment, type of response, date and duration of response and date of subsequent relapse) (*modified by amendment 1*)
- Assessment of baseline toxicity: any unresolved toxicity > CTCAE Grade 1 attributed to any prior therapy/procedure, not due to the underlying disease, excluding alopecia and ≤ CTCAE Grade 2 peripheral neuropathy

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

As study primary endpoint was changed to safety by amendment 6, primary efficacy variable was removed.

7.3.2 Radiological tumor assessments

Section changed by amendment 1, 3, 5 and 6.

After amendment 6 is effective, tumor assessments and their frequency as well as laboratory/clinical tests for WM patients will follow the institution's standard of care.

Radiological tumor assessments with IV (and oral, if indicated) contrast-enhanced CT/MRI will include neck, chest, abdomen and pelvis, and will be evaluated locally at the study site.

The first radiological (IV [and oral, if indicated] contrast-enhanced CT/MRI) tumor assessment will be performed at Screening (including WM patients). Corticosteroids must be stopped or reduced to the allowed dose (less than 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 the 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, radiological (IV [and oral, if indicated] contrast-enhanced CT/MRI) tumor assessment will be performed, per local standard of care of the institution (see Section 7.1.2.3).

For patients switching from placebo to copanlisib therapy after unblinding procedures completed CT/MRI scans are not required if the patient had radiological tumor evaluation performed and documented in eCRF within 4 weeks preceding the start date of copanlisib treatment.

If the patients on placebo treatment had symptoms/signs of clinical progressive disease prior to switching to copanlisib treatment, it is recommended to have radiological tumor assessments before starting copanlisib therapy unless CT/MRI scans performed within 4 weeks prior to a scheduled date of the first copanlisib infusion. For patients who previously

received placebo and will be treated with copanlisib the tumor assessments should be continued as the initial schedule.

The response assessment will be done according to the Lugano Classification (21). For patients with WM, additional criteria apply (see Section 7.3.3).

Detailed instructions on tumor assessment are provided in Appendix 14.1.

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 IV (and oral, if indicated) contrast-enhanced CT is medically contraindicated, sites may acquire contrast-enhanced MRI of the neck, abdomen and pelvis, and an unenhanced CT of the chest above lung apices to the bottom of the adrenals. Chest CT is preferred. Only if a patient develops contra-indication to both CT and MRI contrast medium during the treatment phase of the study, the case examinations should be continued without contrast. In certain countries MRI should be used based on local regulations.

7.3.3 Tumor assessments in patients with WM

Section added by amendment 3 and modified by amendment 5 and 6.

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. However, in cases when WM patients will develop extramedullary disease without simultaneous increase in IgM the radiological assessment should be performed to confirm disease progression (per investigator's assessment).

WM patients who have radiologically measurable lesion at Screening will continue having radiological assessments and, in addition, will have laboratory tests performed at intervals that comply with the institution's standard of care (see Section 7.1.2.3).

Detailed instructions on tumor assessment are provided in Appendix 14.1.

7.4 Pharmacokinetics / pharmacodynamics

Section modified by amendment 1, 3, 5 and 6.

No further PK samples will be collected. However, blood samples already collected may be used for the PK analysis.

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 subject 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).

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 h.
   - 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 v. 4.03. For events not listed in the NCI CTCAE, 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 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 patient's 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 in 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

Section modified by amendment 3, 4 and 6.

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

The 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 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 study 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.

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 study drug.

If any patient dies during the observation phase for AEs, the investigator will inform the sponsor and record the cause of death in detail within 24 h on an SAE form. "Death" should generally not be recorded as an AE on the AE page. Instead, "death" should be recorded as the outcome of underlying AE(s). If death is reported without any associated AE (s), it should be reported as SAE.

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 serious adverse events (SAEs) is given in Section 7.5.1.1. Each SAE must be followed up until resolution or stabilization by submission of updated reports to the designated recipient.

Investigator's notification of the sponsor

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

All SAEs occurring during the observation period defined in Section 7.5.1.3 must immediately (within 24 h of the investigator's awareness) be reported to the recipient detailed

in the manual. An SAE form must also be completed within 24 h of the investigator awareness and forwarded 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 clearly mentioned on the SAE form as an "alternative explanation"** (*clarified by amendment 3*).

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

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

For documentation of laboratory findings as SAE, please refer to Section 7.5.3.1.

Notification of the Independent Ethics Committee / Institutional Review Board

Notification of the Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) about all relevant events (e.g. SAEs, suspected, unexpected, serious adverse reactions (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.

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:

- NIP.

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.

Bayer usually does not gather information of drug exposure via the father, however, if those 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

Text was removed by amendment 5.

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. Dipsticks should be available for urinalysis (*modified by amendment 1 and 3*).

- Complete blood count (CBC): hemoglobin, hematocrit, red blood cell count (RBC), and white blood cell count (WBC) with differential to include absolute neutrophil, lymphocyte, monocyte, basophil and eosinophil counts, and platelet count. Differential blood count in percentage can be provided when absolute count is not available per SOC of the local lab (*modified by amendment 4*).
- Complete chemistry panel: calcium, sodium, potassium, chloride, phosphorus, magnesium, bicarbonate (or carbon dioxide if bicarbonate is not routinely measured at the site), total protein, albumin, glucose, blood urea nitrogen (BUN) (or urea if BUN is not routinely measured at the site), serum creatinine (SCR), uric acid, total bilirubin, creatine phosphokinase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), lipase, amylase (or

pancreatic amylase if total amylase is not routinely measured at the site), cholesterol (total, low-density lipoprotein [LDL]) and triglycerides (*modified by amendment 1*).

- Coagulation panel: prothrombin time (PT), international normalized ratio (INR), and partial thromboplastin time (PTT).
- Urinalysis: blood cells, glucose, ketones, bilirubin, protein, and pH (dipstick). Additional microscopic examinations will be performed if clinically indicated (*modified by amendment 1*).
- Quantification of proteinuria by either a 24 h total urine protein quantification or by UPCR on a random urine sample preferably taken at 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 (*modified by amendment 3*).
- Measurement of GFR according to the MDRD abbreviated formula (see Appendix 14.5).
- 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).
- Hemoglobin A1c (*bullet point added by amendment 3*).
- CD4 (for patients with signs of infection), blood cultures when low ANC of CTCAE Grade 4, PCR for CMV (*bullet point added by amendment 4*).

  For patients with identified risk factors and those who developed opportunistic infections, additional laboratory assessments will include:

  - CD4, CD8 count and ratio, CRP, blood cultures.

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 (SAE definition in Section 7.5.1.1). All laboratory abnormalities, including CTCAE Grade 4 abnormalities, will be documented on 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 (*added by amendment 1*).

7.5.3.2.1 Complete physical examination

Complete physical examination includes ECOG performance status assessment (see grading definitions in Appendix 14.3), NYHA classification (see Appendix 14.4), height (only at Screening), weight, vital signs (see Section 7.5.3.3), and complete review of body systems (*changed by amendment 1*).

All clinical signs and regions that can be brought in context with the underlying disease, with the anticancer 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, acneiforme changes) including clinical assessment of hydration status via hand extensor surface skin turgor (*modified by amendment 3*)
- 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 (*modified by amendment 3*)
- Head and neck
- Lungs: evaluation of new onset or worsening of pulmonary symptoms, and lung examination (*modified by amendment 4*).
- Heart
- Abdomen (pain, tenderness, peristaltic, 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 (see Appendix 14.3), 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 (*modified by amendment 3*)
- Hand and feet (signs of hand-foot-skin-syndrome)
- Throat (presence of petechial bleeding, gingival bleeding) including inspection of oral mucosa for hydration status (*modified by amendment 3*)
- Lungs: evaluation of new onset or worsening of pulmonary symptoms, and lung examination (*modified by amendment 4*)
- 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 every 5-10 min prior to infusion of study drug (no more than 4 measurements) until there are 2 consecutive results < 150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. The patient should rest for 5-10 min before blood pressure is recorded (*modified by amendment 1*).

- On infusion days: blood pressure will be measured at 0 h (pre-dose), 30 min (mid-infusion), 60 min (end of infusion); and 1 h and 2 h after the end of infusion.
- Note: time window of ± 10 min is allowed for all blood pressure measurements except for 0 h (pre-dose) (*changed by amendment 3*)

For details on the management of arterial hypertension, see also Section 6.4.1 and Section 6.4.2.3.

7.5.3.4 12-lead ECG

12-lead ECGs will be performed according to the schedule summarized in the flowchart 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 10 min before the ECG is recorded (*modified by amendment 1*).

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: MUGA scan or echocardiogram. The method chosen at Screening (i.e. either MUGA scan or echocardiogram) must be used throughout the whole study (see flowchart in Table 7–1). Additional cardiac function tests are required if any signs or symptoms of cardiac dysfunction occur.

MUGA scan or echocardiogram scan should be performed for determination of LVEF.

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

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

7.5.3.6 Glucose measurement on infusion days

Section added by amendment 3 and modified by amendment 6.

- On Cycle 1 Day 1: glucose will be measured at pre-dose and post-dose after the end of study drug infusion (0), 1 h and 2 h. Additional measurements to be performed at the clinic as clinically indicated.
- On subsequent infusion days: glucose will be measured prior to study drug infusion and 1 h after the end of study drug infusion.
- On all 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

Section modified by amendment 1, 5 and 6.

No further biomarker samples will be collected. However tumor tissue, plasma and whole blood (if consented) samples collected may be used for the biomarker analysis.

7.6.2 Quality of life questionnaire

Section removed by amendment 5.

7.6.3 Electronic patient-reported outcomes evaluation

Section removed by amendment 5.

7.7 Appropriateness of procedures / measurements

Section modified by amendment 1 and 6.

The tumor 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 Lugano Classification (21) 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 agent 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

Section modified by amendment 1, 5 and 6.

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.

Due to the decision of stopping enrollment as protocol amendment 5 becomes effective, limited number of patients will be included in the analyses. Therefore, the statistical analyses included in this study will be focused on descriptive statistics on safety variables only.

Two sets of analyses will be performed at the primary analysis timing when all patients have completed the study treatment and Safety follow-up period (if applicable).

1) unblinding cutoff: analyze all data available before the unblinding (details in section 6.5);
2) final analysis: analyze all data available until all patients have completed the copanlisib study treatment and Safety follow-up period.

The data cutoffs and treatment groups included for each analysis are summarized in the following table.

Table 8–1 Analysis data cutoffs and treatment group overview

	Analysis cutoff on the date of unblinding	Final analysis cutoff[2]
Patients randomized to Copanlisib[1]	✓	✓
Placebo Patients: Period 1 (before their PD)	✓	Not shown
Placebo Patients: Period 2 (after PD period 2)	Not shown	✓
Placebo Patients: switching to Copanlisib per protocol amend 5	NA	✓

[1] All patients randomized/assigned into Copanlisib arm
[2] When all patients have completed the study treatment and Safety follow-up period.
Table modified by amendment 6.

8.2 Analysis sets

Section modified by amendment 5 and 6.

The statistical analysis sets are defined as follows:

- Safety analysis set (SAF): all patients with at least one intake of study drug. The SAF will be analyzed as treated.

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

The SAF will be used for the analyses of the safety variables.

8.3 Variables

8.3.1 Efficacy variables

Section modified by amendment 5 and 6.

Due to the limited number of patients enrolled in this study, the study efficacy objectives and analyses were removed and the efficacy variables, including but not limited to date of progression, time to progression, and best response will be listed descriptively.

8.3.1.1 Primary efficacy variable

Section removed by amendment 6.

8.3.1.2 Secondary efficacy variables

Section removed by amendment 6.

8.3.1.3 Other efficacy variables

Section removed by amendment 5.

8.3.2 Safety variables

Safety variables will include treatment-emergent AEs (TEAEs), 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 study drug. TEAE 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). For TEAE summaries based on placebo randomized patients switching to copanlisib (see Table 8–1), the baseline reference period will be defined in the SAP (*modified by amendment 4 and 6*).

8.4 Statistical and analytical plans

8.4.1 Population characteristics

Section modified by amendment 5.

Demographics and baseline characteristics will be summarized by treatment and total population, using descriptive statistics and frequency tables as appropriate.

8.4.2 Efficacy

Section modified by amendment 5 and 6.

Due to the limited number of patients enrolled in this study, the study efficacy objectives and analyses were removed and the efficacy variables, including but not limited to date of progression, time to progression, and best response will be listed descriptively.

8.4.2.1 Primary efficacy analysis

Section removed by amendment 5.

8.4.2.2 Secondary efficacy analysis

Section removed by amendment 5.

8.4.2.3 Confirmatory statistical testing strategy

Section removed by amendment 5.

8.4.2.4 Subgroup analyses

Section removed by amendment 5.

8.4.3 Safety

Section modified by amendments 1, 5 and 6.

Safety variables will be summarized by means of descriptive statistics and/or frequency tables as appropriate. Summaries will be given by treatment group and total. As clarified in section 8.1, safety data analyses will be provided based on two sets of data, unblinding cutoff and final data cutoff.

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 v. 4.03 category and worst grade.

In addition, results of physical examination, vital signs, and ECG will be summarized in accordance with SAP.

8.4.4 Pharmacokinetic data

Section modified by amendment 6.

Individual concentration-time data of copanlisib and M-1 may be provided in a clinical study report appendix. Sparse copanlisib concentration data from this study, which might be augmented with PK data from other studies, may be analyzed to evaluate the variability of the copanlisib PK in this Phase III population. The possible effect of relevant covariates on the PK of copanlisib might also be evaluated. A population pharmacokinetic approach will be applied for these evaluations, which will be described in detail in a separate Modeling & Simulation (M&S) Plan if the results will be reported separately in the M&S Report.

8.5 Planned interim analyses

No interim efficacy analyses are planned for this study.

8.6 Determination of sample size

Section modified by amendments 1, 5 and 6.

Determination of sample size has not been applicable since amendment 5 became effective.

9. Data handling and quality assurance

9.1 Data recording

Section modified by amendment 6.

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 in 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 in 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

Section modified by amendment 5.

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).

Clinical data will be entered into Rave by clinical site staff and will be transferred from Rave into SAS datasets. Data review will be performed by sponsor on an ongoing basis to ensure data is accurate, consistent and complete. Data for, external supplier sources will be checked by sponsor. Data corrections will be made under the supervision of clinical site staff.

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

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 must notify 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

Section modified by amendment 5 and 6.

The sponsor has the right to close this study (or, if applicable, individual segments thereof [e.g. centers, treatment arms; dose steps]) 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.

The sponsor’s decision was to stop enrollment due to lack of feasibility to complete this study in reasonable time frame. Therefore, the study design is modified. All patients on study treatment will be offered the possibility to continue treatment with copanlisib after unblinding procedures are completed.

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 Good Clinical Practice (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 IECs/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

Section modified by amendments 1, 3, 5 and 6.

All relevant information on the study will be summarized in an integrated patient information sheet and ICF provided by the sponsor or the study center. Genetic biomarker research of whole blood requires separate ‘genetic’ research consent (optional testing for research). A sample patient information and ICF is provided as a document separate to this protocol.

Based on this patient information sheet, the investigator or designee will explain all relevant aspects of the study to each patient 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 IEC/IRB 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.

As of amendment 5, all patients will be reconsented and need to voluntarily agree to sign the ICF and have to do so, to continue in 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. Documentation of the informed consent process should be recorded in the patient's medical record.

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

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

The ICF 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 ICF. 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 ICF. Any revised written ICF 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.

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 in the CRF, and if the patient name appears on any other document (e.g. pathologist report), it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, the patients will be informed in writing that representatives of the sponsor, IEC/IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

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

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

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26. *Removed by amendment 5*

27. *Removed by amendment 5*

28. *Removed by amendment 5*

29. *Removed by amendment 5*

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38. *Removed by amendment 6*.

13. Protocol amendments

13.1 Amendment 1

Amendment 1 is a global amendment dated 25 NOV 2014.

13.1.1 Overview of changes

13.1.1.1 Modification 1 – administrative changes

The trial name "CHRONOS-2" was added.

The sponsor's medically responsible person (GCL) was changed.

The contact details of Coordinating Investigator were added.

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

13.1.1.2 Modification 2 – introductory information updated

Introductory information on study 16349 (part A) was updated based on most recent data.

Wording regarding population PK analysis was updated accordingly.

Approval of idelalisib was referenced.

Sections affected by this modification: 1.1 Background, 1.1.2 Clinical experience, 1.3 Benefit-risk assessment and 12 Reference list.

13.1.1.3 Modification 3 – tumor response criteria updated

Criteria for assessing tumor response were updated following the most recent publication by Cheson et al. (21). Assessment of response and disease progression will be done according to the Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: 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 14.1). 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).

The change to the Lugano Classification aligns the criteria for assessing tumor response with the most recent guidelines published by a panel of experts in this field. The addition of criteria for assessing WM patients according to the Response Assessment in Waldenström Macroglobulinemia will expand the eligible study population by allowing WM patients to be included on the basis of IgM levels alone if they do not have radiographically measurable disease.

Sections affected by this modification: Synopsis, Definitions of terms, 4 Study design, 5.1.1 Inclusion criteria, 5.2.1.1 Withdrawal from study treatment, 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, 7.1.2.2.2 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 14.1 Evaluation of tumor response.

13.1.1.4 Modification 4 – study eligibility criteria updated

Study eligibility criteria were modified to include also patients with symptomatic rituximab-refractory iNHL based on feedback from experts in the treatment of iNHL and sponsor's additional internal review. Rationale was to maximize the number of patients eligible for treatment in this placebo controlled study:

- The required number of prior lines of treatment was changed from "one or more" to "two or more" to be consistent with the new study population.
- Exclusion criteria related to disease symptoms and node size were removed because the patient population was aligned with the pivotal study 16349 (part B).
- Bulky disease was added as an exclusion criterion to allow placebo control.

After consultation with regulatory authorities, prior exposure to PI3K inhibitors was removed from exclusion criteria. Prior treatment with PI3K inhibitors will be allowed if the patient does not have documented evidence of resistance to idelalisib or other PI3K inhibitors. This change will allow patients who have previously received a PI3K inhibitor, but could not tolerate it, to receive active therapy. Consequently, prior treatment with PI3K inhibitor was added as a new stratification factor (see Section 13.1.1.8).

Exclusion criterion regarding interstitial lung disease was modified for clarity.

Inclusion criteria were clarified to include patients who have previously been exposed to either one or more than one alkylating agent.

Inclusion criteria related to laboratory values of serum beta-2-microglobulin and LDH were removed. Subsequently, serum beta-2-microglobulin measurement was changed to be performed only in patients with LPL/WM instead of total study population.

Inclusion criterion for SCR was removed as assessment of renal function for eligibility will be covered by GFR instead. Subsequently, GFR will also be used instead of creatinine as one of the dosing criteria on Day 1 of Cycle 2 and higher. It is considered that monitoring renal function by using GFR is more precise than creatinine.

Sections affected by this modification: Synopsis, 1.2 Rationale of the study, 2 Study objectives, 4 Study design, 5.1.1 Inclusion criteria, 5.1.2 Exclusion criteria, 6.4 Dosage and administration, 7.1.1 Tabulated overview, 7.1.2.1 Screening period and 7.1.2.2.2 Treatment – Cycle 2 and higher.

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

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). This was due to a change in the patient population to include both symptomatic and asymptomatic patients. Consequently, study objectives and fixed sequence test hierarchy were updated.

Censoring rules for time to deterioration in DRS-P were modified to be in alignment with PFS and time to improvement in DRS-P endpoints.

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 – PFS2 added as other efficacy variable

Secondary PFS (PFS2) was introduced as efficacy variable by the request from European Medicines Agency (EMA). PFS2 will be evaluated only in placebo-treated patients who switch to open-label copanlisib treatment.

Sections affected by this modification: Synopsis, 2 Study objectives, 8.3.1.3 Other efficacy variables and 8.4.2 Efficacy.

13.1.1.7 Modification 7 – 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 to be screened and randomized were re-calculated, with patients divided into FL and other iNHL groups.

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, 2 Study objectives, 4 Study design, 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 testing strategy, 8.4.3 Safety, 8.6 Determination of sample size and 12 Reference list.

13.1.1.8 Modification 8 – randomization ratio and stratification changed

Randomization ratio in the double-blinded treatment arms, copanlisib monotherapy or placebo, was changed from 1:1 to 2:1, respectively. The reason for the change was to allow more patients to be on active treatment from onset of the study.

The number of stratification factors changed from two to three as prior treatment with PI3K inhibitors was added as a new factor. This change was done in order have the possibility to determine if prior treatment with another agent in the same drug class affects response to copanlisib.

Sections affected by this modification: Synopsis, 1.2 Rationale of the study, 4 Study design, 6.3 Treatment assignment and 8.4.2.1 Primary efficacy analysis.

13.1.1.9 Modification 9 – language on switch to open-label treatment modified

Additional language on laboratory measurements that are required to be completed within 7 days prior to the first dose of open-label copanlisib was added and reference to laboratory test criteria in Table 6–2 was added. A patient who switches and starts open-label treatment with copanlisib must have certain laboratory evaluations to ensure that the patient has adequate bone marrow, renal and liver function to receive study drug.

Text was modified to specify that patients who switch to open-label treatment will be treated until further disease progression or they meet other criterion for withdrawal from the treatment. It was also clarified that further progression needs to be assessed centrally.

Sections affected by this modification: 4 Study design, 6.4 Dosage and administration, 7.1.1 Tabulated overview, 7.1.2.2 Treatment period and 7.5.3 Further safety.

13.1.1.10 Modification 10 – language on informed consent, re-screening and re-testing revised

Language related to informed consent was modified. 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 provided that they fall into the protocol-specified time window.

In addition, changes were made to the language regarding re-screening and re-testing to clarify the parameters and guidelines for this study.

Sections affected by this modification: 5.1.1 Inclusion criteria, 5.2.1 Withdrawal, 7.1.1 Tabulated overview, 7.1.2.1 Screening period and 11.2 Patient information and consent.

13.1.1.11 Modification 11 – withdrawal criteria updated

The reason for withdrawal “AEs due to disease-related complications” was removed because AEs due to disease complications need to be considered individually in the context of the patient’s overall condition and the risk vs. benefit of continuing therapy. This decision should be at the discretion of the investigator and not dictated by the protocol.

Explanation was added that required 1 week break is not included in the calculation of delay time of study drug.

Sections affected by this modification: 5.2.1.1 Withdrawal from study treatment.

13.1.1.12 Modification 12 – language on study drug reconstitution modified

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

Statement on cytotoxicity of copanlisib was removed. Based on mechanism of action of copanlisib, it is not considered as cytotoxic agent.

Sections affected by this modification: 6.1 Treatments to be administered, 6.2 Identity of study treatment and 6.4 Dosage and administration.

13.1.1.13 Modification 13 – 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. 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 as safe and beneficial to shorten the time-interval of both fasting requirements and blood glucose assessments.

Language on monitoring blood glucose at home was modified. Guidance for glucose monitoring for non-diabetic patients on Cycle 1 Day 1 was changed: not all non-diabetic patients will be required to monitor their blood glucose at home, but only those who develop hyperglycemia > 250 mg/dL or require insulin administration.

Modifications were made to specify management of short-term and long-term effects on glucose homeostasis.

In addition, language on home glucose monitoring supplies (diary etc.) was added.

Sections affected by this modification: 5.2.1.1 Withdrawal from study treatment, 6.4 Dosage and administration, 6.4.2.1 Management of hyperglycemia that can occur with study treatment, 7.1.1 Tabulated overview 7.1.2 Timing of assessments, 7.1.2.1 Screening period, 7.1.2.2.1 Treatment – Cycle 1 7.1.2.2.2 Treatment – Cycle 2 and higher.

13.1.1.14 Modification 14 – dose modification rules revised

Dose modification guidelines were modified in order to eliminate ambiguity.

A note was added to Table 6–4 (dose modification of study treatment for hematological toxicity) to clarify that this table should not be used to determine patient eligibility for infusion on days 1, 8 and 15. The modification was done to ensure that the patient has adequate bone marrow function prior to receiving study drug infusion, as the recommendations for infusion days are more conservative.

Footnote indicating that the dose decrease by one dose level is not applicable to 45 mg dose level was removed from Table 6–5 and Table 6–6 (Dose modification of study treatment for non-hematological and dermatologic toxicity) as there is no safety concern in allowing dose of patients with these toxicities to be reduced to 30 mg dose level and determine if they can tolerate this dose before mandating that they will be taken off the trial.

Error in Table 6–5 was corrected: Grade 0 was replaced with Grade 1.

Sections affected by this modification: 6.4.1 Dose modification, 6.4.1.1 Hematological toxicity, 6.4.1.2 and Non-hematological toxicity.

13.1.1.15 Modification 15 – information on preservation of blinding removed

Detailed information about the measures to preserve the blinding was removed because it will be described in the Pharmacy Manual. Furthermore, as both copanlisib and placebo solutions are transparent, it was clarified that placebo is colorless.

Section affected by this modification: 6.5 Blinding.

13.1.1.16 Modification 16 – prohibited concomitant modification modified

Modification was added to allow the use short term systemic corticosteroids for the management of acute conditions (e.g. allergic reaction to either study drug or something else or an asthma exacerbation), without need to permanently discontinue the study.

Sections affected by this modification: 6.9.1 Prohibited concomitant therapy.

13.1.1.17 Modification 17 – laboratory evaluations revised

High-density lipoprotein (HDL) measurement was removed from the complete chemistry panel. Only total cholesterol and LDL cholesterol will be checked following recommendations of Busaidy et al. (23).

Reference to turbidity was removed from urinalysis for easier site compliance. Clarification was also made that dipsticks should be available for urinalysis.

The unit for urine creatinine concentration was corrected to be mg/dl.

Sections affected by this modification: 7.1.1 Tabulated overview and 7.5.3.1 Laboratory.

13.1.1.18 Modification 18 – timing of MUGA/echocardiogram and ECG measurements changed

The timing of MUGA scan/echocardiogram and 12-lead ECG measurement at Screening was changed from “less than 14 days before start of the study treatment” to “less than 28 days before start of the treatment”. This modification was done because there is no safety concern with checking cardiac function/ECG up to 4 weeks prior to first dose of study drug as this is unlikely to change within the new time frame.

ECG measurement on Day 15 of every 3rd cycle (associated with PK sampling) was removed (see also Section 13.1.1.22).

Clarification was added that the time window for both pre-dose and end-of-infusion ECG measurements is 2 h.

Clarification was also added that MUGA scan/echocardiogram does not need to be performed at the EOT visit if already done within 4 weeks.

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 Treatment – Cycle 2 and higher and 7.1.2.4 End-of-treatment visit.

13.1.1.19 Modification 19 – clarification of blood pressure and ECG measurements

The required position for the patient before blood pressure and ECG measurement was changed from “lying down” to “rest” as this is more common in clinical practice and as data on position will not be needed for data evaluation.

Time window of 5 min was also added to blood pressure measurements performed from Cycle 1 Day 8 onwards for consistency.

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.

13.1.1.20 Modification 20 – survival sweep language added

Language was added to allow additional contact with the patient before their next scheduled telephone call or visit if the most recent data on survival is needed at specific time point during follow-up periods.

Sections affected by this modification: Synopsis, 4 Study design, 5.2.1.2 Withdrawal from follow-up period, 7.1.1 Tabulated overview, 7.1.2.5 Follow-up periods and 7.1.2.5.3 Survival follow-up.

13.1.1.21 Modification 21 – additional language on radiological tumor assessments introduced

Oral contrast agent for radiological tumor assessment was added to IV contrast to be consistent with the Imaging Manual.

Clarification was added that patient may stay on treatment at the investigator’s discretion until progression is confirmed on the subsequent tumor assessment.

Additional language regarding response assessment of WM patients was introduced for clarification.

Explanation was added that in certain countries MRI should be used based on local regulations.

Guidance related to scans obtained for Screening, treatment period and Active follow-up was added to the protocol: the scans should be forwarded to the designated Imaging Core Laboratory for central review.

The word “screening” was added in front of CT/MRI throughout the protocol for consistency: corticosteroids must be stopped or reduced to the allowed dose at least 7 days before performing the screening CT/MRI.

Inconsistencies regarding the timing and time windows of tumor assessments were addressed.

Deviation of ± 2 days was allowed related to additional procedures that should be performed on the days of tumor assessments for flexibility (sites and imaging centers may be on different locations).

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 and 7.3.2 Radiological tumor assessments.

13.1.1.22 Modification 22 – collection of PK samples revised

PK sampling time points associated with 12-lead ECGs (Cycle 1 Day 1 and on Day 15 of every 3rd cycle) were removed to reduce the burden on the patients and the sites, and to reduce the overall number of samples to be shipped and processed.

Flexibility was added to the PK sampling time on Cycle 1 Day 8.

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 and 7.4 Pharmacokinetics / pharmacodynamics.

13.1.1.23 Modification 23 – collection of tumor tissue/biomarker specimens 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 both pathology and biomarkers. Timing of plasma collection for tumor genetics and non-genetic biomarker analysis was changed to be performed only at cycles 1, 2 (non-genetic sample only), and end-of-treatment visit, i.e. sampling at Day 1 of subsequent cycles was removed. 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.

“Genetic biomarker analysis” was changed to “tumor genetics” throughout the protocol to clarify that separate consent for genetic research is not required to collect these samples.

The collection of material for tumor genetics and non-genetic biomarker analyses was changed from “blood” to “plasma” to clearly distinguish it from the whole blood sample for which genetic consent would be required.

Sections affected by this modification: 4 Study design, 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 and 7.6.1 Biomarker investigations.

13.1.1.24 Modification 24 – responsible person completing the PRO information sheet changed

Responsible person for completing the PRO information sheet (study nurse/investigator) was replaced with study personnel to allow flexibility. This information was also added to flowchart footnote and visit descriptions for clarity.

Language was slightly modified to clarify that patients will complete the QoL questionnaire.

Furthermore, it was clarified that QoL questionnaire does not need to be completed at the SFU evaluation if the post-treatment safety assessment is conducted via telephone.

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, 7.1.2.4 End-of-treatment visit, 7.1.2.5.1 Safety follow-up and 7.6.2 Quality of life questionnaire.

13.1.1.25 Modification 25 – sub-group analysis

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.

Sections affected by this modification: 8.4.2.4 Subgroup analyses.

13.1.1.26 Modification 26 – link to GFR calculator added

Link to specific GFR calculator was provided. The calculator uses MDRD study equation which allows calculation of GFR using either one of two formulas, according to the two different methods of serum creatinine assessment (standardized or non-standardized) used at the site. The change was done because the MDRD formula provided in Appendix 14.5 is based on creatinine values determined by a non-standardized (old method) creatinine assay while currently many labs have changed to a standardized creatinine assay (called Isotope Dilution Mass Spectrometry –IDMS-traceable, which is a more accurate assessment).

Sections affected by this modification: 14.5 Glomerular filtration rate.

13.1.1.27 Modification 27 – other clarifications and corrections

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

- Language on indolent NHL was modified: iNHL was changed to indolent B-cell NHL in exclusion and withdrawal criteria.
- The reference to ISO (International Organization for Standardization) code was removed.

- Carbamazepine was removed from the list of permitted concomitant therapy (narrow therapeutic index medications) because this drug is already listed in the prohibited concomitant therapy.
- IVRS/IWRS transaction was added to Table 7–1 to be performed at Screening as it was erroneously missing from the table.
- Clarification was made that documentation of the first new anticancer treatment also includes documentation of response during survival follow-up.
- In addition to date of response, also duration of response was added to be collected in disease history of the study indication.
- Clarification was added that bone marrow biopsy will be performed as per local standard of care.
- Editorial changes and minor clarifications/corrections were done.

CSP sections affected by this modification: Synopsis, 1.2 Rationale of the study, 4 Study design, 5.1.2 Exclusion criteria, 5.2.1.1 Withdrawal from study treatment, 5.3 Patient identification, 6.9.2 Permitted concomitant therapy, 7.1.1 Tabulated overview, 7.1.2.1 Screening period, 7.1.2.5.3 Survival follow-up and 7.1.2.3 Tumor assessments.

13.1.2 Changes to the protocol text

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. 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 typing errors or omissions are not highlighted in this amendment.

13.1.2.1 Title page

Old text:

A randomized, double-blind Phase III study of copanlisib versus placebo in patients with rituximab-refractory indolent non-Hodgkin's lymphoma (iNHL)

New text:

A randomized, double-blind Phase III study of copanlisib versus placebo in patients with rituximab-refractory indolent non-Hodgkin's lymphoma (iNHL) – CHRONOS-2

13.1.2.2 Signature of the sponsor's medically responsible person

Old text:

Name: PPD MD Role: PPD (PPD)

New text:

Name: PPD MD Role: PPD (PPD)

13.1.2.3 Synopsis

Old text:

Title	**A randomized, double-blind Phase III study of copanlisib versus placebo in patients with rituximab-refractory indolent non-Hodgkin's lymphoma (iNHL)** [...]
Study objectives	The primary objective of this study is: • To investigate whether copanlisib as monotherapy is superior to placebo in prolonging progression free survival (PFS) in patients with ~~asymptomatic~~ rituximab-refractory iNHL who have received ~~one~~ or more prior lines of treatment, have been exposed to rituximab and alkylating agents, and have progressed within six months of the end of the last previous rituximab-containing regimen. The secondary objectives of this study are to evaluate: • Efficacy. • ~~Time to deterioration in~~ disease-related symptoms. • Safety. The other objectives of this study are to evaluate: • Pharmacokinetics. [...]
Duration of treatment	Treatment will be continued until disease progression (PD) (per central independent blinded radiology review) as defined in the ~~Revised Response Criteria for Malignant Lymphoma~~, unacceptable toxicity, or until another criterion is met for withdrawal from the study treatment. [...]
Indication	~~Asymptomatic r~~ituximab-refractory iNHL.

Diagnosis and main criteria for inclusion	[...] Patients must have received ~~one~~ or more prior lines of treatment. A previous regimen is defined as one of the following: at least two months of single-agent therapy, at least two consecutive cycles of polychemotherapy, autologous transplant, radioimmunotherapy. Prior therapy must include rituximab and alkylating agent~~s~~. Patients must be refractory to the last rituximab-based treatment (no response or response lasting < 6 months). Patients must have at least one bi-dimensionally measurable lesion (which has not been previously irradiated) according to the ~~r~~ecommendations ~~of the Revised Response Criteria for Malignant Lymphoma.~~ ~~In addition to the above measurable lesion criterion, p~~atients affected by ~~LPL/~~WM must have ~~also~~ measurable disease, defined as presence of immunoglobulin M (IgM) paraprotein with a minimum IgM level ≥ 2 x upper limit of normal (ULN) ~~or over 10% of lymphoplasmacytic cells in the bone marrow~~. [...]
Main criteria for exclusion	[...] Transformed disease (assessed by investigator): • histological confirmation of transformation, or • clinical and laboratory signs: rapid disease progression, high ~~SUV~~ (> 12) by positron emission tomography (PET) at baseline if PET scans are performed (optional). ~~Presence of B-symptoms (fever above 38°C, night sweats, or weight loss of more than 10% in the previous 6 months).~~ Lymph nodes or tumor mass (except spleen) ~~>~~ ≥ 7 cm. ~~Nodes > 3 cm in 3 distinct areas.~~ ~~Symptoms related to organ compression, pleural effusion, ascites, spleen enlargement, and renal, liver or bone involvement.~~ [...] History or concurrent condition of interstitial lung disease and/or severely impaired lung function [...] ~~P~~rior treatment with PI3K inhibitors.
Study design	A randomized, double-blind, two-arm Phase III study to evaluate the efficacy and safety of copanlisib as monotherapy in comparison to placebo in patients with ~~asymptomatic~~ rituximab-refractory iNHL. Approximately ~~120~~ patients who meet the eligibility criteria will be randomly assigned in a ~~1:1~~ ratio to one of the double-blinded treatment arms: copanlisib monotherapy or placebo. Patients will be stratified at randomization based on NHL histology

	(FL histology vs. other histology) ~~and~~ the time between last course of systemic anticancer therapy and most recent progression (≤ 6 months vs. > 6 months). [...]
Methodology	[...] Secondary efficacy variables are objective tumor response rate (ORR), duration of response (DOR), complete response rate (CRR), time to progression (TTP), overall survival (OS) ~~and the~~ time to deterioration in disease-related symptoms - physical (DRS-P) of ≥ 3 points of lymphoma as measured by the FLymSI-18 questionnaire. 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 following periods: Screening, Treatment, Safety-follow-up, Active follow-up (if applicable) and Survival follow-up. Patients randomized to the copanlisib treatment arm will receive 60 mg copanlisib IV infusion on Days 1, 8 and 15 of each 28-day treatment cycle. Patients randomized to the placebo arm will receive placebo IV infusion on Days 1, 8 and 15 of each 28-day treatment cycle. Treatment will be continued until PD (per central independent blinded radiology review) ~~defined in the Revised Response Criteria for Malignant Lymphoma~~, unacceptable toxicity, or until another criterion is met for withdrawal from the study treatment. [...] All patients will be followed off-study for overall survival at 3-month intervals during the Survival follow-up period (up to 3 years after the last patient started study treatment), except for patients who object to follow-up data collection. Safety evaluations will be done at Screening, on the first day of study drug administration (Cycle 1 Day 1), at each clinic visit during the treatment, and at the SFU visit. The first radiological tumor assessments with IV contrast enhanced computed tomography/magnetic resonance imaging (CT/MRI) scans of neck, chest, abdomen and pelvis will be performed at Screening. Corticosteroids must be stopped or reduced to the allowed dose (less than 15 mg of prednisone or equivalent) at least 7 days before performing the CT/MRI (if a patient is on chronic corticosteroid therapy, corticosteroids should be de-escalated to the maximum allowed dose before the Screening). ~~Tumor scans done up to 28 days prior to first dose can be used as baseline evaluation~~. The method chosen at the baseline must be the same throughout the study. During the treatment period as well as during the Active follow-up period tumor assessments with the same modality will be performed every 12 weeks ~~(±7 days)~~ during Year 1, every 16 weeks ~~(±7 days)~~ during Year 2, and every 24 weeks ~~(±7 days)~~ during Year 3. 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. As long as the patient has not experienced

	PD, investigator's assessment is sufficient for case management. In the event of progression, radiological real-time confirmation by central independent blinded evaluation is required before a final decision to stop the treatment is made. The final evaluation of treatment response (best response: ORR and CRR) will be done by central blinded review retrospectively. [...]
Number of patients	Approximately ~~160~~ patients will be ~~enrolled~~ to this study. Approximately ~~120~~ patients who meet the eligibility criteria will be randomized – approximately ~~60~~ patients ~~per treatment arm~~. [...]
Plan for statistical analysis	Primary efficacy analysis: The primary efficacy variable is PFS as assessed by central review. It will be evaluated whether PFS in copanlisib group is higher compared to PFS in the placebo group. ~~All statistical tests will be one-sided, with a significance level of alpha = 0.01~~. The following null hypothesis will be tested: $H_{0, PFS}$: $S_{Copanlisib}(t) = S_{Placebo}(t)$ for all time points $t \geq 0$ The alternative hypothesis will be: $H_{1,PFS}$: $S_{Copanlisib}(t) > S_{Placebo}(t)$ for at least one time point $t \geq 0$, and $S_{Copanlisib}(t) \geq S_{Placebo}(t)$ for all time points $t \geq 0$, where $S_{Copanlisib}$ denotes the survival function of the copanlisib group and $S_{Placebo}$ denotes the survival function of the placebo group. 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 $H_{0, PFS}$ ~~sufficient close approximation of~~ the one-sided log-rank test to the normal distribution. If the z-value from the one-sided log-rank test (for the difference $S_{Copanlisib}$ - $S_{Placebo}$, stratified by the same factors as used for randomization) is larger than the critical quantile from the normal distribution (~~$z_{0.99} = 2.33$~~), the null hypothesis will be rejected in favor of the alternative hypothesis. Additional analyses of the primary efficacy variable: Kaplan-Meier estimates of median times to PFS (including 98% confidence interval) and Kaplan-Meier curves will be presented for each treatment group. The hazard ratio (including 98% confidence interval) will be derived from a Cox proportional hazards model ~~and~~ stratified by the same factors as used for ~~randomization~~. [...]

New text:

Title	**A randomized, double-blind Phase III study of copanlisib versus placebo in patients with rituximab-refractory indolent non-Hodgkin's lymphoma (iNHL) – CHRONOS-2** [...]
Study objectives	The primary objective of this study is: • To investigate whether copanlisib as monotherapy is superior to placebo in prolonging progression-free survival (PFS) in patients with rituximab-refractory iNHL who have received two or more prior lines of treatment, have been exposed to rituximab and alkylating agent(s), and have progressed within six months of the end of the last previous rituximab-containing regimen. The secondary objectives of this study are to evaluate: • Efficacy including tumor response, time to progression and overall survival. • The following characteristics of disease-related symptoms: time to deterioration and time to improvement. • Safety. The other objectives of this study are to evaluate: • PFS2 in placebo-treated patients who switched to open-label copanlisib treatment. • Pharmacokinetics. [...]
Duration of treatment	Treatment will be continued until disease progression (PD) (per central independent blinded radiology review) as defined in the Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification, unacceptable toxicity, or until another criterion is met for withdrawal from the study treatment. For patients with Waldenström macroglobulinemia (WM), response assessment will be done according to the Response Assessment in Waldenström macroglobulinemia: update from the VIth International Workshop. [...]
Indication	Rituximab-refractory iNHL.

Diagnosis and main criteria for inclusion	[...] Patients must have received two or more prior lines of treatment. A previous regimen is defined as one of the following: at least two months of single-agent therapy, at least two consecutive cycles of polychemotherapy, autologous transplant, radioimmunotherapy. Prior therapy must include rituximab and alkylating agent(s). Prior exposure to idelalisib or other PI3K inhibitors is acceptable provided that there is no resistance. Patients must be refractory to the last rituximab-based treatment (no response or response lasting < 6 months). Patients must have at least one bi-dimensionally measurable lesion (which 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. 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). [...]

Main criteria for exclusion	[...] Transformed disease (assessed by investigator): • histological confirmation of transformation, or • clinical and laboratory signs: rapid disease progression, high standardized uptake value (> 12) by positron emission tomography (PET) at baseline if PET scans are performed (optional). Bulky disease: • Lymph nodes or tumor mass (except spleen) ≥ 7 cm LDi (longest diameter). [...] History or concurrent condition of interstitial lung disease of any severity and/or severely impaired lung function [...] Documented evidence of resistance to a 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 (SD) within 6 months from the end of the therapy with a PI3K inhibitor. Patients who discontinued treatment due to other reason than disease progression, and did not exhibit any signs of PD, will be allowed to enroll in this study after discussion with the sponsor.
Study design	A randomized, double-blind, two-arm Phase III study to evaluate the efficacy and safety of copanlisib as monotherapy in comparison to placebo in patients with rituximab-refractory iNHL. Approximately 189 patients (144 FL and 45 other iNHL) who meet the eligibility criteria will be randomly assigned in a 2:1 ratio to one of the double-blinded treatment arms: copanlisib monotherapy or placebo, respectively. Patients will be stratified at randomization based on NHL histology (FL histology vs. other iNHL histology), the time between last course of systemic anticancer therapy and most recent progression (≤ 6 months vs. > 6 months) and prior treatment with PI3K inhibitors (yes vs. no). [...]
Methodology	[...] 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 deterioration and time to improvement in disease-related symptoms - physical (DRS-P) of at least 3 points of lymphoma as measured by the FLymSI-18 questionnaire.

	Other efficacy variables are PFS2, 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 the copanlisib treatment arm will receive 60 mg copanlisib IV infusion on Days 1, 8 and 15 of each 28-day treatment cycle. Patients randomized to the placebo arm will receive placebo IV infusion on Days 1, 8 and 15 of each 28-day treatment cycle. Treatment will be continued until PD (per central independent blinded radiology review), unacceptable toxicity, or until another criterion is met for withdrawal from the study treatment. [...] All patients will be followed off-study for overall survival at least at 3-month intervals during the Survival follow-up period (up to 3 years after the last patient started study treatment), except for patients who object to follow-up data collection. Safety evaluations will be done at Screening, on the first day of study drug administration (Cycle 1 Day 1), at each clinic visit during the treatment, and at the SFU 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 (less than 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 the baseline must be the same throughout the study. During the treatment period as well as during the Active follow-up period tumor assessments with the same modality will be performed every 12 weeks during Year 1, every 16 weeks during Year 2, and every 24 weeks during Year 3. 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. As long as the patient has not experienced PD, investigator's assessment is sufficient for case management. In the event of progression, radiological real-time confirmation by central independent blinded evaluation is required before a final decision to stop the treatment is made. The final evaluation of treatment response (best response: ORR and CRR) will be done by central blinded review retrospectively. [...]

Number of patients	Approximately 237 patients will be screened for enrollment to this study. Approximately 189 patients who meet the eligibility criteria will be randomized – the copanlisib monotherapy arm will consist of approximately 126 patients and placebo arm of approximately 63 patients. [...]
Plan for statistical analysis	Primary efficacy analysis: The primary efficacy variable is PFS as assessed by central review. It will be evaluated whether PFS in the copanlisib group is higher compared to PFS in the placebo group for the total study population and separately for the FL subgroup. All efficacy analyses will be performed when approximately 82 centrally evaluated PFS events are observed in the FL subgroup. The study-wise alpha of 1% will initially be split, according to the test strategy for this study: with 80% * 1% = 0.8% assigned to the one-sided PFS test in the FL subgroup, and 20% * 1% = 0.2% to the one-sided PFS test in the total study population. The following null hypothesis will be tested: $H_{0,\,PFS}$: $S_{Copanlisib}(t) = S_{Placebo}(t)$ for all time points $t \geq 0$ The alternative hypothesis will be: $H_{1,PFS}$: $S_{Copanlisib}(t) > S_{Placebo}(t)$ for at least one time point $t \geq 0$, and $S_{Copanlisib}(t) \geq S_{Placebo}(t)$ for all time points $t \geq 0$, where $S_{Copanlisib}$ denotes the survival function of the copanlisib group and $S_{Placebo}$ denotes the survival function of the placebo group in the total study population or the FL subgroup, respectively. The following decision rule to test the null hypothesis will be applied: According to the size of this study it is justified to assume that under $H_{0,\,PFS}$ the one-sided log-rank test is a sufficiently close approximation to the normal distribution. If the z-value from the one-sided log-rank test (for the difference $S_{Copanlisib}$ - $S_{Placebo}$, stratified by the same factors as used for randomization) is larger than the respective critical quantile from the normal distribution (for FL subgroup: $z_{0.992} = 2.409$, for the total study population: $z_{0.998} = 2.878$), the null hypothesis will be rejected in favor of the alternative hypothesis. Additional analyses of the primary efficacy variable: Kaplan-Meier estimates of median times to PFS (including 98% confidence interval) and Kaplan-Meier curves for the total study population and the FL subgroup will be presented for each treatment group. The hazard ratio (including 98% confidence interval) will be derived for the total study population and separately for the FL subgroup from a Cox proportional hazards models that are stratified by the same factors as used for the primary efficacy analysis. [...]

13.1.2.4 Definitions of terms

Old text:

~~Throughout this document, the terms "complete response" and "partial response" are used when referring to disease evaluation. Originating from the Response Evaluation Criteria in Solid Tumors, these terms are used synonymously to "complete remission" and "partial remission" for consistency, even when referring to the Revised Response Criteria for Malignant Lymphoma (1) which use the term "remission".~~

New text:

The tumor response assessment will be done according to the Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification (21), henceforth referred to as the Lugano classification.

For patients with WM, response assessment will be done according to the Response Assessment in Waldenström macroglobulinemia: update from the VIth International Workshop (22), henceforth referred to as the Owen criteria.

13.1.2.5 Section 1.1 Background

Old text:

The use of these agents is further constrained by the complex procedures for their administration. For these reasons, ^{90}Y-ibritumomab is used infrequently, and ^{131}I-tositumomab has been withdrawn from the market (~~15~~).

~~Therefore, t~~here is a continuing need for additional, active and safe drugs that can be used in the refractory setting.

New text:

The use of these agents is further constrained by the complex procedures for their administration. For these reasons, ^{90}Y-ibritumomab is used infrequently, and ^{131}I-tositumomab has been withdrawn from the market (14). Very recently, idelalisib (Zydelig) was approved for the treatment of patients with double-refractory FL after two prior lines of therapy (15).

There is a continuing need for additional, active and safe drugs that can be used in the refractory setting.

13.1.2.6 Section 1.1.2 Clinical experience

Old text:

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 MTD 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. ~~Preliminary~~ results of a 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.

In the ongoing study 16349 (part A), a total of 67 patients with various indolent and aggressive lymphomas were treated at a starting dose of 0.8 mg/kg. 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 iNHL, the following histologies were represented: FL (16 patients), CLL/SLL (14 patients), and MZL (3 patients). Median age was 68 years and ~~63~~% of the patients had ≥ 4 previous lines of treatment. At the cut-off date of ~~11~~ NOV 2013 the median duration of treatment was ~~3~~ cycles. The response rate (~~RR~~) was ~~40~~% in FL, ~~43~~% in CLL~~/SLL (~~100% in SLL~~)~~, and ~~66~~% in MZL.

As of 04 ~~SEP~~ 2013, the most frequent TEAEs, regardless of relationship to study drug, occurring in > 20% of the whole study population were hyperglycemia (~~59.7~~%), hypertension (~~58.2~~%), fatigue (~~40.3~~%), diarrhea (~~35.8~~%), nausea, ~~neutropenia (28.4% each),~~ anemia (~~22.4~~%), and oral mucositis (20.9%). The two most common study drug-related TEAEs were hyperglycemia (~~58.2~~%) and hypertension (~~53.7~~%). A total of ~~43~~ patients (~~13~~ with indolent, and ~~30~~ with aggressive lymphomas) discontinued the study treatment. Altogether ~~22~~% of patients stopped treatment because of AEs. No conspicuous cluster of AEs causing treatment discontinuation emerged. Overall 13 out of 67 patients received treatment with short-acting insulin.

New text:

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 MTD 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.

In the ongoing study 16349 (part A), a total of 67 patients with various indolent and aggressive lymphomas were treated at a starting dose of 0.8 mg/kg. 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 iNHL, 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. At the cut-off date of 04 NOV 2013 the median duration of treatment was 4 cycles in the indolent group. The objective response rate (ORR) was 47% in FL, 38% in CLL, 100% in SLL, and 67% in MZL.

As of 04 NOV 2013, the most frequent TEAEs, regardless of relationship to study drug, occurring in > 20% of the whole study population were hyperglycemia (62.7%), hypertension (61.2%), fatigue (44.8%), diarrhea (40.3%), nausea (34.3%), neutrophil count decreased (31.3%), anemia (26.9%), and oral mucositis (20.9%). The two most common study drug-related TEAEs were hyperglycemia (61.2%) and hypertension (58.2%). A total of 50 patients (19 with indolent, and 31 with aggressive lymphomas) discontinued the study treatment. Altogether 25.4% of patients stopped treatment because of AEs. No conspicuous cluster of AEs causing treatment discontinuation emerged. Overall 13 out of 67 patients received treatment with short-acting insulin.

13.1.2.7 Section 1.2 Rationale of the study

Old text:

The natural history of patients with progress~~ing~~ iNHL refractory to rituximab ~~and asymptomatic~~ as per protocol is not known. Copanlisib is a targeted agent that works by controlling the signaling pathway relevant for the survival and proliferation of iNHL cells. In addition to objective responses, copanlisib appears to induce in a number of patients tumor regressions that are below response level, but can nevertheless have a positive effect on the course of the disease. The evaluation of copanlisib's anticancer activity ~~requires~~ a clinical trial design that controls for the natural history of tumor growth ~~and~~ minimize investigator bias in assessing treatment outcomes.

Considering the pre-clinical profile of copanlisib and the clinical activity emerging from Phase I study 12871 and the ongoing Phase II study 16349, it is expected that copanlisib will improve progression free survival (PFS) in patients with ~~asymptomatic~~ rituximab-refractory iNHL who have received ~~one~~ or more prior lines of treatment.

New text:

The natural history of patients with progressive iNHL refractory to rituximab as per protocol is not known. Copanlisib is a targeted agent that works by controlling the signaling pathway relevant for the survival and proliferation of iNHL cells. In addition to objective responses, copanlisib appears to induce, in a number of patients, tumor regressions that are below response level, but can nevertheless have a positive effect on the course of the disease. The evaluation of copanlisib's anticancer activity via a clinical trial design that controls for the natural history of tumor growth minimizes investigator bias in assessing treatment outcomes.

In order to provide a scientifically rigorous answer about copanlisib single agent activity, the randomized study is the most appropriate approach. Because no standard of care is available for the selected patient population, placebo is an appropriate choice of control in this randomized study. To minimize risk, following parameters are included in this study design:

- 2:1 randomization.
- Exclusion of patients with bulky disease.
- Opportunity for patients in the control arm to switch to active treatment after progression will ensure that all patients with radiologically confirmed PD will be treated with copanlisib.

Considering the pre-clinical profile of copanlisib and the evidence of clinical activity emerging from Phase I study 12871 and the ongoing Phase II study 16349, it is expected that copanlisib will improve progression-free survival (PFS) in patients with rituximab-refractory iNHL who have received two or more prior lines of treatment.

13.1.2.8 Section 1.3 Benefit-risk assessment

Old text:

Copanlisib showed activity in patients with iNHL. In the Phase I study 12871 all 6 patients with FL responded (please see Section 1.1.2). In the Phase II study 16349 (part A), response rates in patients with iNHL of various histologies were: ~~40~~% in FL, ~~66~~% in MZL, and 100% in SLL. Responses included complete remissions. Patients with iNHL were heavily pretreated, with ~~88~~% having received ≥ 3, and 36% ≥ 5 lines of treatment prior to study start.

Hyperglycemia and hypertension, the most frequently observed and expected toxicities with copanlisib, have been manageable. ~~No Common Terminology Criteria for Adverse Events (CTCAE) Grade 4 events were observed so far and toxicities~~ will be carefully monitored during the course of the study with a detailed and tailored program of management. A Data Monitoring Committee (DMC) will be instituted to maximize the safety of the patients participating in the study.

New text:

Copanlisib has showed activity in patients with iNHL. In the Phase I study 12871 all 6 patients with FL responded (please see Section 1.1.2). In the Phase II study 16349 (part A),

response rates in patients with iNHL of various histologies were: 47% in FL, 67% in MZL, and 100% in SLL. Responses included complete remissions. Patients with iNHL were heavily pretreated, with 82% having received ≥ 3, and 36% ≥ 5 lines of treatment prior to study start.

Hyperglycemia and hypertension, the most frequently observed and expected toxicities with copanlisib, have been manageable. Toxicities will be carefully monitored during the course of the study with a detailed and tailored program of management. A Data Monitoring Committee (DMC) will be instituted to maximize the safety of the patients participating in the study.

13.1.2.9 Section 2 Study objectives

Old text:

The primary objective of this study is:

- To investigate whether copanlisib as monotherapy is superior to placebo in prolonging progression free survival (PFS) in patients with ~~asymptomatic~~ rituximab-refractory iNHL who have received ~~one~~ or more prior lines of treatment, have been exposed to rituximab and alkylating agents, and have progressed within six months of the end of the last previous rituximab-containing regimen.

The secondary objectives of this study are to evaluate:

- Efficacy.
- ~~Time to deterioration in~~ disease-related symptoms.
- Safety.

The other objectives of this study are to evaluate:

- Pharmacokinetics.
- Biomarkers.
- Quality of life.

New text:

The primary objective of this study is:

- To investigate whether copanlisib as monotherapy is superior to placebo in prolonging progression-free survival (PFS) in patients with rituximab-refractory iNHL who have received two or more prior lines of treatment, have been exposed to rituximab and alkylating agent(s), and have progressed within six months of the end of the last previous rituximab-containing regimen.

The secondary objectives of this study are to evaluate:

- Efficacy including tumor response, time to progression and overall survival.
- The following characteristics of disease-related symptoms: time to deterioration and time to improvement.

- Safety.

The other objectives of this study are to evaluate:

- PFS2 in placebo-treated patients who switched to open-label copanlisib treatment.
- Pharmacokinetics.
- Biomarkers.
- Quality of life.

13.1.2.10 Section 3 Investigator and other study personnel

Old text:

Coordinating Investigator~~:~~

~~The coordinating investigator will be selected among the participating investigators. The coordinating investigator is responsible for signing the clinical study report.~~

New text:

Coordinating Investigator

Name: Grzegorz S. Nowakowski, MD
Address: Division of Hematology
Mayo Clinic
200 First Street SW
Rochester, MN 55905, USA

13.1.2.11 Section 4 Study design

Old text:

Design overview

This is a randomized, double-blind, two-arm Phase III study to evaluate the efficacy and safety of copanlisib as monotherapy in comparison to placebo in patients with ~~asymptomatic~~ rituximab-refractory iNHL.

The patients have failed at least ~~one~~ previous line of therapy. Previous treatments must have included rituximab and alkylating agents; and the patients must have progressed within six months of the end of the last previous rituximab-containing regimen.

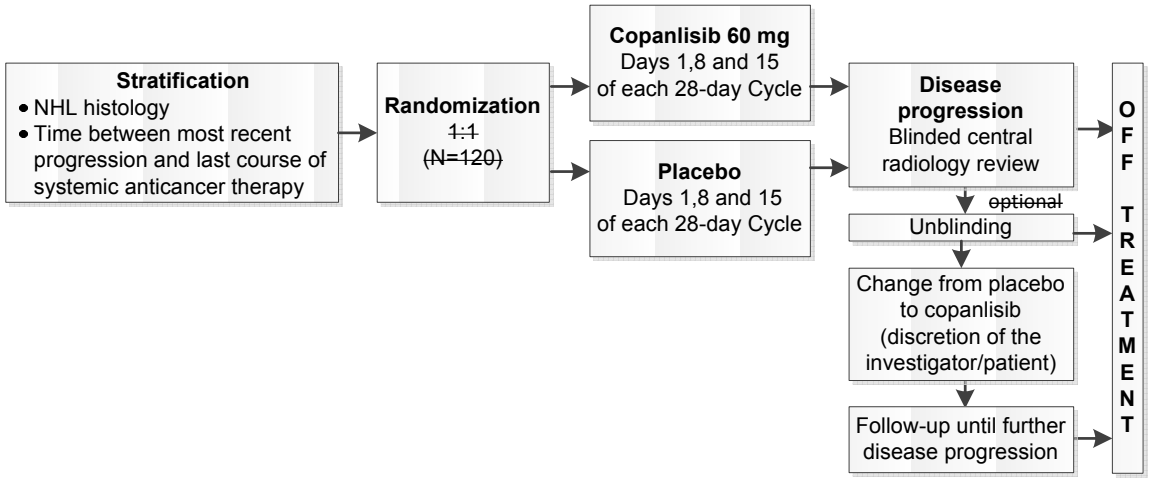
[...]

The start of the study period is defined by signing of the informed consent form (ICF). ~~A~~Approximately ~~160~~ patients will be ~~enrolled~~ to this study ~~and a~~approximately ~~120~~ patients who

meet the eligibility criteria (see Section 5.1) will be randomly assigned in a ~~1:1~~ ratio to one of the double-blinded treatment arms: copanlisib monotherapy or placebo. ~~Both arms~~ will consist of approximately ~~60~~ patients ~~who are fully evaluable for the primary endpoint~~. Patients will be stratified at randomization based on NHL histology (FL histology vs. other histology) ~~and~~ the time between last course of systemic anticancer therapy and most recent progression (≤ 6 months vs. > 6 months) (see Section 6.3).

[...]

Figure 4-2 Overall study design



NHL = Non-Hodgkin's lymphoma.

The start of the treatment period is defined by first administration of study drug (copanlisib or placebo). Copanlisib will be administered IV over 1 h at starting dose of 60 mg on Days 1, 8 and 15 of each 28-day treatment cycle. Patients in the placebo arm will receive a placebo IV infusion at the same schedule. Treatment will be continued until PD (per central independent blinded radiology review) as defined in the ~~Revised Response Criteria for Malignant Lymphoma (1)~~, unacceptable toxicity, or until another criterion is met for withdrawal from the study treatment (see Section 5.2).

Patients who experience PD on placebo treatment (per central independent blinded radiology review) can be offered open-label copanlisib upon discretion of the investigator and patient's consent. After individual patient unblinding, patients receiving placebo who switch to open-label copanlisib will have all study assessments and timing reset to the initial schedule of study evaluations (i.e. as if the patient was restarting the study at Cycle 1 Day 1). These patients will be ~~followed~~ until further disease progression.

[...]

All patients will be followed off-study for overall survival at 3-month intervals during the Survival follow-up period (up to 3 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".

[...]

The first radiological tumor assessment with IV contrast enhanced computed tomography/magnetic resonance imaging (CT/MRI) scans of neck, chest, abdomen and pelvis will be performed at Screening (see Section 7.3.2). Corticosteroids must be stopped or reduced to the allowed dose (less than 15 mg of prednisone or equivalent) at least 7 days before performing the CT/MRI (if a patient is on chronic corticosteroid therapy, corticosteroids should be de-escalated to the maximum allowed dose before the Screening). ~~Tumor scans done up to 28 days prior to first dose can be used as baseline evaluation.~~ The method chosen at the baseline must be the same throughout the study. During the treatment period as well as during the Active follow-up period tumor assessments with the same modality will be performed every 12 weeks ~~(±7 days)~~ during Year 1, every 16 weeks ~~(±7 days)~~ during Year 2, and every 24 weeks ~~(±7 days)~~ during Year 3. 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 ~~Revised Response Criteria for Malignant Lymphoma (1). F~~or patients with WM, ~~additional criteria apply.~~ Detailed instructions on tumor assessment are provided in Appendix 14.1.

[...]

Tumor tissue collection will be mandatory at Screening for central pathology review ~~and biomarker analysis. Fresh tumor tissue is preferred but archival tumor tissue will be requested if fresh tissue is not available (the latest biopsy available should be provided). Both may also be collected if available. Fresh tumor tissue will be collected between Day -28 and Day -8 prior to start of study treatment. Fresh tissue is recommended in patients with clinical suspicion of transformed disease~~.

Sparse blood samples for PK analysis will be collected from all patients to characterize the PK of copanlisib (see Section 7.4).

~~Blood~~ samples for biomarker analyses will be collected from all patients, according to the schedule specified in Section 7.6.1. Blood samples for exploratory genetic biomarker analysis will be collected ~~at Screening~~ from patients who provide “genetic research” consent (voluntary).

[...]

Primary 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). ~~E~~fficacy analyses will be performed when approximately ~~74~~ PFS events are observed in the ~~study~~.

Justification of the design

The pre-clinical profile of copanlisib and preliminary efficacy data from Phase I study 12871 and Phase II study 16349 suggest that copanlisib ~~could~~ improve PFS in patients with

rituximab-refractory iNHL who have received ~~one~~ or more prior lines of treatment~~,~~ have been exposed to rituximab and alkylating agents~~, and who are asymptomatic as per inclusion/exclusion criteria~~.

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

- ~~While causing tumor shrinkage in a proportion of patients with iNHL, the main benefit of copanlisib may reside in the prolonged control of tumor growth.~~
- The natural course of disease in patients with rituximab-refractory iNHL ~~and asymptomatic as per inclusion/exclusion criteria of this protocol~~ is not known.
- Use of placebo can minimize investigator bias in assessing treatment effects beyond tumor shrinkage. This is particularly important when assessing duration endpoints.
- 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 expected rarity of patients ~~with the requested profile~~.

~~Because of the slowly progressing nature of disease, the low symptom burden, and the opportunity to receive open-label copanlisib following PD on placebo, the patients assigned to the placebo arm will not be exposed to undue risk. The primary variable of the study, PFS, would not be influenced by this measure. The study design will be fully disclosed to patients.~~

New text:

Design overview

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

The patients have failed at least <u>two</u> previous line<u>s</u> of therapy. Previous treatments must have included rituximab and alkylating agent<u>(s)</u>; and the patients must have progressed within six months of the end of the last previous rituximab-containing regimen.

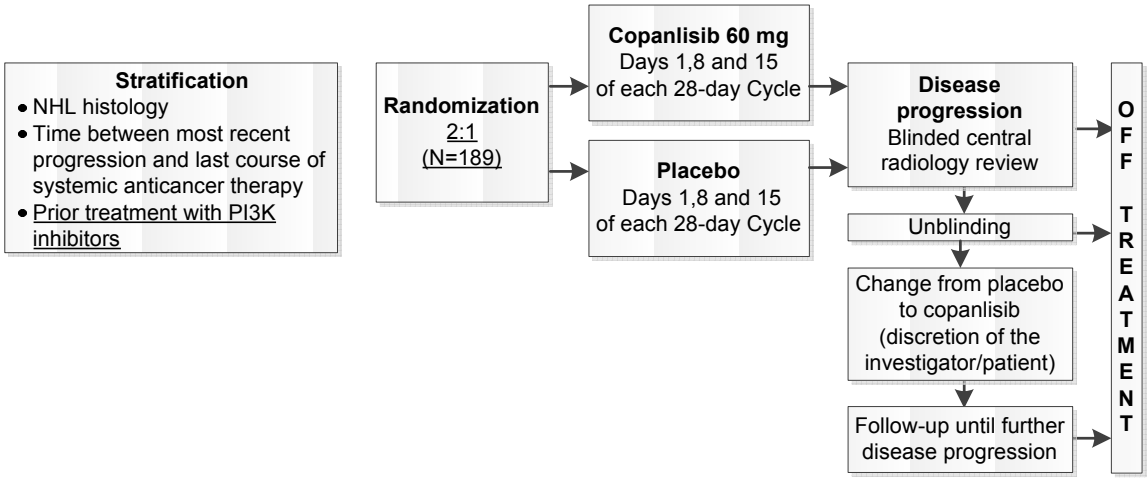
[...]

The start of the study period is defined by signing of the informed consent form (ICF). <u>Assuming a 20% screen failure rate, a</u>pproximately <u>237</u> patients will be <u>screened for enrollment</u> to this study. <u>A</u>pproximately <u>189</u> patients who meet the eligibility criteria (see Section 5.1) will be randomly assigned in a <u>2:1</u> ratio to one of the double-blinded treatment arms: copanlisib monotherapy or placebo. <u>The copanlisib monotherapy arm</u> will consist of approximately <u>126 patients and placebo arm of approximately 63</u> patients. Patients will be stratified at randomization based on NHL histology (FL histology vs. other <u>iNHL</u> histology)<u>,</u> the time between last course of systemic anticancer therapy and most recent progression (≤ 6 months vs. > 6 months) <u>and prior treatment with PI3K inhibitors (yes vs. no)</u> (see Section 6.3).

The study is planned to include approximately 144 patients with FL histology and 45 patients with other iNHL histologies.

[...]

Figure 4-2 Overall study design



NHL = Non-Hodgkin's lymphoma, PI3K = Phosphatidylinositol 3-kinase.

The start of the treatment period is defined by first administration of study drug (copanlisib or placebo). Copanlisib will be administered IV over 1 h at starting dose of 60 mg on Days 1, 8 and 15 of each 28-day treatment cycle. Patients in the placebo arm will receive a placebo IV infusion at the same schedule. Treatment will be continued until PD (per central independent blinded radiology review) as defined in the Lugano Classification (21), unacceptable toxicity, or until another criterion is met for withdrawal from the study treatment (see Section 5.2). For patients with WM, response assessment will be done according to the Owen criteria (22).

Patients who experience PD on placebo treatment (per central independent blinded radiology review) can be offered open-label copanlisib upon discretion of the investigator and patient's consent. After individual patient unblinding, patients receiving placebo who switch to open-label copanlisib will have all study assessments and timing reset to the initial schedule of study evaluations (i.e. as if the patient was restarting the study at Cycle 1 Day 1). These patients will be treated until further disease progression (per central review) unacceptable toxicity, or until another criterion is met for withdrawal from the study treatment (see Section 5.2).

[...]

All patients will be followed off-study for overall survival at least at 3-month intervals during the Survival follow-up period (up to 3 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".

[...]

The first radiological tumor assessment 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) (see Table 7-1 and Section 7.3.2). Corticosteroids must be stopped or reduced to the allowed dose (less than 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 the baseline must be the same throughout the study. During the treatment period as well as during the Active follow-up period tumor assessments with the same modality will be performed every 12 weeks during Year 1, every 16 weeks during Year 2, and every 24 weeks during Year 3. 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 (21), and for patients with WM, according to the Owen criteria (22). Detailed instructions on tumor assessment are provided in Appendix 14.1.

[...]

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).

Sparse blood samples for PK analysis will be collected from all patients to characterize the PK of copanlisib (see Section 7.4).

Plasma samples for biomarker analyses will be collected from all patients, according to the schedule specified in Section 7.6.1. Blood samples for exploratory genetic biomarker analysis will be collected on Cycle 1 Day 1 from patients who provide “genetic research” consent (voluntary).

[...]

Primary 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). All efficacy analyses will be performed when approximately 82 centrally evaluated PFS events are observed in the FL subgroup.

Justification of the design

The pre-clinical profile of copanlisib and preliminary efficacy data from Phase I study 12871 and Phase II study 16349 suggest that copanlisib may improve PFS in patients with rituximab-refractory iNHL who have received two or more prior lines of treatment and have been exposed to rituximab and alkylating agent(s). The purpose of this study is to demonstrate

efficacy and safety of treatment with copanlisib in patients where treatment is indicated, with a controlled randomized study with PFS as the primary endpoint.

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

- No standard of care is available for the defined patient population.
- Published data indicates multiple options of chemotherapy combinations or single agent therapy used in these patients based on data from, often small, single arm studies.
- No randomized study has confirmed efficacy or safety of these therapeutic options, including for those agents where regulatory approval was granted (bendamustine, idelalisib). Potential control agents have limited data on PFS.
- The natural course of disease in patients with rituximab-refractory iNHL is not known.
- Use of placebo can minimize investigator bias in assessing treatment effects beyond tumor shrinkage. This is particularly important when assessing duration endpoints.
- This study is designed to show significant improvement in PFS for study drug vs. control (132% improvement in median PFS).
- 2:1 randomization will assure that the majority of patients will be treated with copanlisib from onset.
- Exclusion of patients with bulky disease.
- Available opportunity for patients in the control arm to switch to active treatment after progression will ensure that all patients with radiologically confirmed PD will be treated with copanlisib. Additional exploratory efficacy endpoint is PFS2, which will assess PFS for patients on placebo arm who switched to receive therapy with copanlisib.
- 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 expected rarity of patients eligible for enrollment.

13.1.2.12 Section 5.1.1 Inclusion criteria

Old text:

1. Ability to understand and willingness to sign written informed consent. Signed informed consent must be obtained before any study specific procedure.

[...]

3. Patients must have received ~~one~~ or more prior lines of treatment. A previous regimen is defined as one of the following: at least two months of single-agent therapy, at least two consecutive cycles of polychemotherapy, autologous transplant, radioimmunotherapy.
4. Prior therapy must include rituximab and alkylating agents.

[...]

6. Patients must have at least one bi-dimensionally measurable lesion (which has not been previously irradiated) according to the ~~r~~recommendations ~~of the Revised Response Criteria for Malignant Lymphoma (1)~~.
7. ~~In addition to the above measurable lesion criterion, p~~patients affected by ~~LPL/~~WM must have ~~also~~ measurable disease, defined as presence of immunoglobulin M (IgM) paraprotein with a minimum IgM level ≥ 2 x upper limit of normal (ULN) ~~**or** over 10% of lymphoplasmacytic cells in the bone marrow~~.

[...]

13. Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements conducted within 7 days before start of study treatment:

[...]

- Amylase and lipase ≤ 1.5 x the ULN.
- ~~Serum creatinine (SCR) ≤ 1.5 x the ULN.~~
- Glomerular filtration rate (GFR) ≥ 30 ml/min/1.73 m^2 according to the Modification of Diet in Renal Disease (MDRD) abbreviated formula.

[...]

- Absolute neutrophil count (ANC) ≥ 1500/mm^3.
- ~~Serum lactate dehydrogenase (LDH) ≤ ULN.~~
- ~~Serum beta-2-microglobulin ≤ ULN.~~

New text:

1. Ability to understand and willingness to sign written informed consent. Signed informed consent must be obtained before any study specific procedure[1].
   [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 as noted in the protocol as well as results from CT/MRI scans, bone marrow sample,

MUGA/echocardiogram and hepatitis testing which may also be used provided that they fall into the protocol-specified time window. Archival tissue obtained from the patients at any time during the course of their iNHL may also be used prior to the informed consent date and time if performed as part of the standard of practice. CT/MRI must also meet the quality standards of the Imaging Manual.

[...]

3. Patients must have received two or more prior lines of treatment. A previous regimen is defined as one of the following: at least two months of single-agent therapy, at least two consecutive cycles of polychemotherapy, autologous transplant, radioimmunotherapy.
4. Prior therapy must include rituximab and alkylating agent(s). Prior exposure to idelalisib or other PI3K inhibitors is acceptable provided that there is no resistance.

[...]

6. Patients must have at least one bi-dimensionally measurable lesion (which 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 (21).
7. 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).

[...]

13. Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements conducted within 7 days before start of study treatment:

[...]

- Amylase and lipase ≤ 1.5 x the ULN.
- Glomerular filtration rate (GFR) ≥ 30 ml/min/1.73 m^2 according to the Modification of Diet in Renal Disease (MDRD) abbreviated formula.

[...]

- Absolute neutrophil count (ANC) ≥ 1500/mm^3.

13.1.2.13 Section 5.1.2 Exclusion criteria

Old text:

6. Previous or concurrent cancer that is distinct in primary site or histology from ~~i~~NHL within 5 years before start of study treatment **except** for curatively treated cervical cancer *in situ*, non-melanoma skin cancer and superficial bladder tumors [Ta (non-invasive tumor), Tis (carcinoma *in situ*) and T1 (tumor invades lamina propria)].

~~7. Presence of B-symptoms (fever above 38°C, night sweats, or weight loss of more than 10% in the previous 6 months).~~

8. Lymph nodes or tumor mass (except spleen) ~~>~~ 7 cm.

~~9. Nodes > 3 cm in 3 distinct areas.~~

~~10. Symptoms related to organ compression, pleural effusion, ascites, spleen enlargement, and renal, liver or bone involvement.~~

11. Known lymphomatous involvement of the central nervous system.

[...]

25. History or concurrent condition of interstitial lung disease and/or severely impaired lung function (as judged by the investigator)

[...]

Excluded previous therapies and medications

~~32. Prior treatment with PI3K inhibitors.~~

33. Treatment with investigational drugs ~~other than PI3K inhibitors~~ within 28 days before start of study treatment.

[...]

44. Use of strong inducers of CYP3A4 is prohibited from Day -14 of Cycle 1 until the SFU visit.

For prohibited concomitant therapy please refer to Section 6.9.1.

New text:

6. Previous or concurrent cancer that is distinct in primary site or histology from <u>indolent B-cell</u> NHL within 5 years before start of study treatment **except** for curatively treated cervical cancer *in situ*, non-melanoma skin cancer and superficial bladder tumors [Ta (non-invasive tumor), Tis (carcinoma *in situ*) and T1 (tumor invades lamina propria)].

7.

8. <u>Bulky disease:</u>
    - Lymph nodes or tumor mass (except spleen) <u>≥</u> 7 cm <u>LDi (longest diameter)</u>.

9.

10.

11. Known lymphomatous involvement of the central nervous system.

[...]

25. History or concurrent condition of interstitial lung disease <u>of any severity</u> and/or severely impaired lung function (as judged by the investigator)

[...]

Excluded previous therapies and medications

32.

33. Treatment with investigational drugs within 28 days before start of study treatment.

[...]

44. Use of strong inducers of CYP3A4 is prohibited from Day -14 of Cycle 1 until the SFU visit.

45. Documented evidence of resistance to a prior treatment with idelalisib or other PI3K inhibitors defined as:

    - No response (response defined as PR or CR) at any time during therapy, **or**
    - Progression (PD) after any response (PR/CR) or after stable disease (SD) within 6 months from the end of the therapy with a PI3K inhibitor.

      Patients who discontinued treatment due to other reason than disease progression, and did not exhibit any signs of PD, will be allowed to enroll in this study after discussion with the sponsor.

For prohibited concomitant therapy please refer to Section 6.9.1.

13.1.2.14 Section 5.2.1 Withdrawal

Old text:

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. ~~No re-consent will be required for re-screened patients.~~

If one or more screening laboratory tests do not support eligibility, laboratory re-test is permitted only once. Only the laboratory tests which ~~resulted~~ 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 ~~and screening procedures already performed and resulted within required ranges for eligibility will not need to be repeated again. All screening laboratory tests will need to be taken within 7 days prior to start of study treatment~~.

~~In patients with newly diagnosed diabetes mellitus, if plasma glucose and/or HbA1c do not support eligibility, re-testing can be performed within 28 days of the initial test and all other screening procedures will be repeated again, if necessary, to meet the required time frame prior to start of study treatment.~~

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.

New text:

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 re-screening will start again by signing a new informed consent form and being assigned a new PID.

All initial screening laboratory tests will need to be taken within 7 days prior to planned Cycle 1 Day 1. 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 which are 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 re-testing cannot be completed within 7 days of the Cycle 1 Day 1, all blood and urinary tests that are required to be within 7 days of Cycle 1 Day 1 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 glucose and HbA1c.

13.1.2.15 Section 5.2.1.1 Withdrawal from study treatment

Old text:

- Disease progression (PD) as defined in the ~~Revised Response Criteria for Malignant Lymphoma (1). F~~or patients with WM, ~~additional criteria apply~~. Detailed instructions on tumor assessment are provided in Appendix 14.1. Radiological PD must be assessed by central independent blinded review before unblinding of study treatment (copanlisib or placebo). The result of PD per central review instead of investigational site image assessment will be used to unblind the patient. Patients who have received placebo can be offered open-label copanlisib upon discretion of the investigator and patient's consent.
- ~~AEs due to disease-related complications.~~
- Occurrence of unacceptable toxicity.
- CTCAE Grade 4 arterial hypertension.
- CTCAE Grade 4 symptomatic hyperglycemia.

[...]

- Development of a malignancy other than ~~i~~NHL. New malignancy will be reported as a SAE.

[...]

- Delay in study drug administration due to toxicities for > 21 days (a delay of study drug dosing due to reasons other than toxicity is not included in this definition~~)~~.

New text:

- Disease progression (PD) as defined in the Lugano Classification (21), and for patients with WM, according to the Owen criteria (22). Detailed instructions on tumor assessment are provided in Appendix 14.1. Radiological PD must be assessed by central independent blinded review before unblinding of study treatment (copanlisib or placebo). The result of PD per central review instead of investigational site image assessment will be used to unblind the patient. Patients who have received placebo can be offered open-label copanlisib upon discretion of the investigator and patient's consent.
- Occurrence of unacceptable toxicity.
- CTCAE Grade 4 arterial hypertension.
- CTCAE Grade 4 symptomatic hyperglycemia or glucose intolerance.

[...]

- Development of a malignancy other than indolent B-cell NHL. New malignancy will be reported as a SAE.

[...]

- Delay in study drug administration due to toxicities for > 21 days (this does not include the required 1 week break), a delay of study drug dosing due to reasons other than toxicity is not included in this definition.

13.1.2.16 Section 5.2.1.2 Withdrawal from follow-up period

Old text:

All patients will be contacted every 3 months to determine survival status during the Survival follow-up period (up to 3 years after the last patient started study treatment).

New text:

All patients will be contacted at least every 3 months to determine survival status during the Survival follow-up period (up to 3 years after the last patient started study treatment).

13.1.2.17 Section 5.3 Patient identification

Old text:

a. Digits 1 to 2: Unique country code ~~(International Organization for Standardization [ISO] code)~~.

New text:

a. Digits 1 to 2: Unique country code.

13.1.2.18 Section 6.1 Treatments to be administered

Old text:

should the administered dose exceed the starting dose of 60 mg. Patients who do not tolerate the dose of at least 30 mg must discontinue study treatment permanently (see Section 5.2).

New text:

should the administered dose exceed the starting dose of 60 mg. Patients who do not tolerate the dose of at least 30 mg must discontinue study treatment permanently (see Section 5.2).

See Pharmacy Manual for additional details.

13.1.2.19 Section 6.2 Identity of study treatment

Old text:

of the lyophilisate with normal saline solution. Reconstitution and dilution should be performed according to separate handling instructions.

[...]

~~Copanlisib is a cytotoxic drug without mutagenic properties.~~ Refer to IB for copanlisib for more details regarding drug properties and formulation.

New text:

of the lyophilisate with normal saline solution. Reconstitution and dilution should be performed according to separate handling instructions specified in the Pharmacy Manual.

[...]

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

13.1.2.20 Section 6.3 Treatment assignment

Old text:

At the end of the Screening period, eligible patients will be randomly assigned in a ~~1:1~~ ratio to one of the double-blinded treatment arms: copanlisib monotherapy or placebo. The randomization must be performed within 48 h before the first dose of study drug.

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

IVRS/IWRS will stratify patients according to ~~two~~ factors based on baseline characteristics:

- NHL histology, with categories:
  - FL histology
  - Other NHL histology, and
- ~~t~~ime between last course of systemic anticancer therapy and most recent progression, with categories:
  - ≤ 6 months
  - > 6 months

Resulting from the combination of these ~~two~~ stratification factors, patients will be randomized into ~~4~~ different strata.

New text:

At the end of the Screening period, eligible patients will be randomly assigned in a 2:1 ratio to one of the double-blinded treatment arms: copanlisib monotherapy or placebo, respectively. The randomization must be performed within 48 h before the first dose of study drug.

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

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

- NHL histology, with categories:
  - FL histology
  - Other NHL histology, and
- Time between last course of systemic anticancer therapy and most recent progression, with categories:
  - ≤ 6 months

- > 6 months, and

- Prior treatment with PI3K inhibitors:
  - Yes
  - No

Resulting from the combination of these three stratification factors, patients will be randomized into 8 different strata.

13.1.2.21 Section 6.4 Dosage and administration

Old text:

Study drug (copanlisib or placebo) is administered in a normal saline solution, ~~100 mL,~~ intravenously, over 1 h. 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).

~~On Cycle 1 Day 1, patients should be fasting for at least 8 h prior to the dose and until 2 h after completion of the infusion. During the fasting period, water and beverages with artificial sweeteners may be consumed. Patient's fasting pre-dose glucose level should be ≤ 125 mg/dL (non-diabetic patients) or < 160 mg/dL (diabetic patients) before the first infusion. Approximately 3 h after the start of the infusion, patients should have a low carbohydrate meal (eggs, cheese and/or plain yoghurt, vegetables, meat). If no hyperglycemia CTCAE Grade 2 (fasting glucose increase > 160 mg/dL) occurs after the first infusion on Cycle 1 Day 1, investigators may allow patients to have a low carbohydrate breakfast before the subsequent infusions (e.g. eggs, cheese, plain yoghurt, vegetables, meat). Pre-dose glucose levels for subsequent infusions should be < 160 mg/dL (fasting) or < 200 mg/dL (non-fasting).~~

[...]

Patients will continue study treatment until PD (per central independent blinded radiology review) or they meet the criteria described in Section 5.2. Patients who experience PD on placebo treatment can be offered open-label copanlisib upon discretion of the investigator and patient's consent. After individual patient unblinding, patients receiving placebo who switch to open-label copanlisib will have all study assessments and timing reset to the initial schedule of study evaluations (i.e. as if the patient was restarting the study at Cycle 1 Day 1). These patients will be ~~followed~~ until further disease progression.

[...]

Table 6-~~1~~ 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
Platelets	≥ 50,000/mm^3
ALT	≤ 5 x ULN
AST	≤ 5 x ULN
Total bilirubin	≤ 3 x ULN
~~Creatinine~~	~~≤ 1.5 x ULN~~

ANC = Absolute neutrophil count; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; ULN = Upper limit of normal.

a: If ~~the~~ hemoglobin is < ~~9 g/dL~~ on the day of planned study drug administration~~, and the patient is hemodynamically stable,~~ it is permissible to give the study drug dose on schedule and transfuse within 48 h after the dose.

New text:

Study drug (copanlisib or placebo) is administered in a normal saline solution, intravenously, over 1 h. No intravenous glucose preparations should be administered on the days of infusion. See Pharmacy Manual for additional details.

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 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	Fasting required before study drug infusion
Day 1 of cycle 1	Yes	≤125 mg/dL (non-diabetic patients) <160 mg/dL (diabetic patients)	No [a]
Day 1 of subsequent cycles	Yes	<160 mg/dL (fasting) < 200 mg/dL (non-fasting) [c]	No [b]
Days 8 and 15 of each cycle	No	<160 mg/dL (fasting) <200 mg/dL (non-fasting)	No [b]

a: Within 1 h before the start of study drug infusion patients may have a low carbohydrate breakfast (e.g. eggs, cheese, plain yoghurt, vegetables, meat).

b: Patients may have a low carbohydrate breakfast (e.g. eggs, cheese, plain yoghurt, vegetables, meat) at any time after pre-dose glucose measurement.

c: In case of non-compliance with the fasting requirement.

The investigator will accurately document fasting/non-fasting for each glucose measurement done at the site. Fasting for this purpose refers to a ≥ 8 h fast.

[...]

Patients will continue study treatment until PD (per central independent blinded radiology review) or they meet the criteria described in Section 5.2. Patients who experience PD on placebo treatment can be offered open-label copanlisib upon discretion of the investigator and patient's consent. After individual patient unblinding, patients receiving placebo who switch to open-label copanlisib will have all study assessments and timing reset to the initial schedule of study evaluations (i.e. as if the patient was restarting the study at Cycle 1 Day 1). If not previously done within 7 days, patients switching to open-label copanlisib must complete the following within 7 days prior to the first dose of open-label copanlisib: UPCR measurement, GFR measurement, urinalysis, HbA1c, CBC, chemistry and coagulation panels Dosing criteria outlined in Table 6–2 apply also for patients who switch to open-label treatment. These patients will be treated until further disease progression (per central review) unacceptable toxicity, or until another criterion is met for withdrawal from the study treatment (see Section 5.2).

[...]

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
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

ANC = Absolute neutrophil count; ALT = Alanine aminotransferase; 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 on schedule 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 the source documentation and in the eCRF.

13.1.2.22 Section 6.4.1 Dose modification

Old text:

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 trials: e.g., hyperglycemia and arterial hypertension. Based on this knowledge the investigator may decide on the necessary dose modifications. If the dose is reduced or interrupted, the investigator's decision is to be clearly documented in the patient's records and in the eCRF.

New text:

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 trials:

e.g., hyperglycemia and arterial hypertension. Based on this knowledge the investigator may decide on the necessary dose modifications. If the dose is reduced or interrupted, the investigator's decision is to be clearly documented in the patient's records and in the eCRF.

Dose modifications must be done according to the guidelines given in Section 6.4.1.1 and Section 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.

13.1.2.23 Section 6.4.1.1 Hematological toxicity

Old text:

Neutropenia and febrile neutropenia are listed in the current version of IB as expected adverse events. ~~The clinician should proceed as dictated by the clinical situation, medical practice, and their experience as an investigator. The guidelines in Table 6-3 can be used as support for the clinical decision. If these guidelines are not followed, the rationale for other measures is to be documented in detail in the patient's medical record~~.

Table 6-~~3~~ Dose modification of study treatment for hematological toxicity

Hematological toxicity of CTCAE Grade (any of the following)	Study drug action (for all toxicities)

New text:

Neutropenia and febrile neutropenia are listed in the current version of IB as expected adverse events. The guidelines for dose modifications in case of hematological toxicity are given in Table 6-4.

Table 6-4 Dose modification of study treatment for hematological toxicity

Note: This table should not be used to determine patient eligibility for infusion on days 1, 8 and 15. Please follow specific guidance given for laboratory test criteria on days 1, 8 and 15

Hematological toxicity of CTCAE Grade (any of the following)	Study drug action (for all toxicities)

13.1.2.24 Section 6.4.1.2 Non-hematological toxicity

Old text:

Dose modifications for non-hematologic toxicities except hyperglycemia, dermatologic toxicity, NIP and arterial hypertension are outlined in Table 6-4.

Table 6–~~4~~ Dose modification of study treatment for non-hematological toxicity (except hyperglycemia, dermatologic toxicity, non-infectious pneumonitis and arterial hypertension)

		Study drug action	
Toxicity (CTCAE)	**Occurrence**	**For current course of therapy**	**For next course of therapy**
Grade ~~0~~-2	Any appearance	No change	No change
Grade 3[a]	1st appearance	Interruption until Grade ≤ 2	No change
	2nd appearance	Interruption until Grade ≤ 2	Decrease by one dose level[b]
	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 > 21 days		Permanent discontinuation	–

CTCAE = Common Terminology Criteria of Adverse Events.
a: Despite maximum supportive therapy.
b: Not applicable for 30 mg dose level.
~~c: Not applicable for 30 mg and 45 mg dose levels.~~
A delay > 21 days in study drug administration due to toxicities will cause permanent discontinuation of study treatment.
Study treatment 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

~~According to the grade and incidence of dermatologic reaction for a given patient, the clinician should proceed as dictated by the clinical situation, medical practice, and their experience as an investigator. The guidelines in Table 6-5 can be used as support for the clinical decision. If these guidelines are not followed, the rationale for other measures is to be documented in detail in the patient's medical record~~.

Table 6–~~5~~ Dose modification of study treatment for dermatologic toxicity

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

CTCAE = Common Terminology Criteria of Adverse Events. Toxicities according to CTCAE version 4.03.
a: Despite maximum supportive therapy.

b: Not applicable for 30 mg dose level.
~~c: Not applicable for 30 mg and 45 mg dose levels.~~
The lowest dose level is 30 mg; if a patient is already on the 30 mg dose level and meets criteria for further dose decrease, study treatment will be discontinued permanently.

[…]

Hyperglycemia and arterial hypertension

a) Hyperglycemia

Patients who develop transient post-infusion hyperglycemia ~~of CTCAE Grade 3~~ (glucose ~~level~~ > 250 mg/dL~~)~~ after study drug 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 treatment of hyperglycemia are given in Section 6.4.2.1.

A dose reduction of study drug by one dose level is mandatory in the event of ~~CTCAE Grade 4~~ asymptomatic hyperglycemia. No further dose reductions will be allowed in the event of re-occurrence of ~~CTCAE Grade 4~~ asymptomatic hyperglycemia and the ~~patient~~ will be permanently discontinued.

If ~~symptomatic~~ CTCAE Grade 4 ~~hyperglycemia~~ occurs, permanent discontinuation of the study drug is mandatory.

New text:

Dose modifications for non-hematologic toxicities except hyperglycemia, dermatologic toxicity, NIP and arterial hypertension are outlined in Table 6-5.

Table 6–5 Dose modification of study treatment for non-hematological toxicity (except hyperglycemia, dermatologic toxicity, non-infectious pneumonitis and arterial hypertension)

		Study drug action	
Toxicity (CTCAE)	**Occurrence**	**For current course of therapy**	**For next course of therapy**
Grade 1-2	Any appearance	No change	No change
Grade 3[a]	1st appearance	Interruption until Grade ≤ 2	No change
	2nd appearance	Interruption until Grade ≤ 2	Decrease by one dose level[b]
	3rd appearance	Interruption until Grade ≤ 2	Decrease by one dose level[b]
	4th appearance	Permanent discontinuation	–
Grade 4	Any appearance	Permanent discontinuation	–
Toxicity requiring delay for > 21 days		Permanent discontinuation	–

CTCAE = Common Terminology Criteria of Adverse Events.
a: Despite maximum supportive therapy.
b: Not applicable for 30 mg dose level.
A delay > 21 days in study drug administration due to toxicities will cause permanent discontinuation of study treatment.
Study treatment 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 case of dermatologic toxicity are given in Table 6-6.

Table 6–6 Dose modification of study treatment for dermatologic toxicity

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

CTCAE = Common Terminology Criteria of Adverse Events. Toxicities according to CTCAE version 4.03.
a: Despite maximum supportive therapy.
b: Not applicable for 30 mg dose level.
The lowest dose level is 30 mg; if a patient is already on the 30 mg dose level and meets criteria for further dose decrease, study treatment will be discontinued permanently.

[…]

Hyperglycemia and arterial hypertension

Hyperglycemia

Patients who develop transient post-infusion hyperglycemia (glucose intolerance) of > 250 mg/dL after study drug 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 treatment of hyperglycemia are given in Section 6.4.2.1.

A dose reduction of study drug by one dose level is mandatory in the event of asymptomatic hyperglycemia > 500 mg/dL. No further dose reductions will be allowed in the event of re-occurrence of asymptomatic hyperglycemia > 500 mg/dL and the treatment will be permanently discontinued.

If CTCAE Grade 4 glucose intolerance occurs, permanent discontinuation of the study drug is mandatory.

13.1.2.25 Section 6.4.2.1 Management of hyperglycemia that can occur with study treatment

Old text:

a) Management of transient post-infusion hyperglycemia

Only the use of rapid or short acting (regular) insulin is allowed for the treatment of transient hyperglycemia. The prophylactic administration of rapid or short acting (regular) insulin prior to study drug infusion is not permitted.

In the event of ~~CTCAE Grade 3 hyperglycemia (~~post-dose glucose > 250 mg/dL~~)~~ on the day of infusion, the administration of rapid or short acting (regular) insulin is recommended according the institution's insulin sliding scale regimen.

All patients (diabetic and non-diabetic) should be kept under close observation if the glucose level is > 250 mg/dL ~~(CTCAE Grade 3 hyperglycemia)~~ until the glucose level decreases to < 160 mg/dL at any cycle. In the event of rapid or short acting (regular) insulin administration at any cycle, a 3 h close observation time is required post-administration. Meals should be provided for patients who are kept for continued observation. A low dose carbohydrate diet is recommended for the first 48 h after study drug infusion. However, carbohydrate restriction is not meant as caloric restriction in the population under study.

Patients will be trained to measure their capillary blood glucose levels at home starting at Screening and will be provided with glucose meter and strips, if applicable. The appropriate calibration of glucose meters will be documented.

[…]

Monitoring of non-diabetic patients

~~On Cycle 1 Day 1 a~~ll non-diabetic patients ~~(regardless of their post-infusion glucose value)~~ will be instructed to check blood glucose at home at least 3 times per full day for at least 72 h after the start of infusion. This includes fasting glucose (morning before breakfast) and 2 further random non-fasting measurements approximately 2 h after intake of food. ~~This monitoring will continue until blood glucose values are at goal~~ (fasting glucose ≤ 125 mg/dL or random non-fasting glucose ≤ 160 mg/dL).

~~From Cycle 1 Day 8, the need to keep home monitoring will be re-assessed after each infusion. Non-diabetic patients will be instructed to check blood glucose at home only if they experience CTCAE Grade 3 hyperglycemia or require insulin administration. The measurements will be taken at least 3 times per full day for at least 72 h after the start of infusion. This includes fasting glucose (morning before breakfast) and 2 further random non-fasting measurements approximately 2 h after intake of food. This monitoring will continue until blood glucose values are at goal (fasting glucose ≤ 125 mg/dL or random non-fasting glucose ≤ 160 mg/dL).~~

Monitoring of diabetic patients

All diabetic patients will be instructed to check blood glucose at home at least 3 times per full day for at least 72 h after start of each infusion. This includes fasting glucose (morning before breakfast) and 2 further random non-fasting measurements approximately 2 h after intake of food. ~~This monitoring will continue until blood glucose values are at goal~~ (fasting glucose < 160 mg/dL or random non fasting glucose < 200 mg/dL).

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. In this situation, patients should add the study specific measurements to their routine, if applicable. ~~When~~ blood glucose values are at goal (fasting glucose < 160 mg/dL or random non-fasting glucose < 200 mg/dL) after each infusion, patients can then stop only the study specific measurements until the next day of infusion, but should keep their routine measurements unchanged and ongoing as usual.

Sites recruiting patients with diabetes should have the option to extend glucose monitoring overnight.

b) Management of diabetic patients (non-transient hyperglycemia) for the duration of the study

[...]

To monitor non-transient hyperglycemia fasting glucose is recommended. Glucose measurement prior to the infusion on Day 1 of each cycle is ~~recommended~~ for the management of non-transient hyperglycemia. The following guideline applies:

New text:

a) Management of transient post-infusion hyperglycemia

Only the use of rapid or short acting (regular) insulin is allowed for the treatment of transient hyperglycemia <u>(glucose intolerance)</u>. The prophylactic administration of rapid or short acting (regular) insulin prior to study drug infusion is not permitted.

In the event of post-dose glucose > 250 mg/dL on the day of infusion, the administration of rapid or short acting (regular) insulin is recommended according the institution's insulin sliding scale regimen.

All patients (diabetic and non-diabetic) should be kept under close observation if the glucose level is > 250 mg/dL until the glucose level decreases to < 160 mg/dL at any cycle. In the event of rapid or short acting (regular) insulin administration at any cycle, a 3 h close observation time is required post-administration. Meals should be provided for patients who are kept for continued observation. A low dose carbohydrate diet is recommended for the first 48 h after study drug infusion. However, carbohydrate restriction is not meant as caloric restriction in the population under study.

Patients will be trained to measure their capillary blood glucose levels at home starting at Screening and will be provided with glucose meter and <u>supplies (lancets, test</u> strips <u>and diary)</u>

to register measured values and record insulin administration, if applicable. The appropriate calibration of glucose meters will be documented.

[…]

Monitoring of non-diabetic patients

All non-diabetic patients who experience hyperglycemia > 250 mg/dL or require insulin administration will be instructed to check blood glucose at home at least 3 times per full day for at least 72 h after the start of infusion. This includes fasting glucose (morning before breakfast) and 2 further random non-fasting measurements approximately 2 h after intake of food. If after the required 72 h the glucose values are not at goal (fasting glucose ≤ 125 mg/dL or random non-fasting glucose ≤ 160 mg/dL), this monitoring will continue until blood glucose values are at goal.

Monitoring of diabetic patients

All diabetic patients will be instructed to check blood glucose at home at least 3 times per full day for at least 72 h after start of each infusion. This includes fasting glucose (morning before breakfast) and 2 further random non-fasting measurements approximately 2 h after intake of food. If after the required 72 h the glucose values are not at goal (fasting glucose < 160 mg/dL or random non fasting glucose < 200 mg/dL), this monitoring will continue until blood glucose values are at goal, and the patient should be immediately referred to the local diabetes center/endocrinologist to adjust treatment.

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. In this situation, patients should add the study specific measurements to their routine, if applicable. After the required 72 h, if blood glucose values are at goal (fasting glucose < 160 mg/dL or random non-fasting glucose < 200 mg/dL) after each infusion, patients can then stop only the study specific measurements until the next day of infusion, but should keep their routine measurements unchanged and ongoing as usual.

Sites recruiting patients with diabetes should have the option to extend glucose monitoring overnight.

b) Management of diabetic patients (non-transient hyperglycemia) for the duration of the study

[...]

To monitor non-transient hyperglycemia fasting glucose is recommended. Glucose measurement prior to the infusion on Day 1 of each cycle is needed for the management of non-transient hyperglycemia. The following guideline applies:

13.1.2.26 Section 6.5 Blinding

Old text:

Because copanlisib solution may have a yellowish color while the placebo solution is ~~transparent~~, ~~the following~~ measures will be taken to preserve the blind~~:~~

- ~~Yellow syringes must be used.~~
- ~~All tissues used for removing any spillage must be colored.~~

~~A~~n unblinded, study-independent pharmacist (or qualified person) will handle the preparation of the study drug.

New text:

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

13.1.2.27 Section 6.9.1 Prohibited concomitant therapy

Old text:

- 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 7 days prior to the screening CT/MRI and again prior to the first administration of study drug. If a patient is on chronic corticosteroid therapy, corticosteroids should be de-escalated to the maximum allowed dose before the Screening. Patients may use topical or inhaled corticosteroids. ~~S~~ystemic corticosteroids will be allowed for the treatment of NIP. The use of corticosteroids as antiemetics prior to study drug administration will not be allowed.

New text:

- 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 7 days prior to the screening CT/MRI and again prior to the first administration of study drug. If a patient is on chronic corticosteroid therapy, corticosteroids should be de-escalated to the maximum allowed dose before the Screening. Patients may use topical or inhaled corticosteroids. Short term systemic corticosteroids above 15 mg prednisolone or equivalent will be allowed for the management of acute conditions (e.g. treatment of NIP). The use of corticosteroids as antiemetics prior to study drug administration will not be allowed.

13.1.2.28 Section 6.9.2 Permitted concomitant therapy

Old text:

- Patients taking narrow therapeutic index medications should be monitored proactively, if these medications cannot be avoided. These medications may include quinidine, ~~carbamazepine,~~ cyclosporine and digoxin.

New text:

- Patients taking narrow therapeutic index medications should be monitored proactively, if these medications cannot be avoided. These medications may include quinidine, cyclosporine and digoxin.

13.1.2.29 Section 7.1.1 Tabulated overview

Old text:

Table 7–1 Study flow chart

	Screening maximum days before C1D1			Treatment *									EOT	SFU	Active follow-up [aa]	Survival follow-up [bb]
				Cycle 1					Cycle 2 and higher				Within (days) after			
Days	**-28**	**-14**	**-7**	**D1**	**D4**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22 [y]**	**7**	**30-35 [z]**		**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 informed consent must be obtained prior to any study-specific procedures~~															
Check in- and exclusion criteria		X	X	X												
Medical history [a]		X														
IVRS/IWRS transaction [b]	X			X[b]					X				X			
HBsAg, HBcAb, HCV IgG	X															
~~Serum beta-2-microglobulin~~		~~X~~														
Serum pregnancy test (if applicable) [c]			X						X[c]							
UPCR			X													
GFR			X													
Safety																
Toxicity / AE assessment [d]		X		X		X	X	X	X	X	X		X	X	(X)[d]	
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)~~		(X)		
12-lead ECG [g]		~~X~~		X[g]					X[g]		~~X~~[g]		X[g]			
MUGA scan or echocardiogram [h]		~~X~~[h]							X[h]				X[h]			
~~Hemoglobin A1c (~~HbA1c~~)~~ [i]			X						X[i]				X			
Complete blood count [j]			X			X[x]	X[x]	X	X[x]	C2 only[x]	C2 only[x]		X	(X)		
Hemoglobin, ANC and platelet counts (C3->)										X[x]	X[x]					
Chemistry panel [k]			X[k]			X[x]	X[x]	X	X[k,x]	C2 only[x]	C2 only[x]		X[k]	(X)		
Coagulation panel: PT, INR and PTT			X				X[x]		X[x]				X	(X)		
Urinalysis (dipstick)			X						X				X			

Table 7–1 Study flow chart

	Screening maximum days before C1D1			Treatment *									EOT	SFU	Active follow-up [aa]	Survival follow-up [bb]
				Cycle 1					Cycle 2 and higher				Within (days) after			
Days	**-28**	**-14**	**-7**	**D1**	**D4**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22 [y]**	**7**	**30-35 [z]**		**every 3 months**
Acceptable deviation (in days)				-1 to +2 days					-1 to +2 days				Decision to stop	Last dose		±14 days
Glucose [l]				X		X	X		X	X	X					
Home glucose ~~test (training, strips, review)~~ [m]			X	X	X	X	X	X	X	X	X		X			
Blood pressure [n]				X		X	X		X	X	X					
Efficacy																
Bone marrow biopsy [o]	X											X[o]				
CT/MRI and tumor evaluations [p]	X											X[p]	X[p]		X[p]	
Quality of life questionnaire (FLymSI-18) [q]				X					X				X	X		
Pharmacokinetic sampling [r]				~~X[g]~~		X					~~X[g]~~					
Biomarkers																
Tumor tissue [s]	X															
Plasma for genetic ~~biomarker analysis~~ [t]				X					~~X[t]~~				X			
Plasma for non-genetic biomarker analysis [u]				X		X	X		~~X~~	C2 only	C2 only		X			
Whole blood for biomarkers [v]				X												
[…]																X
For LPL/WM patients only																
Serum protein electrophoresis [w]		X[w]										X[w]	(X)[w]			
Immunofixation [w]		X[w]										X[w]	(X)[w]			
Serum quantitative IgM test [w]		X[w]										X[w]	(X)[w]			
Serum or plasma viscosity [w]		X[w]							(X)[w]				(X)[w]			

[...]

* **NOTE**: Patients who experience PD on placebo treatment (per central independent blinded radiology review) can be offered open-label copanlisib upon discretion of the investigator and patient's consent. After individual patient unblinding, patients receiving placebo who switch to open-label copanlisib will have all study assessments and timing reset to the initial schedule of study evaluations (i.e. as if the patient was restarting the study at Cycle 1 Day 1).

a Demographics, relevant medical history findings, concomitant illnesses, allergy history, prior surgeries, most recent histology of tumor, most recent staging and grading of tumor, FLIPI score (for patients with FL), history of anticancer treatments (including type of treatment, type of response, date of response and date of subsequent relapse), assessment of baseline toxicity and smoking history.

b IVRS/IWRS randomization transaction will take place within 48 h before the first dose of study drug. 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 for France, Belgium, Canada and other countries where it is required by local regulations.

d After Screening: AE assessment and concomitant medication review must be updated before each dose and 30-35 days after last dose. 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. 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 a complete review of body systems ~~(including physical examination for lymphadenopathy, abdominal masses, or organomegaly)~~.

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).

g 12-lead ECG (including QTcB and QTcF evaluation) will be performed at Screening (within ~~14~~ days before Cycle 1 Day 1) ~~and within 7 days prior to dosing~~ on Day 1 of every 3rd cycle (3, 6, 9, etc.). At the EOT visit, a 12-lead ECG is necessary only if not recorded within the previous ~~4~~ weeks. ~~At centers with adequate facilities and equipment: additional 12-lead ECGs will be recorded on Cycle 1 Day 1 and on Day 15 of every 3rd cycle (3, 6, 9 etc.) pre-infusion and at the end of infusion (C_{max}). At these centers, a PK sample is to be drawn after each 12-lead ECG recording on Cycle 1 Day 1, and on Day 15 of every 3rd cycle (3, 6, 9 etc.).~~

h MUGA scan or 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 visit. The method chosen at Screening must be the same throughout the whole study.

i ~~Hemoglobin A1c (~~HbA1c~~)~~ at Screening, on Day 1 of every odd cycle (3, 5, 7, etc.) starting from Cycle 3 and at the EOT visit.

j ~~Complete blood count (~~CBC~~)~~: Hemoglobin, hematocrit, RBC, WBC (with differential to include absolute neutrophil, lymphocyte, monocyte, basophil and eosinophil counts and platelet count). From Cycle 3 onwards, only hemoglobin, platelet and ANC counts will be performed on Day 8 and Day 15 prior to each infusion.

k 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), SCR, uric acid, total bilirubin, creatine phosphokinase, ALT, AST, LDH, ALP, lipase, amylase (or pancreatic amylase, if total amylase is not routinely measured at the site), cholesterol (total~~,~~ LDL~~, HDL~~) and triglycerides. Total cholesterol, LDL and triglycerides will be tested only at Screening, on Day 1 of every 2nd cycle starting from Cycle 2, and at the EOT visit. On these dates patients must be fasting for 11 h prior to sampling. If a patient can't adhere to fasting requirements, the evaluation of lipid-panels including triglycerides is considered not feasible.

l On Cycle 1 Day 1, glucose will be measured at pre-dose~~,~~ and ~~3 h, 5 h, 6 h and 8 h~~ after the start of ~~the~~ infusion. Additional measurements to be performed as clinically indicated. The ~~first~~ pre-dose glucose sample on ~~Cycle 1~~ Day 1 should be after an 8 h fasting. ~~P~~patient's fasting pre-dose glucose level should be ≤ 125 mg/dL (non-diabetic patients) or < 160 mg/dL (diabetic patients) before the ~~first~~ infusion. ~~On subsequent infusions, glucose will be measured prior to and after infusion.~~ Pre-dose glucose levels for subsequent infusions should be < 160 mg/dL (fasting) or < 200 mg/dL (non-fasting). For ~~details~~, see Section 6.4.

m Home glucose ~~measurement~~ is required for all diabetic patients after each infusion. For non-diabetic patients home glucose measurement is required ~~on Cycle 1 Day 1 (regardless of their post infusion glucose value), and from Cycle 1 Day 8 onwards only~~ if ~~they~~ develop ~~CTCAE Grade 3~~ hyperglycemia or require insulin administration after any infusion. Measurements should be taken at least 3 times per full day for at least 72 h after the start of infusion. This includes fasting glucose (morning before breakfast) and 2 further random non-fasting measurements approximately 2 h after intake of food. ~~This monitoring will continue until blood glucose values are at goal~~ (fasting glucose ≤ 125 mg/dL/< 160 mg/dL or random non-fasting glucose ≤ 160 mg/dL/< 200 mg/dL for non-diabetic/diabetic patients, respectively). For details see Section 6.4.2.1.

n Blood pressure will be measured every 5-10 min prior to infusion of study drug (no more than 4 measurements) until there are 2 consecutive results < 150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. At Cycle 1 Day 1 blood pressure will be measured at 0 h (pre-dose), 30 min (mid-infusion), 60 min (end of infusion), 90 min, 2 h, 3 h, 4 h and 6 h after the start of infusion (deviation ±5 min). From Cycle 1 Day 8 onwards a single blood pressure measurement is to be performed prior to each infusion, 30 min after the start of infusion and at the end of each infusion.

o Bone marrow biopsy is mandatory at Screening (biopsy done up to 28 days prior to first dose can be used as baseline evaluation) and to confirm the first complete response, if positive at baseline.

p The first IV contrast enhanced CT/MRI scans of neck, chest, abdomen and pelvis must be performed at Screening. Corticosteroids must be stopped or reduced to the allowed dose (less than 15 mg of prednisone or equivalent) at least 7 days before performing the 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 evaluation.~~ The method chosen at the baseline must be the same throughout the study. During treatment, tumor scans will be done with the same modality every 12 weeks ~~(±7 days)~~ during Year 1, every 16 weeks ~~(±7 days)~~ during Year 2, and every 24 weeks ~~(±7 days)~~ during Year 3. 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. During Active follow-up period patients will have radiological assessments ~~as outlined in this protocol~~ until PD is documented or new anti-tumor treatment is administered~~, whichever occurs first.~~

q FLymSI-18 questionnaire is to be completed on Cycle 1 Day 1 and every cycle thereafter (i.e. on Day 1 of Cycles 2, 3, 4 etc.), at the EOT visit and at the SFU visit in both treatment arms. Questionnaire should be self-administered by the patient via an ePRO at the start of the visit before ~~contact with the investigator or other investigative site personnel~~.

r PK sampling will be performed for copanlisib, its metabolite M-1 and other metabolites, if needed, in all patients on ~~On~~ Cycle 1 Day 8: pre-infusion, 5 to 15 min, 55 min (within 5 min prior to end of infusion) and 1.5 to 5 h after start of infusion. If sampling is not feasible at Cycle 1, samples may be collected at Cycle 2. A separate IV line should be used for PK draws. ~~At centers with adequate facilities and equipment: additional PK sampling will be performed after each 12-lead ECG recording pre- infusion and end of infusion (within 5 min prior to the end of infusion) on Cycle 1 Day 1, and on Day 15 of every 3rd cycle (3, 6, 9 etc.).~~

s Tumor tissue ~~for central pathology review and biomarker analysis (mandatory). Fresh tumor tissue (preferred) will be collected between Day -28 and Day -8 prior to the start of study treatment. Detailed guidance on fresh biopsy sample preparation and storage will be provided to the sites. Archival tumor tissue will be requested if fresh tissue is not available (the latest biopsy available should be provided). Both may also be collected if available. Archival 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 will be described in separate documents (e.g. Sample Handling Sheets or laboratory manual)~~.

t Plasma for genetic ~~biomarker analysis~~: blood samples will be collected ~~at~~ Cycle 1 Day 1~~, on Day 1 of every odd cycle (3, 5, 7 etc.),~~ and at the EOT visit. On treatment days, 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. Samples are to be collected on Cycle 1 (Days 1, 8 and 15), Cycle 2 (Days 1, 8 and 15), ~~on Day 1 of all subsequent cycles~~ and at the EOT visit.

v Whole blood for biomarkers will be collected on Cycle 1 Day 1 (only from patients who provide a separate consent for genetic research).

w Only for patients affected by LPL/WM: Serum protein electrophoresis, immunofixation ~~and~~ serum quantitative IgM test will be performed at Screening. Serum or plasma viscosity will 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 will be performed on the days of tumor evaluation and at the EOT visit only if the last assessment is older than 4 weeks. If serum or plasma viscosity is abnormal at baseline, the measurement will be repeated every 3rd cycle starting from Day 1 of Cycle 3, and at the EOT visit.

x Laboratory tests prior to each infusion may be performed either the day before or on the planned date of infusion, with the exception of blood glucose, which must be performed on the day of infusion. For dosing criteria, see Section 6.4.

y 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.~~

z The post-treatment follow-up ~~within~~ 30-35 days after the last administration of study drug can be conducted via telephone if the patient is no longer being actively seen at the clinic or has started another therapy. Procedures marked with “(X)” are only to be performed, if clinically indicated.

aa 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 radiological 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.

bb 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 3 years after the last patient started study treatment), whichever comes first. Information to be recorded: date of contact, survival status, the first new anticancer regimen (if applicable), and date and cause of death (if applicable).

New text:

Table 7–1 Study flow chart

	Screening			Treatment *									EOT	SFU	Active follow-up [aa]	Survival follow-up [bb]
	maximum days before C1D1			Cycle 1					Cycle 2 and higher				Within (days) after			
Days	**-28**	**-14**	**-7**	**D1**	**D4**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22 [y]**	**7**	**30-35 [z]**		**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)	X[cc,dd]															
Check in- and exclusion criteria		X	X	X												
Medical history [a]		X														
IVRS/IWRS transaction [b, dd]	X			X[b]					X				X			
HBsAg, HBcAb, HCV IgG	X															
Serum pregnancy test (if applicable) [c]			X						X[c]							
UPCR			X													
GFR [dd]			X						X							
Safety																
Toxicity / AE assessment [d]		X		X		X	X	X	X	X	X		X	X	(X)[d]	
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, dd]						X	X	X		X	X			(X)		
12-lead ECG [g, dd]	X			X					X[g]				X[g]			
MUGA scan or echocardiogram [h, dd]	X[h]								X[h]				X[h]			
HbA1c [i]			X						X[i]				X			
Complete blood count [j]			X			X[x]	X[x]	X	X[x]	C2 only[x]	C2 only[x]		X	(X)		
Hemoglobin, ANC and platelet counts (C3->)										X[x]	X[x]					
Chemistry panel [k]			X[k]			X[x]	X[x]	X	X[k,x]	C2 only[x]	C2 only[x]		X[k]	(X)		
Coagulation panel: PT, INR and PTT			X				X[x]		X[x]				X	(X)		
Urinalysis (dipstick)			X						X				X			
Glucose [l]				X		X	X		X	X	X					

Table 7–1 Study flow chart

	Screening maximum days before C1D1			Treatment *									EOT	SFU	Active follow-up [aa]	Survival follow-up [bb]
				Cycle 1					Cycle 2 and higher				Within (days) after			
Days	**-28**	**-14**	**-7**	**D1**	**D4**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22 [y]**	**7**	**30-35 [z]**		**every 3 months**
Acceptable deviation (in days)				-1 to +2 days					-1 to +2 days				Decision to stop	Last dose		±14 days
Home glucose monitoring [m, dd]			X	X	X	X	X	X	X	X	X		X			
Blood pressure [n]				X		X	X		X	X	X					
Efficacy																
Bone marrow biopsy [o]	X											X[o]				
CT/MRI and tumor evaluations [p]	X[p]											X[p]	X[p]		X[p]	
Quality of life questionnaire (FLymSI-18) [q]				X					X				X	X		
Pharmacokinetic sampling [r, dd]						X										
Biomarkers																
Tumor tissue for central pathology and biomarkers [s, dd]	X												(X)			
Plasma for tumor genetics [t, dd]				X									X			
Plasma for non-genetic biomarker analysis [u dd]				X		X	X		C2 only	C2 only	C2 only		X			
Whole blood for biomarkers [v]				X												
[…]																X
For LPL/WM patients only																
Serum protein electrophoresis [w]		X[w]										X[w]	(X)[w]			
Immunofixation [w]		X[w]										X[w]	(X)[w]			
Serum quantitative IgM test [w]		X[w]										X[w]	(X)[w]			
Serum beta-2-microglobulin [dd]		X[w]														
Serum or plasma viscosity [w]		X[w]							(X)[w]				(X)[w]			

[...]

* **NOTE**: Patients who experience PD on placebo treatment (per central independent blinded radiology review) can be offered open-label copanlisib upon discretion of the investigator and patient's consent. After individual patient unblinding, patients receiving placebo who switch to open-label copanlisib will have all study assessments and timing reset to the initial schedule of study evaluations (i.e. as if the patient was restarting the study at Cycle 1 Day 1). If not previously done within 7 days, patients switching to open-label copanlisib must complete the following within 7 days prior to the first dose of open-label copanlisib: UPCR measurement, GFR measurement, urinalysis, HbA1c, CBC, chemistry and coagulation panels (see dosing criteria in Table 6–2).

a Demographics, relevant medical history findings, concomitant illnesses, allergy history, prior surgeries, most recent histology of tumor, most recent staging and grading of tumor, FLIPI score (for patients with FL), history of anticancer treatments (including type of treatment, type of response, date and duration of response and date of subsequent relapse), assessment of baseline toxicity and smoking history.

b IVRS/IWRS transaction to register the patient in the system will be at Screening. IVRS/IWRS randomization transaction will take place within 48 h before the first dose of study drug. 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 for France, Belgium, Canada and other countries where it is required by local regulations.

d After Screening: AE assessment and concomitant medication review must be updated before each dose and 30-35 days after last dose. 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. 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 a complete review of body systems.

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).

g 12-lead ECG (including QTcB and QTcF evaluation) will be performed at Screening (within 28 days before 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). At the EOT visit, a 12-lead ECG is necessary only if not recorded within the previous 4 weeks.

h MUGA scan or echocardiogram to measure LVEF at Screening (within 28 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 visit (if not previously done within 4 weeks). The method chosen at Screening must be the same throughout the whole study.

i HbA1c at Screening, on Day 1 of every odd cycle (3, 5, 7, etc.) starting from Cycle 3 and at the EOT visit.

j CBC: Hemoglobin, hematocrit, RBC, WBC (with differential to include absolute neutrophil, lymphocyte, monocyte, basophil and eosinophil counts and platelet count). From Cycle 3 onwards, only hemoglobin, platelet and ANC counts will be performed on Day 8 and Day 15 prior to each infusion.

k 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), SCR, uric acid, total bilirubin, creatine phosphokinase, ALT, AST, LDH, ALP, lipase, amylase (or pancreatic amylase, if total amylase is not routinely measured at the site), cholesterol (total and LDL) and triglycerides. Total cholesterol, LDL and triglycerides will be tested only at Screening, on Day 1 of every 2nd cycle starting from Cycle 2, and at the EOT visit. On these dates patients must be fasting for 11 h prior to sampling. If a patient can't adhere to fasting requirements, the evaluation of lipid-panels including triglycerides is considered not feasible.

l On Cycle 1 Day 1, glucose will be measured at pre-dose and after the start of study drug infusion (post-infusion). For patients who had a low carbohydrate breakfast prior to the start of infusion, glucose monitoring will be up to 3 h post-infusion (1 h, 2 h and 3 h). For patients who did not have a low carbohydrate breakfast prior to infusion, monitoring will continue for up to 5 h post-infusion (1 h, 2 h and 5 h). Additional measurements to be performed at the clinic as clinically indicated. On subsequent infusions, glucose will be measured prior to and after infusion. The pre-dose glucose sample on Day 1 of each cycle should be after an 8 h fasting. On Cycle 1 Day 1, patient's fasting pre-dose glucose level should be ≤ 125 mg/dL (non-diabetic patients) or < 160 mg/dL (diabetic patients) before the infusion. Pre-dose glucose levels for subsequent infusions should be < 160 mg/dL (fasting) or < 200 mg/dL (non-fasting). For fasting requirements, see Section 6.4.

m Home glucose monitoring is required for all diabetic patients after each infusion. For non-diabetic patients home glucose measurement is required if patients develop hyperglycemia > 250 mg/dL or require insulin administration after any infusion. Measurements should be taken at least 3 times per full day for at least 72 h after the start of infusion. This includes fasting glucose (morning before breakfast) and 2 further random non-fasting measurements approximately 2 h after intake of food. If after the required 72 h the glucose values are not at goal (fasting glucose ≤ 125 mg/dL/< 160 mg/dL or random non-fasting glucose ≤ 160 mg/dL/< 200 mg/dL for non-diabetic/diabetic patients, respectively), this monitoring will continue until blood glucose values are at goal. Patients will be trained to measure their capillary blood glucose levels at home starting at Screening. On Cycle 1 Day 1, patients will be provided with glucose meter and supplies, (lancets, test strips and diary) to record glucose values and insulin doses, if applicable. For details see Section 6.4.2.1.

n Blood pressure will be measured every 5-10 min prior to infusion of study drug (no more than 4 measurements) until there are 2 consecutive results < 150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. At Cycle 1 Day 1 blood pressure will be measured at 0 h (pre-dose), 30 min (mid-infusion), 60 min (end of infusion), 90 min, 2 h, 3 h, 4 h and 6 h after the start of infusion (deviation ±5 min). From Cycle 1 Day 8 onwards a single blood pressure measurement is to be performed prior to each infusion, 30 min after the start of infusion and at the end of each infusion (deviation of ± 5 min is allowed). The patient should rest for 5-10 min before blood pressure is recorded.

o Bone marrow biopsy is mandatory at Screening (biopsy done up to 28 days prior to first dose can be used as baseline evaluation) and to confirm the first complete response, if positive at baseline. Biopsy will be performed as per local standard of care.

p 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 be stopped or reduced to the allowed dose (less than 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 the baseline must be the same throughout the study. During treatment, tumor scans will be done with the same modality every 12 weeks during Year 1, every 16 weeks during Year 2, and every 24 weeks during Year 3. Time points for assessments are calculated from Cycle 1 Day 1. Tumor assessments must be performed within 14 days after the last dose (Day 15) and before the next dose (Day 1 of the subsequent cycle) starting from Cycle 3. 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. During Active follow-up period patients will have radiological assessments at same intervals as during treatment (time window of ±14 days is allowed) until PD is documented or new anti-tumor treatment is administered (see Section 7.1.2.3 and 7.3.2).

q FLymSI-18 questionnaire is to be completed on Cycle 1 Day 1 and every cycle thereafter (i.e. on Day 1 of Cycles 2, 3, 4 etc.), at the EOT visit and at the SFU visit in both treatment arms. Questionnaire should be self-administered by the patient via an ePRO at the start of the visit before the patient sees the physician. A PRO information sheet will be provided and completed by the study personnel at each visit at which the FLymSI-18 questionnaire is to be administered, regardless of whether or not the FLymSI-18 questionnaire is completed by the patient.

r PK sampling will be performed for copanlisib, its metabolite M-1 and other metabolites, if needed, in all patients on Cycle 1 Day 8: pre-infusion, 5 to 15 min, 55 min (or within 5 min prior to end of infusion) and 1.5 to 5 h after start of infusion. If sampling is not feasible at Cycle 1, samples may be collected at Cycle 2. A separate IV line should be used for PK draws.

s 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. 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) (see Section 7.6.1).

t Plasma for tumor genetics: blood samples will be collected on Cycle 1 Day 1 and at the EOT visit. 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. Samples are to be collected on Cycle 1 (Days 1, 8 and 15), Cycle 2 (Days 1, 8 and 15), and at the EOT visit.

v Whole blood for biomarkers will be collected on Cycle 1 Day 1 prior to drug administration (only from patients who provide a separate consent for genetic research).

w Only for patients affected by LPL/WM: Serum protein electrophoresis, immunofixation, serum quantitative IgM test and serum beta-2-microglobulin measurement will be performed at Screening. Serum or plasma viscosity will 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 will be performed on the days of tumor evaluation and at the EOT visit only if the last assessment is older than 4 weeks. If serum or plasma viscosity is abnormal at baseline, the measurement will be repeated every 3rd cycle starting from Day 1 of Cycle 3, and at the EOT visit.

x Laboratory tests prior to each infusion may be performed either the day before or on the planned date of infusion, with the exception of blood glucose (or capillary glucose sampling via glucose meter), which must be performed on the day of infusion. For dosing criteria, see Section 6.4.

y After Cycle 1, there are no mandatory procedures on Day 22 of subsequent cycles. Tumor assessments and related procedures marked for Day 22 will be done according to schedule specified in Section 7.1.2.3.

z The post-treatment follow-up 30-35 days after the last administration of study drug can be conducted via telephone if the patient is no longer being actively seen at the clinic or has started another therapy. In this case, FLymSI-18 questionnaire does not need to be completed at the SFU evaluation. Procedures marked with "(X)" are only to be performed, if clinically indicated.

aa 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 radiological 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.

bb 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 at least every 3 months (± 14 days), until death or until the end of the trial (up to 3 years after the last patient started study treatment), whichever comes first. Information to be recorded: date of contact, survival status, the first new anticancer regimen including response (if applicable), and date and cause of death (if applicable).

cc Written informed consent must be obtained prior to any study-specific procedures.Certain results from diagnostic testing performed as part of the standard of practice prior to the informed consent date and time may be used to fulfill screening criteria. This includes fresh tissue as noted in the protocol as well as results from CT/MRI scans, bone marrow sample, MUGA/echocardiogram and hepatitis testing which may also be used provided that they fall into the protocol-specified time window. Archival tissue obtained from the patients at any time during the course of their iNHL may also be used prior to the informed consent date and time if performed as part of the standard of practice. 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).

dd *Modified by amendment 1.*

13.1.2.30 Section 7.1.2 Timing of assessments

Old text:

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

New text:

All procedures during the treatment period should be done according to the relative days mentioned in this CSP. Deviations of -1 day and +2 days are acceptable with the exception of blood glucose (or capillary glucose sampling via glucose meter) and blood pressure measurement before study drug infusion.

13.1.2.31 Section 7.1.2.1 Screening period

Old text:

Screening examinations will ~~only~~ be performed after the patient has given written informed consent. The maximum interval allowed between signature of informed consent and start of treatment is 28 days.

Less than 28 days before the first administration of study drug:

- IVRS/IWRS transaction to register the patient in the system.
- Blood test for HBV and HCV: HBsAg, HBcAb and HCV IgG.
  (If HBsAg or HBcAb positive also HBV DNA; if HCV IgG positive also HCV RNA).
- Bone marrow biopsy: mandatory at Screening ~~(biopsy done up to 28 days prior to first dose can be used as baseline evaluation)~~ and to confirm the first complete response, if positive at baseline.
- IV contrast-enhanced CT/MRI of neck, chest, abdomen and pelvis. Corticosteroids must be stopped or reduced to the allowed dose (less than 15 mg of prednisone or equivalent) at least 7 days before performing the 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 evaluation.~~ The method chosen at the baseline must be the same throughout the study (see Section 7.3.2).
- Tumor tissue for central pathology review ~~and biomarker analysis (mandatory)~~ (see Section 7.6.1):
  - ~~Fresh tumor tissue (preferred) will be collected between Day -28 and Day -8 prior to the start of study treatment. Fresh tissue is recommended in patients with clinical suspicion of transformed disease. Detailed guidance on fresh biopsy sample preparation and storage will be provided to the sites.~~

- ~~Archival tumor tissue will be requested if fresh tissue is not available (the latest biopsy available should be provided). Archival 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 will be described in separate documents (e.g. Sample Handling Sheets or laboratory manual).~~

Less than 14 days before the first administration of study drug:

- Check inclusion and exclusion criteria (see Section 5.1).
- Complete medical and surgical history including demographics, relevant medical history findings, concomitant illnesses, allergy history, prior surgeries, most recent histology of tumor, most recent staging and grading of tumor, FLIPI score (for patients with FL), history of anticancer treatments (including type of treatment, type of response, date of response and date of subsequent relapse), presence of B symptoms, assessment of baseline toxicity and smoking history (see Section 7.2).
- ~~Serum beta-2-microglobulin.~~
- 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 AEs (see Section 7.5.1.3).

[...]

- Complete physical examination including ECOG performance status (see grading definitions in Appendix 14.3), NYHA classification (see Appendix 14.4), height, weight, vital signs (temperature, pulse and blood pressure), and a complete review of body systems ~~(including physical examination for lymphadenopathy, abdominal masses, or organomegaly)~~ (see Section 7.5.3.2).
- ~~12-lead ECG including QTcB and QTcF evaluation (see Section 7.5.3.4).~~
- ~~Multiple gated acquisition (MUGA) scan or echocardiogram to measure LVEF. The method chosen at Screening must be the same throughout the whole study (see Section 7.5.3.5).~~
- Only in patients affected by Lymphoplasmacytoid lymphoma/Waldenström macroglobulinemia (LPL/WM):
  - Serum protein electrophoresis.
  - Immunofixation.
  - Serum quantitative IgM test.
  - Serum or plasma viscosity (if hyperviscosity syndrome is suspected).

New text:

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 as noted in the protocol as well as results from CT/MRI scans, bone marrow sample, MUGA/echocardiogram and hepatitis testing which may also be used provided that they fall into the protocol-specified time window. Archival tissue obtained from the patients at any time during the course of their iNHL may also be used prior to the informed consent date and time if performed as part of the standard of practice. 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).

Less than 28 days before the first administration of study drug:

- IVRS/IWRS transaction to register the patient in the system.
- Blood test for HBV and HCV: HBsAg, HBcAb and HCV IgG.
  (If HBsAg or HBcAb positive also HBV DNA; if HCV IgG positive also HCV RNA).
- 12-lead ECG including QTcB and QTcF evaluation (see Section 7.5.3.4).
- Multiple gated acquisition (MUGA) scan or echocardiogram to measure LVEF. The method chosen at Screening must be the same throughout the whole study (see Section 7.5.3.5).
- Bone marrow biopsy: mandatory at Screening and to confirm the first complete response, if positive at baseline. Biopsy will be performed as per local standard of care.
- IV (and oral, if indicated, per Imaging Manual) contrast-enhanced CT/MRI of neck, chest, abdomen and pelvis (including WM patients). Corticosteroids must be stopped or reduced to the allowed dose (less than 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 the baseline must be the same throughout the study (see Section 7.3.2).
- 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).

Less than 14 days before the first administration of study drug:

- Check inclusion and exclusion criteria (see Section 5.1).
- Complete medical and surgical history including demographics, relevant medical history findings, concomitant illnesses, allergy history, prior surgeries, most recent histology of tumor, most recent staging and grading of tumor, FLIPI score (for patients with FL), history of anticancer treatments (including type of treatment, type of

response, date and duration of response and date of subsequent relapse), presence of B symptoms, assessment of baseline toxicity and smoking history (see Section 7.2).

- 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 AEs (see Section 7.5.1.3).

[...]

- Complete physical examination including ECOG performance status (see grading definitions in Appendix 14.3), NYHA classification (see Appendix 14.4), height, weight, vital signs (temperature, pulse and blood pressure), and a complete review of body systems (see Section 7.5.3.2).
- Only in patients affected by Lymphoplasmacytoid lymphoma/Waldenström macroglobulinemia (LPL/WM):
    - Serum protein electrophoresis.
    - Immunofixation.
    - Serum quantitative IgM test.
    - Serum beta-2-microglobulin.
    - Serum or plasma viscosity (if hyperviscosity syndrome is suspected).

13.1.2.32 Section 7.1.2.2 Treatment period

Old text:

The following assessments should be performed both in patients on double-blinded study treatment (copanlisib or placebo) as well as those who are randomized to placebo and change to copanlisib. After individual patient unblinding, patients receiving placebo who switch to open-label copanlisib will have all study assessments and timing reset to the initial schedule of study evaluations (i.e. as if the patient was restarting the study at Cycle 1 Day 1).

New text:

The following assessments should be performed both in patients on double-blinded study treatment (copanlisib or placebo) as well as those who are randomized to placebo and change to copanlisib. After individual patient unblinding, patients receiving placebo who switch to open-label copanlisib will have all study assessments and timing reset to the initial schedule of study evaluations (i.e. as if the patient was restarting the study at Cycle 1 Day 1). If not previously done within 7 days, patients switching to open-label copanlisib must complete the following within 7 days prior to the first dose of open-label copanlisib: UPCR measurement, GFR measurement, urinalysis, HbA1c, CBC, chemistry and coagulation panels. Dosing criteria outlined in Table 6–2 apply also for patients who switch to open-label treatment.

13.1.2.33 Section 7.1.2.2.1 Treatment – Cycle 1

Old text:

Cycle 1 Day 1

On Cycle 1 Day 1 patients should be fasting for at least 8 h prior to the ~~dose and until 2 h after completion of the infusion (see also Section 6.4). During the fasting period, patients may drink water and beverages with artificial sweeteners. Approximately 3 h after the start of the infusion, the patients should have a low carbohydrate meal. Their~~ pre-dose glucose level should be ≤ 125 mg/dL (non-diabetic patients) or < 160 mg/dL (diabetic patients).

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 a visit, before the patient sees the physician. To be completed by electronic patient-reported outcome (ePRO) device (see Section 7.6.2).

[...]

- Complete physical examination including ECOG performance status, NYHA classification, weight, vital signs (temperature, pulse and blood pressure), and complete review of body systems ~~(including physical examination for lymphadenopathy, abdominal masses, or organomegaly)~~ (see Section 7.5.3.2).
- ~~At centers with adequate facilities and equipment:~~ 12-lead ECG including QTcB and QTcF evaluation ~~will be recorded pre-infusion and at the end of infusion (C_{max}). A PK sample is to be drawn after each of these 12-lead ECG recordings~~ (see Section 7.5.3.4).
- Glucose measurement: on Cycle 1 Day 1 glucose will be measured at pre-dose~~,~~ and ~~3 h, 5 h, 6 h, and 8 h~~ after the start of ~~the~~ infusion. Additional measurements to be performed at the clinic as clinically indicated. The ~~first~~ pre-dose glucose sample on Cycle 1 Day 1 should be after an 8 h fasting (see Section 6.4).
- Home blood glucose monitoring: all patients.
- Training on glucose self-monitoring with a glucose meter, if needed.
- Blood pressure will be measured every 5-10 min prior to infusion of study drug (no more than 4 measurements) until there are 2 consecutive results < 150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. On Cycle 1 Day 1 blood pressure will be measured at 0 h (pre-dose), 30 min (mid-infusion), 60 min (end of infusion), 90 min, 2 h, 3 h, 4 h and 6 h after the start of infusion (deviation of ± 5 min is allowed). The patient should ~~lie down~~ for 5-10 min before blood pressure is recorded.
- ~~At centers with adequate facilities and equipment: PK sampling for copanlisib, its metabolite M-1 and other metabolites, if needed, will be performed after each 12-lead ECG recording pre- infusion and end of infusion (within 5 min prior to the end of infusion) (see Section 7.4)~~.

- Collection of blood for biomarker analyses prior to infusion (see Section 7.6.1):
  - Plasma for genetic ~~biomarker analysis~~.
  - Plasma for non-genetic biomarker analysis.

[...]

Cycle 1 Day 8

[...]

- Glucose test prior to and after study drug IV infusion (see Section 6.4).
- Review of the home blood glucose measurements/insulin administration, if applicable. Provide ~~strips~~ if necessary (see Section 6.4.2.1).
- Home blood glucose monitoring:
  - Diabetic patients: all patients.
  - Non-diabetic patients who experience ~~CTCAE Grade 3~~ hyperglycemia or require insulin administration.
- Blood pressure will be measured every 5-10 min prior to infusion of study drug (no more than 4 measurements) until there are 2 consecutive results < 150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. From Cycle 1 Day 8 onwards a single blood pressure measurement is to be performed prior to each infusion, 30 min after the start of infusion and at the end of each infusion. The patient should ~~lie down~~ for 5-10 min before blood pressure is recorded.
- PK sampling for copanlisib, its metabolite M-1 and other metabolites, if needed: pre-infusion, 5 to 15 min, 55 min (within 5 min prior to end of infusion) and 1.5 to 5 h after start of infusion (see Section 7.4).
- Collection of ~~blood~~ for non-genetic biomarker analyses prior to infusion (see Section 7.6.1).

[...]

Cycle 1 Day 15

[...]

- Glucose test prior to and after study drug IV infusion (see Section 6.4).
- Review of the home blood glucose measurements/insulin administration, if applicable. Provide ~~strips~~ if necessary (see Section 6.4.2.1).
- Home blood glucose monitoring:
  - Diabetic patients: all patients.

- Non-diabetic patients who experience ~~CTCAE Grade 3~~ hyperglycemia or require insulin administration.

- Blood pressure will be measured every 5-10 min prior to infusion of study drug (no more than 4 measurements) until there are 2 consecutive results < 150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. From Cycle 1 Day 8 onwards a single blood pressure measurement is to be performed prior to each infusion, 30 min after the start of infusion and at the end of each infusion. The patient should ~~lie down~~ for 5-10 min before blood pressure is recorded.
- Collection of ~~blood~~ for non-genetic biomarker analyses prior to infusion (see Section 7.6.1).

[...]

Cycle 1 Day 22

[...]

- Review of the home blood glucose measurements/insulin administration, if applicable. Provide ~~strips~~ if necessary (see Section 6.4.2.1).

~~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.~~

New text:

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. After pre-dose glucose measurement and approximately within 1 h before the start of study drug infusion patients can have a low carbohydrate breakfast. Patient's fasting pre-dose glucose level should be ≤ 125 mg/dL (non-diabetic patients) or < 160 mg/dL (diabetic patients) (see also 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): Patient completes the questionnaire at the start of a visit, before the patient sees the physician. To be completed by electronic patient-reported outcome (ePRO) device. A PRO information sheet will be provided and completed by the study personnel at each visit at which the FLymSI-18 questionnaire is to be administered, regardless of whether or not the FLymSI-18 questionnaire is completed by the patient (see Section 7.6.2).

[...]

- 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).
- Glucose measurement: on Cycle 1 Day 1 glucose will be measured at pre-dose and after the start of study drug infusion (post-infusion). For patients who had a low carbohydrate breakfast prior to the start of infusion, glucose monitoring will be up to 3 h post-infusion (1 h, 2 h and 3 h). For patients who did not have a low carbohydrate breakfast prior to infusion, monitoring will continue for up to 5 h post-infusion (1 h, 2 h and 5 h). Additional measurements to be performed at the clinic as clinically indicated. The pre-dose glucose sample on Cycle 1 Day 1 should be after an 8 h fasting (see Section 6.4).
- Home blood glucose monitoring:
  - Diabetic patients: all patients.
  - Non-diabetic patients who experience hyperglycemia > 250 mg/dL or require insulin administration.
- Training on glucose self-monitoring with a glucose meter, if needed. Patients will be provided with glucose meter and supplies (lancets, test strips and diary) to record glucose values and insulin doses, if applicable.
- Blood pressure will be measured every 5-10 min prior to infusion of study drug (no more than 4 measurements) until there are 2 consecutive results < 150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. On Cycle 1 Day 1 blood pressure will be measured at 0 h (pre-dose), 30 min (mid-infusion), 60 min (end of infusion), 90 min, 2 h, 3 h, 4 h and 6 h after the start of infusion (deviation of ± 5 min is allowed). The patient should rest for 5-10 min before blood pressure is recorded.
- Collection of blood for biomarker analyses prior to infusion (see Section 7.6.1):
  - Plasma for tumor genetics.
  - Plasma for non-genetic biomarker analysis.

[...]

- **Cycle 1 Day 8**

[...]

- Glucose test prior to and after study drug IV infusion. Patients are not required to be fasting prior to pre-dose glucose measurement (see Section 6.4).
- Review of the home blood glucose measurements/insulin administration, if applicable. Provide glucose monitoring supplies if necessary (see Section 6.4.2.1).
- Home blood glucose monitoring:
  - Diabetic patients: all patients.

- Non-diabetic patients who experience hyperglycemia > 250 mg/dL or require insulin administration.

- Blood pressure will be measured every 5-10 min prior to infusion of study drug (no more than 4 measurements) until there are 2 consecutive results < 150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. From Cycle 1 Day 8 onwards a single blood pressure measurement is to be performed prior to each infusion, 30 min after the start of infusion and at the end of each infusion (deviation of ± 5 min is allowed). The patient should rest for 5-10 min before blood pressure is recorded.
- PK sampling for copanlisib, its metabolite M-1 and other metabolites, if needed: pre-infusion, 5 to 15 min, 55 min (or within 5 min prior to end of infusion) and 1.5 to 5 h after start of infusion. If sampling is not feasible at Cycle 1, samples may be collected at Cycle 2. A separate IV line should be used for PK draws (see Section 7.4).
- Collection of plasma for non-genetic biomarker analyses prior to infusion (see Section 7.6.1).

[...]

- **Cycle 1 Day 15**

[...]

- Glucose test prior to and after study drug IV infusion. Patients are not required to be fasting prior to pre-dose glucose measurement (see Section 6.4).
- Review of the home blood glucose measurements/insulin administration, if applicable. Provide glucose monitoring supplies if necessary (see Section 6.4.2.1).
- Home blood glucose monitoring:
  - Diabetic patients: all patients.
  - Non-diabetic patients who experience hyperglycemia > 250 mg/dL or require insulin administration.
- Blood pressure will be measured every 5-10 min prior to infusion of study drug (no more than 4 measurements) until there are 2 consecutive results < 150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. From Cycle 1 Day 8 onwards a single blood pressure measurement is to be performed prior to each infusion, 30 min after the start of infusion and at the end of each infusion (deviation of ± 5 min is allowed). The patient should rest for 5-10 min before blood pressure is recorded.
- Collection of plasma for non-genetic biomarker analyses prior to infusion (see Section 7.6.1).

[...]

Cycle 1 Day 22

[...]

- Review of the home blood glucose measurements/insulin administration, if applicable. Provide glucose monitoring supplies if necessary (see Section 6.4.2.1).

13.1.2.34 Section 7.1.2.2.2 Treatment – Cycle 2 and higher

Old text:

Cycle 2 and higher, Day 1

- QoL questionnaire (FLymSI-18) on Day 1 of each cycle (i.e. on Day 1 of Cycles 2, 3, 4 etc.): at the start of a visit, before the patient sees the physician. To be completed by ePRO device (see Section 7.6.2).
- IVRS/IWRS transaction for medication dispensing.
- Serum pregnancy test: after Cycle 1 serum pregnancy test is mandatory at every cycle for France, Belgium, Canada and other countries where it is required by local regulations.
- Toxicity/AE assessment (see Section 7.5.1.3).

[...]

- Complete physical examination including ECOG performance status, NYHA classification, weight, vital signs (temperature, pulse and blood pressure), and complete review of body systems ~~(including physical examination for lymphadenopathy, abdominal masses, or organomegaly)~~ (see Section 7.5.3.2).
- 12-lead ECG including QTcB and QTcF evaluation ~~within 7 days prior to dosing~~ on Day 1 of every 3rd cycle (3, 6, 9 etc.) (see Section 7.5.3.4).

[...]

- Glucose test prior to and after study drug IV infusion (see Section 6.4).
- Review of the home capillary blood glucose measurements/insulin administration, if applicable. Provide ~~strips~~ if necessary (see Section 6.4.2.1).
- Home blood glucose monitoring:
    - Diabetic patients: all patients.
    - Non-diabetic patients who experience ~~CTCAE Grade 3~~ hyperglycemia or require insulin administration.

- Blood pressure will be measured every 5-10 min prior to infusion of study drug (no more than 4 measurements) until there are 2 consecutive results < 150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. From Cycle 1 Day 8 onwards a single blood pressure measurement is to be performed prior to each infusion, 30 min after the start of infusion and at the end of each infusion. The patient should ~~lie down~~ for 5-10 min before blood pressure is recorded.
- Collection of ~~blood~~ for biomarker analyses prior to infusion (see Section 7.6.1):
    - ~~Plasma for genetic biomarker analysis on Day 1 of every odd cycle (3, 5, 7 etc.) starting from Cycle 3.~~
    - ~~Plasma for non-genetic biomarker analysis.~~

[...]

Cycle 2 and higher, Day 8

[...]

- Glucose test prior to and after study drug IV infusion (see Section 6.4).
- Review of the home blood glucose measurements/insulin administration, if applicable. Provide ~~strips~~ if necessary (see Section 6.4.2.1).
- Home blood glucose monitoring:
    - Diabetic patients: all patients.
    - Non-diabetic patients who experience ~~CTCAE Grade 3~~ hyperglycemia or require insulin administration.
- Blood pressure will be measured every 5-10 min prior to infusion of study drug (no more than 4 measurements) until there are 2 consecutive results < 150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. From Cycle 1 Day 8 onwards a single blood pressure measurement is to be performed prior to each infusion, 30 min after the start of infusion and at the end of each infusion. The patient should ~~lie down~~ for 5-10 min before blood pressure is recorded.
- Only in Cycle 2: collection of ~~blood~~ for non-genetic biomarker analyses prior to infusion (see Section 7.6.1).

[...]

Cycle 2 and higher, Day 15

[...]

- ~~At centers with adequate facilities and equipment, 12-lead ECG including QTcB and QTcF evaluation will be recorded on Day 15 of every 3rd cycle (3, 6, 9 etc.) pre-~~

~~infusion and at the end of infusion (C_{max}). A PK sample is to be drawn after each of these 12-lead ECG recordings (see Section 7.5.3.4).~~

- On Cycle 2, blood tests for CBC and chemistry panel (excluding total cholesterol, LDL and triglycerides) will be performed. From Cycle 3 onwards, only hemoglobin, platelet and ANC counts will be performed prior to each infusion (see Section 6.4 and Section 7.5.3.1).
- Glucose test prior to and after study drug IV infusion (see Section 6.4).
- Review of the home blood glucose measurements/insulin administration, if applicable. Provide ~~strips~~ if necessary (see Section 6.4.2.1).
- Home blood glucose monitoring:
    - Diabetic patients: all patients.
    - Non-diabetic patients who experience ~~CTCAE Grade 3~~ hyperglycemia or require insulin administration.
- Blood pressure will be measured every 5-10 min prior to infusion of study drug (no more than 4 measurements) until there are 2 consecutive results < 150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. From Cycle 1 Day 8 onwards a single blood pressure measurement is to be performed prior to each infusion, 30 min after the start of infusion and at the end of each infusion. The patient should ~~lie down~~ for 5-10 min before blood pressure is recorded.
- ~~At centers with adequate facilities and equipment: PK sampling for copanlisib, its metabolite M-1 and other metabolites, if needed, will be performed on Day 15 of every 3rd cycle (3, 6, 9 etc.) after each 12-lead ECG recording pre- infusion and end of infusion (within 5 min prior to the end of infusion) (see Section 7.4).~~
- Only in Cycle 2: collection of ~~blood~~ for non-genetic biomarker analyses prior to infusion (see Section 7.6.1)
- Study drug IV infusion.

New text:

Cycle 2 and higher, Day 1

On Day 1 of each subsequent cycle, patients should be fasting for at least 8 h prior to the pre-dose glucose measurement. After pre-dose glucose measurement patients can have a low carbohydrate breakfast. Patient's fasting pre-dose glucose level should be < 160 mg/dL (fasting) or, in case of non-compliance with fasting requirements, < 200 mg/dL (non-fasting) (see also Section 6.4).

- QoL questionnaire (FLymSI-18) on Day 1 of each cycle (i.e. on Day 1 of Cycles 2, 3, 4 etc.): Patient completes the questionnaire at the start of a visit, before the patient sees the physician. To be completed by ePRO device (see Section 7.6.2).
- IVRS/IWRS transaction for medication dispensing.
- Serum pregnancy test: after Cycle 1 serum pregnancy test is mandatory at every cycle for France, Belgium, Canada and other countries where it is required by local regulations.
- GFR measurement (see Section 7.5.3.1 and Appendix 14.5).
- Toxicity/AE assessment (see Section 7.5.1.3).

[...]

- 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 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) (see Section 7.5.3.4).

[...]

- Glucose test prior to and after study drug IV infusion. The pre-dose glucose sample on Day 1 of each cycle should be after an 8 hour fasting (see Section 6.4).
- Review of the home blood glucose measurements/insulin administration, if applicable. Provide glucose monitoring supplies if necessary (see Section 6.4.2.1).
- Home blood glucose monitoring:
    - Diabetic patients: all patients.
    - Non-diabetic patients who experience hyperglycemia ≥ 250 mg/dL or require insulin administration.
- Blood pressure will be measured every 5-10 min prior to infusion of study drug (no more than 4 measurements) until there are 2 consecutive results < 150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. From Cycle 1 Day 8 onwards a single blood

pressure measurement is to be performed prior to each infusion, 30 min after the start of infusion and at the end of each infusion (deviation of ± 5 min is allowed). The patient should rest for 5-10 min before blood pressure is recorded.

- Only in Cycle 2: collection of plasma for non-genetic biomarker analyses prior to infusion (see Section 7.6.1).

[...]

- **Cycle 2 and higher, Day 8**

[...]

- Glucose test prior to and after study drug IV infusion. Patients are not required to be fasting prior to pre-dose glucose measurement (see Section 6.4).
- Review of the home blood glucose measurements/insulin administration, if applicable. Provide glucose monitoring supplies if necessary (see Section 6.4.2.1).
- Home blood glucose monitoring:
  - Diabetic patients: all patients.
  - Non-diabetic patients who experience hyperglycemia ≥ 250 mg/dL or require insulin administration.
- Blood pressure will be measured every 5-10 min prior to infusion of study drug (no more than 4 measurements) until there are 2 consecutive results < 150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. From Cycle 1 Day 8 onwards a single blood pressure measurement is to be performed prior to each infusion, 30 min after the start of infusion and at the end of each infusion (deviation of ± 5 min is allowed). The patient should rest for 5-10 min before blood pressure is recorded.
- Only in Cycle 2: Collection of plasma for non-genetic biomarker analyses prior to infusion (see Section 7.6.1).

[...]

Cycle 2 and higher, Day 15

[...]

- On Cycle 2, blood tests for CBC and chemistry panel (excluding total cholesterol, LDL and triglycerides) will be performed. From Cycle 3 onwards, only hemoglobin, platelet and ANC counts will be performed prior to each infusion (see Section 6.4 and Section 7.5.3.1).
- Glucose test prior to and after study drug IV infusion. Patients are not required to be fasting prior to pre-dose glucose measurement (see Section 6.4).
- Review of the home blood glucose measurements/insulin administration, if applicable. Provide glucose monitoring supplies if necessary (see Section 6.4.2.1).

- Home blood glucose monitoring:
    - Diabetic patients: all patients.
    - Non-diabetic patients who experience hyperglycemia ≥ 250 mg/dL or require insulin administration.
- Blood pressure will be measured every 5-10 min prior to infusion of study drug (no more than 4 measurements) until there are 2 consecutive results < 150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. From Cycle 1 Day 8 onwards a single blood pressure measurement is to be performed prior to each infusion, 30 min after the start of infusion and at the end of each infusion (deviation of ± 5 min is allowed). The patient should rest for 5-10 min before blood pressure is recorded.
- Only in Cycle 2: collection of plasma for non-genetic biomarker analyses prior to infusion (see Section 7.6.1).
- Study drug IV infusion.

Cycle 2 and higher, Day 22

After Cycle 1, there are no mandatory procedures on Day 22 of subsequent cycles. Tumor assessments and related procedures marked for Day 22 will be done according to schedule specified in Section 7.1.2.3.

13.1.2.35 Section 7.1.2.3 Tumor assessments

Old text:

~~7.1.2.2.3~~ Tumor assessments

Radiological tumor evaluations (IV contrast-enhanced CT/MRI scans of neck, chest, abdomen and pelvis) will be performed during the treatment period as well as during the Active follow-up period at the following intervals. ~~Deviation of ±7 days is allowed.~~ The method chosen at the baseline must be the same throughout the study (see also Section 7.3.2):

[...]

Bone marrow biopsy will be mandatory at baseline and if positive at Screening, will be repeated for confirmation of the first CR.

In addition, the following procedures will be performed on the days of tumor assessments:

- ~~Physical examination for lymphadenopathy, abdominal masses, or organomegaly.~~
- ~~Collection of B symptoms (fever above 38°C, night sweats, or weight loss of more than 10% in the previous 6 months).~~
- Only in patients affected by WM:

New text:

7.1.2.3 Tumor assessments (*changed to level 4 heading*)

Radiological tumor evaluations (IV [and oral, if indicated, per Imaging Manual] contrast-enhanced CT/MRI scans of neck, chest, abdomen and pelvis) will be performed during the treatment period as well as during the Active follow-up period at the following intervals. Time points for assessments are calculated from Cycle 1 Day 1. The method chosen at the baseline must be the same throughout the study (see also Section 7.3.2):

[...]

During treatment, tumor assessments must be performed within 14 days after the last dose (Day 15) and before the next dose (Day 1 of the subsequent cycle) starting from Cycle 3.

During Active follow-up, tumor assessments will be done until PD is documented or new anti-tumor treatment is administered. Time window of ±14 days is allowed for scheduling the visit for response assessment.

Bone marrow biopsy will be mandatory at baseline and if positive at Screening, will be repeated for confirmation of the first CR. Biopsy will be performed as per local standard of care.

In addition, the following procedures will be performed on the days of tumor assessments (deviation of ± 2 days is allowed):

- Only in patients affected by WM:

13.1.2.36 Section 7.1.2.4 End-of-treatment visit

Old text:

- QoL questionnaire (FLymSI-18): at the start of a visit, before the patient sees the physician. To be completed by ePRO device (see Section 7.6.2).

[...]

- Complete physical examination including ECOG performance status, NYHA classification, weight, vital signs (temperature, pulse and blood pressure), and complete review of body systems ~~(including physical examination for lymphadenopathy, abdominal masses, or organomegaly)~~ (see Section 7.5.3.2).

[...]

- MUGA scan or echocardiogram to measure LVEF. The method chosen at Screening must be the same throughout the whole study (see Section 7.5.3.5).

[...]

- Review of the home ~~capillary~~ blood glucose measurements/insulin administration, if applicable (see Section 6.4.2.1).

- IV 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).
- Collection of ~~blood~~ for genetic and non-genetic biomarker analyses (see Section 7.6.1).

New text:

- QoL questionnaire (FLymSI-18): Patient completes the questionnaire at the start of a visit, before the patient sees the physician. To be completed by ePRO device (see Section 7.6.2).

[...]

- 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)

[...]

- MUGA scan or echocardiogram to measure LVEF if not previously done within 4 weeks. The method chosen at Screening must be the same throughout the whole study (see Section 7.5.3.5).

[...]

- Review of the home blood glucose measurements/insulin administration, if applicable (see Section 6.4.2.1).
- 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).
- 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).
- Collection of plasma for tumor genetics and non-genetic biomarker analyses (see Section 7.6.1).

13.1.2.37 Section 7.1.2.5 Follow-up periods/Safety follow-up

Old text:

~~7.1.2.4~~ 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) SFU visit will take place **30-35 days after** the last administration of study drug. This visit includes:

QoL questionnaire (FLymSI-18): at the start of a visit, before the patient sees the physician. To be completed by ePRO device (see Section 7.6.2).

[...]

If a patient has begun treatment with another anticancer agent and is no longer being seen in the clinic, the post-treatment safety assessment can be conducted via telephone.

New text:

7.1.2.5 Follow-up periods (*new level 4 heading added*)

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).

7.1.2.5.1 Safety follow-up (*changed to level 5 heading*)

If a patient discontinues study treatment at any time during the study for any reason (except death or lost to follow-up) SFU visit will take place **30-35 days after** the last administration of study drug. This visit includes:

QoL questionnaire (FLymSI-18): Patient completes the questionnaire at the start of a visit, before the patient sees the physician. To be completed by ePRO device (see Section 7.6.2).

[...]

If a patient has begun treatment with another anticancer 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 SFU evaluation.

13.1.2.38 Section 7.1.2.5.3 Survival follow-up

Old text:

~~7.1.2.6~~ Survival follow-up

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

[...]

- Documentation of the first new anticancer treatment regimen, if given.

New text:

7.1.2.5.3 Survival follow-up (*changed to level 5 heading*)

All patients will be followed off study for overall survival at least at 3-month intervals during the Survival follow-up period (up to 3 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.

[...]

- Documentation of the first new anticancer treatment regimen including response, if given.

13.1.2.39 Section 7.2.2 Medical history

Old text:

- History of anticancer treatments (including type of treatment, type of response, date of response and date of subsequent relapse)

New text:

- History of anticancer treatments (including type of treatment, type of response, date and duration of response and date of subsequent relapse)

13.1.2.40 Section 7.3.2 Radiological tumor assessments

Old text:

Radiological tumor assessments with IV contrast-enhanced CT/MRI will include neck, chest, abdomen and pelvis, and will be evaluated locally at the study site and by the central independent blinded review.

The first radiological (IV contrast-enhanced CT/MRI) tumor assessment will be performed at Screening. Corticosteroids must be stopped or reduced to the allowed dose (less than 15 mg of prednisone or equivalent) at least 7 days before performing the CT/MRI (if a patient is on chronic corticosteroid therapy, corticosteroids should be de-escalated to the maximum allowed dose before the Screening). ~~Tumor scans done up to 28 days prior to first dose can be used as baseline.~~ The method chosen at the baseline must be the same throughout the study.

During the treatment phase as well as during the Active follow-up period, radiological (IV contrast-enhanced CT/MRI) tumor assessment will be performed every 12 weeks ~~(±7 days)~~ during Year 1, every 16 weeks ~~(±7 days)~~ during Year 2, and every 24 weeks ~~(±7 days)~~ during Year 3. 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 ~~Revised Response Criteria for Malignant Lymphoma (1). For patients with WM, additional criteria apply. Detailed instructions on tumor assessment are provided in Appendix 14.1.~~ As long as the patient has not experienced PD, investigator's assessment is sufficient for case management. In the event of progression, radiological real-time confirmation by central independent blinded evaluation is required before a final decision to stop the treatment is made. The final evaluation of treatment response (best response: ORR and CRR) will be done by central blinded review retrospectively.

Patients who experience PD on placebo treatment (per central independent blinded radiology review) can be offered open-label copanlisib upon discretion of the investigator and patient's consent. After individual patient unblinding, patients receiving placebo who switch to open-label copanlisib will have tumor assessments reset to the initial schedule as if the patient was restarting the study at Cycle 1 Day 1.

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 meet the standard of care for imaging of lesions in the respective organ system(s). If IV contrast-enhanced CT is medically contraindicated, sites may acquire contrast-enhanced MRI of the neck, abdomen and pelvis, and an unenhanced CT of the chest above lung apices to the bottom of the adrenals. Chest CT is preferred. If a patient develops contra-indication to any contrast medium during the study, the case examinations should be continued without contrast.

A prospective planned central image evaluation by independent radiology experts will be performed independent from the conduct of the clinical part of the study in order to facilitate an independent evaluation of efficacy in this study. The independent reviewers will be

experienced radiologists, who will not have been involved in the clinical part of the study and are considered independent from the study. They will be blinded to patient data (excluding those which are specified in the Independent Review Charter, e.g. for bone marrow biopsy, ~~presence of organomegaly, presence of B symptoms~~). The primary efficacy variable will be analyzed based on the assessment of the central image evaluation, as outlined in the imaging manual (or charter).

New text:

Radiological tumor assessments with IV (and oral, if indicated, per Imaging Manual) contrast-enhanced CT/MRI will include neck, chest, abdomen and pelvis, and will be evaluated locally at the study site and by the central independent blinded review.

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 (less than 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 the baseline must be the same throughout the study.

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 12 weeks during Year 1, every 16 weeks during Year 2, and every 24 weeks during Year 3 (see Section 7.1.2.3). 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.

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 (21). As long as the patient has not experienced PD, investigator's assessment is sufficient for case management. In the event of progression, radiological real-time confirmation by central independent blinded evaluation is required before a final decision to stop the treatment is made. In case of uncertain radiological disease progression the patient may stay on treatment at the investigator's discretion until progression is definitely confirmed on the subsequent tumor assessment. The final evaluation of treatment response (best response: ORR and CRR) will be done by central blinded review retrospectively.

For patients with WM, response assessment will be performed according to the Owen criteria (22). However, CT scan will be done and collected for all patients according to the schedule specified in the protocol. According to this guidance, disease progression can be confirmed based on laboratory parameters. In such case when PD was assessed by an investigator based on laboratory parameters alone, no independent confirmation of PD by central independent blinded review is necessary. Site must notify the sponsor about disease progression and follow procedures outlined in the protocol for patients on study and control arm respectively. For patients with WM who had measurable disease at baseline and had PD assessed based on

CT scan, scans must be submitted for review to confirm disease progression by central blinded review.

Detailed instructions on tumor assessment are provided in Appendix 14.1.

Patients who experience PD on placebo treatment (per central independent blinded radiology review) can be offered open-label copanlisib upon discretion of the investigator and patient's consent. After individual patient unblinding, patients receiving placebo who switch to open-label copanlisib will have tumor assessments reset to the initial schedule as if the patient was restarting the study at Cycle 1 Day 1. For further instructions please refer to the Imaging Manual.

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 meet the standard of care for imaging of lesions in the respective organ system(s). If IV (or oral) contrast-enhanced CT is medically contraindicated, sites may acquire contrast-enhanced MRI of the neck, abdomen and pelvis, and an unenhanced CT of the chest above lung apices to the bottom of the adrenals. Chest CT is preferred. If a patient develops contra-indication to any contrast medium during the study, the case examinations should be continued without contrast. In certain countries MRI should be used based on local regulations.

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

The independent reviewers will be experienced radiologists, who will not have been involved in the clinical part of the study and are considered independent from the study. They will be blinded to patient data (excluding those which are specified in the Independent Review Charter, e.g. for bone marrow biopsy). The primary efficacy variable will be analyzed based on the assessment of the central image evaluation, as outlined in the imaging manual (or charter).

13.1.2.41 Section 7.4 Pharmacokinetics / pharmacodynamics

Old text:

- Cycle 1 Day 8:
  Pre- infusion, 5 to 15 min, 55 min (within 5 min prior to end of infusion) and 1.5 to 5 h after start of infusion
  If sampling is not feasible at Cycle 1, samples may be collected at Cycle 2. A separate IV line should be used for PK draws.
- ~~At centers with adequate facilities and equipment: additional PK samples will be drawn after 12-lead ECG recordings at:~~

- ~~Cycle 1 Day 1:~~
  ~~Pre-infusion and end of infusion (within 5 min prior to the end of infusion).~~
- ~~Cycle 3, 6, 9 etc. Day 15 (every 3rd cycle):~~
  ~~Pre-infusion and end of infusion (within 5 min prior to the end of infusion).~~

Patients who experience PD on placebo treatment (per blinded central independent blinded radiology review) can be offered open-label copanlisib upon discretion of the investigator and patient's consent.

New text:

- Cycle 1 Day 8:
  Pre- infusion, 5 to 15 min, 55 min (or within 5 min prior to end of infusion) and 1.5 to 5 h after start of infusion
  If sampling is not feasible at Cycle 1, samples may be collected at Cycle 2. A separate IV line should be used for PK draws.

Patients who experience PD on placebo treatment (per blinded central independent blinded radiology review) can be offered open-label copanlisib upon discretion of the investigator and patient's consent.

13.1.2.42 Section 7.5.3 Further safety

Old text:

The following assessments should be performed both in patients on double-blinded study treatment (copanlisib or placebo) as well as those who are randomized to placebo and change to copanlisib. After individual patient unblinding, patients receiving placebo who switch to open-label copanlisib will have all study assessments and timing reset to the initial schedule of study evaluations (i.e. as if the patient was restarting the study at Cycle 1 Day 1).

New text:

The following assessments should be performed both in patients on double-blinded study treatment (copanlisib or placebo) as well as those who are randomized to placebo and change to copanlisib. After individual patient unblinding, patients receiving placebo who switch to open-label copanlisib will have all study assessments and timing reset to the initial schedule of study evaluations (i.e. as if the patient was restarting the study at Cycle 1 Day 1). If not previously done within 7 days, patients switching to open-label copanlisib must complete the following within 7 days prior to the first dose of open-label copanlisib: UPCR measurement, GFR measurement, urinalysis, HbA1c, CBC, chemistry and coagulation panels. Dosing criteria outlined in Table 6-2 apply also for patients who switch to open-label treatment.

13.1.2.43 Section 7.5.3.1 Laboratory

Old text:

All laboratory analyses will be performed locally. Dipsticks ~~will be provided to be used~~ for urinalysis.

[...]

- Complete chemistry panel: calcium, sodium, potassium, chloride, phosphorus, magnesium, bicarbonate (or carbon dioxide if bicarbonate is not routinely measured at the site), total protein, albumin, glucose, blood urea nitrogen (BUN) (or urea if BUN is not routinely measured at the site), serum creatinine (SCR), uric acid, total bilirubin, creatine phosphokinase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), lipase, amylase (or pancreatic amylase if total amylase is not routinely measured at the site), cholesterol (total, ~~high-density lipoprotein [HDL]~~, low-density lipoprotein [LDL]) and triglycerides.

[...]

- Urinalysis: ~~turbidity~~, blood cells, glucose, ketones, bilirubin, protein, and pH (dipstick).
  Additional microscopic examinations will be performed if clinically indicated.
- Quantification of proteinuria by UPCR on a random urine sample preferably taken at mid-morning. This should be reported as the ratio of concentrations of total urine protein (in mg/dl) to urine creatinine (in g/dl).

New text:

All laboratory analyses will be performed locally. Dipsticks <u>should be available</u> for urinalysis.

[...]

- Complete chemistry panel: calcium, sodium, potassium, chloride, phosphorus, magnesium, bicarbonate (or carbon dioxide if bicarbonate is not routinely measured at the site), total protein, albumin, glucose, blood urea nitrogen (BUN) (or urea if BUN is not routinely measured at the site), serum creatinine (SCR), uric acid, total bilirubin, creatine phosphokinase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), lipase, amylase (or pancreatic amylase if total amylase is not routinely measured at the site), cholesterol (total, low-density lipoprotein [LDL]) and triglycerides.

[...]

- Urinalysis: blood cells, glucose, ketones, bilirubin, protein, and pH (dipstick).
  Additional microscopic examinations will be performed if clinically indicated.
- Quantification of proteinuria by UPCR on a random urine sample preferably taken at mid-morning. This should be reported as the ratio of concentrations of total urine protein (in mg/dl) to urine creatinine (in <u>mg</u>/dl).

13.1.2.44 Section 7.5.3.2 Physical examinations

Old text:

New text:

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

13.1.2.45 Section 7.5.3.2.1 Complete physical examination

Old text:

~~Physical examinations will be performed according to the schedule summarized in the flow chart of Section 7.1~~ (*sentence transferred to 7.5.3.2*).

Complete physical examination includes ECOG performance status assessment (see grading definitions in Appendix 14.3), NYHA classification (see Appendix 14.4), height (only at Screening), weight, vital signs (see Section 7.5.3.3), and complete review of body systems ~~(including physical examination for lymphadenopathy, abdominal masses, or organomegaly).~~

New text:

Complete physical examination includes ECOG performance status assessment (see grading definitions in Appendix 14.3), NYHA classification (see Appendix 14.4), height (only at Screening), weight, vital signs (see Section 7.5.3.3), and complete review of body systems.

13.1.2.46 Section 7.5.3.3 Vital signs

Old text:

- Blood pressure will be measured every 5-10 min prior to infusion of study drug (no more than 4 measurements) until there are 2 consecutive results < 150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. The patient should ~~lie down~~ for 5-10 min before blood pressure is recorded.
    - At Cycle 1 Day 1 blood pressure will be measured at 0 h (pre-dose), 30 min (mid-infusion), 60 min (end of infusion), 90 min, 2 h, 3 h, 4 h and 6 h after the start of infusion (deviation ±5 min).

- From Cycle 1 Day 8 onwards a single blood pressure measurement is to be performed prior to each infusion, 30 min after the start of infusion and at the end of each infusion.

New text:

- Blood pressure will be measured every 5-10 min prior to infusion of study drug (no more than 4 measurements) until there are 2 consecutive results < 150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. The patient should rest for 5-10 min before blood pressure is recorded.
  - At Cycle 1 Day 1 blood pressure will be measured at 0 h (pre-dose), 30 min (mid-infusion), 60 min (end of infusion), 90 min, 2 h, 3 h, 4 h and 6 h after the start of infusion (deviation ±5 min).
  - From Cycle 1 Day 8 onwards a single blood pressure measurement is to be performed prior to each infusion, 30 min after the start of infusion and at the end of each infusion (deviation ±5 min).

13.1.2.47 Section 7.5.3.4 12-lead ECG

Old text:

The patient should ~~lie down~~ for 10 min before the ECG is recorded.

New text:

The patient should rest for 10 min before the ECG is recorded.

13.1.2.48 Section 7.6.1 Biomarker investigations

Old text:

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

1. Tumor-genetic research of fresh (preferred) or archival tumor tissue
2. Non-genetic biomarker testing
3. Genetic biomarker research

[...]

Collection and use of biomarker specimens

Tumor Tissue ~~(mandatory)~~:

- ~~Fresh tumor tissue (preferred) will be collected between Day -28 and Day -8 prior to the start of study treatment. Fresh tissue is recommended in patients with clinical suspicion of transformed disease. Detailed guidance on fresh biopsy sample preparation and storage will be provided to the sites.~~
- ~~A sample of archival tumor tissue will be requested during Screening if fresh tissue is not available (the latest biopsy available should be provided).~~ Archival formalin-fixed paraffin-embedded (FFPE) tissue may be supplied as a block (preferred) or as precut slides. Details on the preparation of slides and number of slides to be prepared 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). ~~This DNA evaluation may also be performed on the archival tumor tissue.~~

Plasma for 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 as a source of circulating tumor DNA for the evaluation of mutations in tumor-related genes of interest.

[...]

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

Patients who experience PD on placebo treatment (per blinded central independent blinded radiology review) can be offered open-label copanlisib upon discretion of the investigator and patient's consent. After individual patient unblinding, patients receiving placebo who switch to open-label copanlisib will have biomarker ~~assessments reset~~ to the initial schedule as if the patient was restarting the study at Cycle 1 Day 1.

New text:

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

1. Tumor-genetic research of fresh (preferred) or archival tumor tissue<u>, and possibly of circulating tumor DNA isolated from plasma</u>.
2. Non-genetic biomarker testing
3. Genetic biomarker research

[...]

Collection and use of biomarker specimens

Tumor Tissue:

Tumor tissue collection will be mandatory at Screening for central pathology review. Patients without historical material or fresh tissue biopsy will not be eligible for randomization.

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

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

A tumor biopsy is also encouraged at the time of progression (optional) to allow investigation of copanlisib resistance. 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 formalin-fixed paraffin-embedded (FFPE) tissue may be supplied as a block (preferred) or as precut slides. Details on the preparation of slides and number of slides to be prepared as well as detailed guidance on fresh biopsy sample preparation and storage will be described in separate documents (e.g. Sample Handling Sheets or laboratory manual).

All tumor tissues may be used as a source of RNA or protein for the study of gene and protein expression. The tumor tissue may 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 tumor genetics 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 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): On Cycle 1 Day 1, a whole blood sample will be obtained. The blood sample will be used as a source of DNA and gene products for the evaluation factors that are associated with the drug or the pathomechanisms of the disease. Results will be reported under separate cover, if the evaluations are performed.

Patients who experience PD on placebo treatment (per blinded central independent blinded radiology review) can be offered open-label copanlisib upon discretion of the investigator and patient's consent. After individual patient unblinding, patients receiving placebo who switch to open-label copanlisib will have biomarker plasma sampling analogous to the initial schedule as if the patient was restarting the study at Cycle 1 Day 1.

13.1.2.49 Section 7.6.2 Quality of life questionnaire

Old text:

The main purpose of the symptom assessment in this study is to describe any differences between the treatment groups in the time to deterioration in disease-related symptoms – physical (DRS-P) ≥ 3 points.

[...]

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

New text:

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

[...]

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

13.1.2.50 Section 7.6.3 Electronic patient-reported outcomes evaluation

Old text:

ePRO devices will be implemented in this study. They will be used to complete the FLymSI-18 questionnaire ~~and, if needed, may be used to collect data on home blood glucose measurements/insulin doses~~. A Site Manual will be provided to sites and each patient to help them understand how the ePRO devices work and how to use them correctly. If, for any reason, a device is not available at the site, or technical problems prevent it from working properly, a paper PRO questionnaire may be used.

New text:

ePRO devices will be implemented in this study. They will be used to complete the FLymSI-18 questionnaire. A Site Manual will be provided to sites and each patient to help them understand how the ePRO devices work and how to use them correctly. If, for any reason, a device is not available at the site, or technical problems prevent it from working properly, a paper PRO questionnaire may be used.

13.1.2.51 Section 7.7 Appropriateness of procedures / measurements

Old text:

The efficacy assessments used in this study include those considered standard of care to evaluate objective tumor response rate in patients with iNHL. ~~For patients affected by WM, in order to harmonize the response assessment allowing integration into the primary endpoint analysis, instead of using the Response Categories published by the VIth International Workshop on WM (26) it was decided to adapt the categorical response definitions only for complete response (CR), partial response (PR), stable disease, relapsed disease/disease progression (RD/PD) including the serum IgM response, and to eliminate the very good partial response (VGPR) and the minor response (MR) categories.~~

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

New text:

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 Lugano Classification (21) 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 agent 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.

13.1.2.52 Section 8.1 General considerations

Old text:

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 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 will be provided in the SAP that will be approved before database release.

New text:

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.

13.1.2.53 Section 8.3.1.2 Secondary efficacy variables

Old text:

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 the time of analysis of PFS) of complete response (CR) or partial response (PR) according to the ~~Revised Response Criteria for Malignant Lymphoma (1). F~~or patients with WM, ~~additional criteria apply~~. Detailed instructions on tumor assessment are provided in Appendix 14.1.

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

[...]

Time to deterioration in disease-related symptoms – physical (DRS-P) ≥ 3 points, as measured by the FLymSI-18 questionnaire. Patients will be considered as "censored" ~~on their last day of visit~~, 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 ~~on the day of dropout/progression.~~ Further sensitivity 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 ≥ 3 points decline 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.

New text:

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 the time of analysis of PFS) of complete response (CR) or partial response (PR) according to theLugano Classification (21), 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 (22). Detailed instructions on tumor assessment are provided in Appendix 14.1.

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.

[...]

Time to deterioration in disease-related symptoms – physical (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. Due to the symptom-related inclusion criteria (i.e. ECOG performance status ≤ 1), a worsening of symptoms can potentially occur in all patients. Therefore all patients will be included into this analysis.

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 subjects evaluated for improvement), plus 1 day.

Further sensitivity analyses for the DRS-P 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.

13.1.2.54 Section 8.3.1.3 Other efficacy variables

Old text:

- AUC across all data of FLymSI-18 DRS-P subscale score.

New text:

- PFS2 defined as the time (in days) from first PD after start of study treatment to second PD (both assessed by central review) or death from any cause (if no progression is documented). PFS2 will be evaluated only in placebo-treated patients who switched to open-label copanlisib treatment after first PD.
- AUC across all data of FLymSI-18 DRS-P subscale score.

13.1.2.55 Section 8.4.1 Population characteristics

Old text:

Demographics and baseline characteristics will be summarized by treatment and total population, using descriptive statistics and frequency tables as appropriate.

New text:

Demographics and baseline characteristics will be summarized by treatment and total population, using descriptive statistics and frequency tables as appropriate. In addition, the same summaries will be provided separately by FL and other iNHL subgroups.

13.1.2.56 Section 8.4.2 Efficacy

Old text:

All efficacy analyses will be performed when approximately ~~74~~ centrally evaluated PFS events are observed in the ~~study~~ (see Section 8.6). Evaluations from central blinded review will be used for the primary efficacy analyses of primary and secondary variables containing radiological tumor assessments. ~~All statistical tests will be one-sided, with a significance level of alpha = 0.01.~~

New text:

All efficacy analyses will be performed when approximately 82 centrally evaluated PFS events are observed in the FL subgroup (see Section 8.6). Evaluations from central blinded review will be used for the primary efficacy analyses of primary and secondary variables containing radiological tumor assessments.

The study-wise alpha of 1% will initially be split, according to the test strategy for this study (see Figure 8-1): with 80% * 1% = 0.8% assigned to the one-sided PFS test in the FL subgroup, and 20% * 1% = 0.2% to the one-sided PFS test in the total study population.

13.1.2.57 Section 8.4.2.1 Primary efficacy analysis

Old text:

Primary efficacy analysis

The primary efficacy variable is PFS as assessed by central review (for definition see Section 8.3.1.1). It will be evaluated whether PFS in copanlisib group is higher compared to PFS in the placebo group.

The following null hypothesis will be tested:

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

The alternative hypothesis will be:

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

$S_{Copanlisib}(t) \geq S_{Placebo}(t)$ for all time points $t \geq 0$,

where $S_{Copanlisib}$ denotes the survival function of the copanlisib group and $S_{Placebo}$ denotes the survival function of the placebo group.

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 $H_{0, PFS}$ ~~sufficient close approximation of~~ the one-sided log-rank test (~~27~~) to the normal distribution. If the z-value from the one-sided log-rank test (for the difference $S_{Copanlisib}$ - $S_{Placebo}$, stratified by the same factors as used for randomization) is larger than the critical quantile from the normal distribution ~~($z_{0.99} = 2.33$)~~, the null hypothesis will be rejected in favor of the alternative hypothesis.

Additional analyses of the primary efficacy variable

Kaplan-Meier estimates of median times to PFS (including 98% confidence interval) and Kaplan-Meier curves will be presented for each treatment group.

The hazard ratio (including 98% confidence interval) will be derived from ~~a~~ Cox proportional hazards model ~~and~~ stratified by the same factors as used for ~~randomization~~.

[...]

~~**Fixed sequence test hierarchy**~~

~~If the null hypothesis in the primary efficacy variable is rejected, a fixed sequence testing of the secondary efficacy variables ORR and time to ≥ 3 points deterioration in DRS-P subscale of FLymSI-18 will be performed.~~

~~In case of success in the primary efficacy variable, the first secondary endpoint being tested in this sequence will be ORR. If this succeeds, the next and last endpoint in the hierarchy will be the time to ≥ 3 points deterioration in DRS-P subscale of FlymSI-18. In case of the first non-successful p-value occurring, the hierarchical testing will stop. Further technical details of this sequence of tests will be included in the SAP.~~

~~OS, CRR, TTP as well as DOR will not be included into the testing hierarchy.~~

New text:

8.4.2.1 Primary efficacy analysis (*level 4 heading added*).

The primary efficacy variable is PFS as assessed by central review (for definition see Section 8.3.1.1). It will be evaluated whether PFS in the copanlisib group is higher compared to PFS in the placebo group for the total study population and separately for the FL subgroup.

The following null hypothesis will be tested:

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

The alternative hypothesis will be:

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

$S_{Copanlisib}(t) \geq S_{Placebo}(t)$ for all time points $t \geq 0$,

where $S_{Copanlisib}$ denotes the survival function of the copanlisib group and $S_{Placebo}$ denotes the survival function of the placebo group in the total study population or the FL subgroup, respectively.

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

According to the size of this study it is justified to assume that under $H_{0, PFS}$ the one-sided log-rank test (28) is a sufficiently close approximation to the normal distribution. If the z-value from the one-sided log-rank test (for the difference $S_{Copanlisib}$ - $S_{Placebo}$, stratified by the same factors as used for randomization: FL vs. other iNHL histology [in the test for total study population only], the time between last course of systemic anticancer therapy and most recent progression [≤ 6 months vs. > 6 months] and previous treatment with PI3K inhibitors [yes vs. no]) is larger than the respective critical quantile from the normal distribution (for FL subgroup: $z_{0.992} = 2.409$, for the total study population: $z_{0.998} = 2.878$), the null hypothesis will be rejected in favor of the alternative hypothesis.

Additional analyses of the primary efficacy variable

Kaplan-Meier estimates of median times to PFS (including 98% confidence interval) and Kaplan-Meier curves for the total study population and the FL subgroup will be presented for each treatment group.

The hazard ratio (including 98% confidence interval) will be derived for the total study population and separately for the FL subgroup from Cox proportional hazards models that are stratified by the same factors as used for the primary efficacy analysis.

13.1.2.58 Section 8.4.2.2 Secondary efficacy analysis

Old text:

Secondary efficacy analysis

OS will be analyzed using stratified log-rank tests similar to that for the primary variable, PFS. In addition, statistical methods to include the time after change to copanlisib by placebo patients in an analysis of OS will be investigated. Further details will be included in the SAP.

For variables other than OS, the data collected after the change from placebo to copanlisib will be summarized separately.

TTP, DOR ~~and~~ time to ~~decline~~ in DRS-P of ≥ 3 points will be analyzed using stratified log-rank tests similar to that for the primary variable, PFS.

~~ORR and~~ CRR will be analyzed using the Cochran-Mantel-Haenszel test~~,~~ adjusted for the same stratification factors as used for PFS.

New text:

8.4.2.2. Secondary efficacy analysis (*level 4 heading added*).

Depending on study success in the primary efficacy variable in the FL subgroup the secondary efficacy variables ORR, time to deterioration and time to improvement in DRS-P subscale of FLymSI-18 of at least 3 points will be tested hierarchically in the FL subgroup according to the multiple testing strategy outlined in Figure 8-1.

If the study shows success in all secondary endpoints in the FL subgroup and in the primary efficacy endpoint for the total study population, then the secondary efficacy endpoints ORR, time to deterioration and time to improvement in DRS-P subscale of FLymSI-18 of at least 3 points will also be tested hierarchically in the total study population.

Despite the initial split of study-wise alpha for the primary efficacy tests of PFS, the applied multiple test strategy includes the chance of so-called re-tests at full study-wise alpha-level of 1% in certain cases. The details are described in Section 8.4.2.3 below.

The ORR will be analyzed using the Cochran-Mantel-Haenszel test (29), stratified for the same stratification factors as used for PFS. The null hypothesis is defined as:

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

The alternative hypothesis will be:

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

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 twice the available significance level for the respective test and the estimated difference $ORR_{Copanlisib}$ - $ORR_{Placebo}$ (comparing copanlisib vs. placebo) 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 according to the testing strategy.

OS, CRR, TTP as well as DOR will not be included into the confirmatory testing strategy but analyzed supportively only.

OS will be analyzed using stratified log-rank tests similar to that for the primary variable, PFS. In addition, statistical methods to include the time after change to copanlisib by placebo patients in an analysis of OS will be investigated. Further details will be included in the SAP.

For variables other than OS, the data collected after the change from placebo to copanlisib will be summarized separately using descriptive statistics and frequency tables. Further details will be included in the SAP.

TTP, DOR, time to deterioration and time to improvement in DRS-P of at least 3 points will be analyzed using stratified log-rank tests similar to that for the primary variable, PFS.

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

13.1.2.59 Section 8.4.2.3 Confirmatory statistical testing strategy

Old text:

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 based on AUC. Total FLymSI-18 and subscales will be evaluated descriptively. Further details on PRO data analysis will be provided in the SAP.

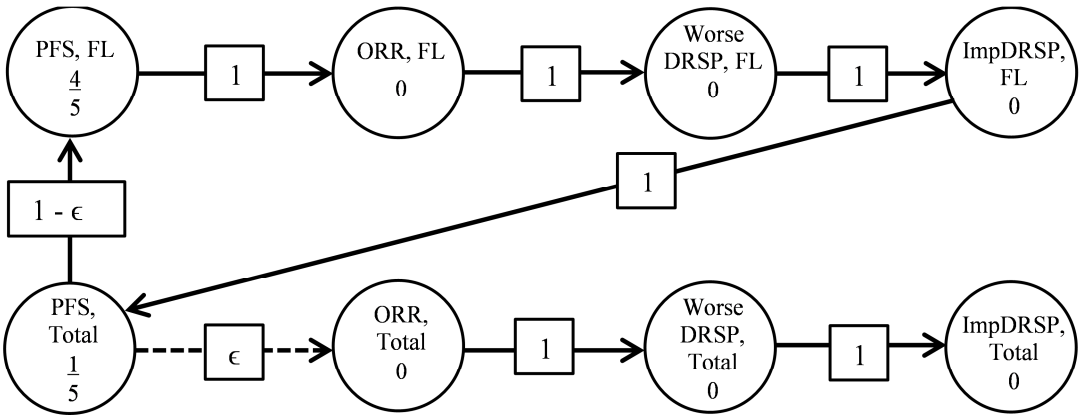
ECOG performance status will be summarized using descriptive statistics for the original score, as well as for the change from baseline score by treatment group.

New text:

8.4.2.3 Confirmatory statistical testing strategy (*level 4 heading added*)

A graphical summary of the testing strategy is displayed in Figure 8-1, using methodology as outlined in "A graphical approach to sequentially rejective multiple test procedures" (30). Package "gMCP" for the statistical software R has been used for display (31, 32).

Figure 8-1 Confirmatory statistical testing strategy



FL = follicular lymphoma; ImpDRSP = improvement in disease-related symptoms – physical; ORR = objective tumor response rate; PFS = progression-free survival; total = total study population; WorseDRSP = worsening of disease-related symptoms – physical.

Note: This design involving ε is a technical construct to potentially allow propagation of alpha to secondary endpoints in the total study population, in case all FL secondary endpoints can be rejected. The amount ε will be close to zero, and will be exactly defined in the SAP.

PFS is tested in parallel in the FL subgroup (tested at significance level of 0.8%), and in the total study population (tested at significance level of 0.2%).

The secondary endpoints in the FL subgroup and in the total study population, respectively, will only be tested if the test for the primary endpoint PFS is successful in the respective (sub-) population. A sequentially rejective multiple test procedure (30) will be used for the secondary efficacy endpoints in order to control the study-wise alpha level of 1%.

Tests on primary endpoint PFS in the FL subgroup and total study population

As the study is powered to show a success in the FL subgroup, the multiple testing strategy also reflects the priority of the FL subgroup by propagating alpha-level first to the FL subgroup. After a successful test in the FL subgroup, the alpha-level of 0.8% will be propagated to the secondary endpoints in the FL subgroup.

In case of a successful test of PFS in the total study population, the respective alpha-level of 0.2% will be propagated to the test hierarchy in the FL subgroup except for an amount ε (with ε close to zero). The remaining proportion ε of available alpha of 0.2% will be propagated to the secondary endpoints in the total study population.

Test hierarchy in secondary endpoints

The secondary endpoints are tested hierarchically both within the FL subgroup and the total study population.

Within each (sub-) group, ORR is tested first, followed by worsening in DRS-P, followed by improvement in DRS-P according to the pre-defined test sequence.

If both the primary and all secondary efficacy endpoints within the FL subgroup are tested successfully, the respective alpha-level is then finally propagated to the test sequence in the total study population. This means that for all practical purposes, the secondary endpoints for the total study population are only tested if all tests in the FL subgroup and the primary efficacy endpoint PFS in the total study population were successful.

Potential for re-tests

Therefore, re-tests at (practically) the full study-wise alpha level of 1% could occur, if either:

1. PFS test in the total study population is successful: Then the FL-related test hierarchy, starting from PFS in FL subgroup, can be re-tested at full alpha-level (except for the small ε part), or
2. Primary as well as all secondary assessments in the FL subgroup are successful: In this case, PFS and secondary efficacy hierarchy in the total study population can be tested at full alpha.

Other efficacy evaluations

PFS2 will be descriptively evaluated using Kaplan-Meier estimates for quantiles, including 98% two-sided confidence intervals.

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 both in the total study population and the FL subgroup based on AUC. Total FLymSI-18 and subscales will be evaluated descriptively. Further details on PRO data analysis will be provided in the SAP.

ECOG performance status will be summarized using descriptive statistics for the original score, as well as for the change from baseline score by treatment group in the total study population and in the FL subgroup.

13.1.2.60 Section 8.4.2.4 Subgroup analyses

Old text:

This section is not included in the original protocol.

New text:

Countries will be combined into regions as US vs. Europe vs. rest of world in order to defined 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.

As an efficacious result in the confirmatory multiple testing strategy in the FL subgroup could dominate the result for the total population, a pre-defined consistency assessment across iNHL subtypes will be pre-specified in the SAP.

13.1.2.61 Section 8.4.3 Safety

Old text:

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

New text:

Safety variables will be summarized by means of descriptive statistics and/or frequency tables as appropriate. Summaries will be given by treatment group and total. Summaries will be provided for the total study population and separately for the FL subgroup.

13.1.2.62 Section 8.6 Determination of sample size

Old text:

Sample size is based on the evaluation of the primary efficacy variable, PFS.

Copanlisib versus placebo treatment groups will be compared.

For the placebo arm, a median PFS of 6 months is assumed, whereas the copanlisib arm will be considered to have a median PFS of 14 months.

The study is planned to detect a 132% increase in median PFS in copanlisib versus placebo comparison (i.e. to detect a hazard ratio of 0.43), using a stratified log-rank test. ~~Statistical test is planned for 90% power and the alpha for the one-sided test is set to be 0.01.~~ Randomization ratio will be ~~1~~:1 between ~~the two treatment groups.~~

Using the software PASS 11, it was determined that this study can be evaluated after approximately ~~74~~ PFS events are observed.

To determine the number of patients required to reach this number of events, a drop-out rate of 20% (equally distributed among treatment arms and time), and an accrual time of 12 months (including 6 month ramp-up phase for study site openings) with a maximum of 10 month follow-up for last recruited patient was assumed.

PASS 11 calculations (assuming exponential distribution of events) resulted in a required number of ~~60~~ patients per group (total of ~~120~~ patients) for the study.

~~The required number of events is assumed to be reached after 22 months.~~

New text:

Sample size <u>estimation</u> is based on the evaluation of the primary efficacy variable, PFS, <u>in the primary subgroup of follicular lymphoma (FL). Study recruitment will be closed as soon as the required number of evaluable FL patients is reached.</u>

Copanlisib versus placebo treatment groups will be compared. <u>The stratification factor NHL histology (FL vs. other iNHL) will be used to derive two subgroups of patients. Superiority of the copanlisib arm over the placebo arm will be tested for the total study population and separately for the FL subgroup. A study-wise alpha level of 1% will be used to show superiority in the FL subgroup and/or the total study population.</u>

For the placebo arm, a median PFS of 6 months is assumed, whereas the copanlisib arm will be considered to have a median PFS of 14 months.

The study is planned to detect a 132% increase in median PFS in copanlisib versus placebo comparison (i.e. to detect a hazard ratio of 0.43), using a stratified log-rank test.

<u>Study-wise alpha level of 1% will be split in terms of the test strategy planned (see Figure 8-1), performing the one-sided primary efficacy test (and successive test hierarchy) with an initial alpha level of 0.8% for FL subgroup, and an initial alpha of 0.2% for the one-sided efficacy test in PFS for the total study population. Depending on the outcome of the primary efficacy tests, respective alpha will be propagated to further hypotheses in accordance with the planned test procedure.</u>

Randomization ratio will be 2:1 between copanlisib group and placebo group, respectively.

Sample size justification for primary efficacy test on PFS in FL patients

Using the software PASS 11 and with the above assumptions (especially alpha level of 0.8%), it was determined that this study can be evaluated after approximately 82 PFS events are observed in the FL subgroup to achieve a statistical power of 90% of observing a significant result in the primary efficacy test in the FL subgroup.

In case a re-test in the test strategy is possible, because the test of PFS in the total study population was significant at the 0.2% level, the power of showing success in PFS for FL patients would increase to 91.4%, which is not considered as an excessive overpowering.

To determine the number of FL patients required to reach this number of events, a drop-out rate of 20% (equally distributed among treatment arms and time), and an accrual time of 12 months (including 6 month ramp-up phase for study site openings) with a maximum of 10 month follow-up for last recruited patient was assumed.

PASS 11 calculations (assuming exponential distribution of events) resulted in a required number of patients per group: approximately 96 patients in the copanlisib monotherapy arm and approximately 48 patients in the placebo arm (total of 144 FL patients) for the study.

Sample size assumptions for other iNHL patients

Recruitment will be open to several types of iNHL patients. The size of the other iNHL subgroup is expected to reach between 20% and 25% of overall patients. Inclusion of these patients in addition to FL subgroup was encouraged by advice from EMA Scientific Advice Working Party to seek significance in FL subgroup, but to not exclude other subtypes. Assuming 23% of patients in the total population have other iNHL histologies, we expect ~45 other iNHL patients to also be included into the study.

The total study population will thus comprise approximately189 recruited patients.

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

Under comparable assumptions as for the FL subjects (but using alpha level of 0.2%), the power to detect a difference in PFS for the total study population will be 91.3%. In case the tests on primary and all secondary efficacy variables are significant in the FL subgroup, the total study population can be re-tested with the full study alpha of 1.0% in accordance with the test strategy. Under this assumption a power of 96.8% in the primary efficacy test for PFS in the total study population is achieved.

As an efficacious result in the FL subgroup could dominate the result for the total population, a pre-defined consistency assessment across iNHL subtypes will be pre-specified in the SAP.

13.1.2.63 Section 11.2 Patient information and consent

Old text:

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 ICF 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 ICF.

New text:

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

The ICF 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 ICF.

13.1.2.64 Section 12 Reference list

Old text:

~~Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25:579-86.~~

New text:

FDA approves Zydelig for three types of blood cancers. FDA news release, Silver Spring, MD, USA, July 23, 2014.

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.

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.

Bretz F, Maurer W, Brannath W, Posch M. A graphical approach to sequentially rejective multiple test procedures. Stat Med. 2009;28:586-604.

Bretz F, Posch M, Glimm E, Klinglmueller F, Maurer W, Rohmeyer K. Graphical approaches for multiple comparison procedures using weighted Bonferroni, Simes or parametric tests. Biometrical Journal. 2011;53:894-913.

Rohmeyer K, Klinglmueller F, Bomkamp B. gMCP: Graph Based Multiple Test Procedures, R package version 0.8-5.2013. Available from: http://CRAN.R-project.org/package=gMCP.

13.1.2.65 Section 14.1 Evaluation of tumor response

Old text:

Tumor response will be evaluated according to ~~Revised Criteria for Malignant Lymphoma.~~

	Target Lesions ~~(lymph node)~~	Target lesions ~~(hepatic/splenic)~~	Non target lesions	~~Organ enlargement~~	New lesion	Bone marrow	~~B symptoms~~
CR	All normal	All disappeared	All normal	Normal size	No	Normal *If not assessable:* *IHC negative*	~~No~~
PR	Decrease ≥ 50% in the SPD	Decrease ≥ 50% in the SPD	All normal or Stable	~~Normal size or~~ ~~Stable size~~	No	Not relevant	~~Not relevant~~
~~**Stable disease**~~	~~Increase < 50% or~~ decrease < 50% in the SPD	~~Increase < 50% or~~ decrease < 50% in the SPD	All Normal or Stable	Normal size or Stable size	No	Not relevant	~~Not relevant~~
~~**RD/PD**~~	~~Increase ≥ 50% in the SPD from nadir~~ ~~Increase ≥ 50% in the GTD of any single previously identified node with a short axis > 1 cm or, for nodes with short axis < 1 cm, increase ≥ 50% in the GTD to a final GTD > 1.5 cm~~	~~Increase ≥ 50% in the SPD from nadir~~ ~~Increase ≥ 50% in the GTD of any single previously identified nodule to a final size of at least 1.5 cm~~	New or increased	~~Increased size~~	Yes	Lymphoma infiltration (*new or % increased respect to baseline*)	~~Not relevant~~

CR = complete response; ~~GTD = greatest transverse diameter;~~ IHC = Immunohistochemistry; PD = progressive disease; PR = partial response; ~~RD = relapsed disease;~~ SPD = sum of the product of the diameters.
Source: (1)

~~Additional r~~response criteria in patients affected by Waldenstr~~o~~m macroglobulinemia (WM).

CR	Absence of serum monoclonal IgM by immunofixation ; normal serum IgM level and ~~negative~~ bone marrow
PR	~~At least 50% reduction of serum monoclonal IgM from baseline~~
~~RD~~/PD	~~At least 25% increase of serum monoclonal IgM from the lowest nadir~~
~~Stable Disease~~	~~A less than 50% reduction and less than 25% increase of serum monoclonal IgM from baseline~~

CR = complete response; IgM = immunoglobulin M; PD = disease progression; PR = partial response; RD = relapsed disease.
Source: Adapted from (26)

New text:

Tumor response will be evaluated according to Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification (21).

	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
SD	• 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)	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)	Lymphoma infiltration (new or % increased respect to baseline)

Target lesions (nodal)	Target lesions (extranodal)	Non-target lesions	Spleen	New lesion	Bone marrow

CR = complete response; IHC = Immunohistochemistry; LDi = longest diameter; PD = progressive disease; PPD = product of perpendicular diameters; PR = partial response; SD =stable disease; SDi = shortest diameter; SPD = sum of the product of the diameters

Response criteria in patients affected by Waldenström macroglobulinemia (WM):

CR	• Absence of serum monoclonal IgM by immunofixation AND normal serum IgM level • Complete resolution of extramedullary disease • Normal bone marrow
VGPR	• IgM M protein still detectable by immunofixation BUT ≥ 90% reduction in serum IgM level from baseline • Complete resolution of extramedullary disease • No new sings/symptoms of active disease
PR	• 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
MR	• 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
SD	• 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
PD	**After PR:** • ≥ 25% increase in serum IgM level from lowest nadir (an absolute value of 5 g/L is required if IgM level is the only criterion) OR • Progression in clinical features (signs/symptoms) attributable to disease **After CR:** • Reappearance of IgM M protein OR • Recurrence of bone marrow involvement, extramedullary disease, symptoms attributable to disease

CR = complete response; IgM = immunoglobulin M; MR = minor response; PD = progressive disease; PR = partial response; SD = stable disease; VGPR = very good partial response
Source: Adapted from (22).

13.1.2.66 Section 14.5 Glomerular filtration rate

Old text:

The formula is as follows:

GFR (mL/min/1.73m^2) = k x 186 x SCR$^{-1.154}$ x age$^{-0.203}$

where k = 1 (men) or 0.742 (women), GFR indicates glomerular filtration rate, and serum creatinine level (SCR) 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.

New text:

The formula is as follows:

GFR (mL/min/1.73m^2) = k x 186 x SCR$^{-1.154}$ x age$^{-0.203}$

where k = 1 (men) or 0.742 (women), GFR indicates glomerular filtration rate, and serum creatinine level (SCR) 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 IDMS.
<u>If standardized IDMS-traceable creatinine assay is used, please use the calculator provided in the following link: http://www.kidney.org/professionals/kdoqi/gfr_calculator.</u>

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

13.2 Amendment 3

Amendment 3 is a global amendment dated 16 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.

Sections affected by this modification: 1.1.2 Clinical experience, 1.3 Benefit-risk assessment

13.2.1.2 Modification 2 – clarification of rituximab-refractoriness assessment

Inclusion criterion related to rituximab-refractoriness was clarified. The modification was done because protocol did not provide clear guidance on how the refractoriness assessment should be done and some sites were not able to tell whether their patients would qualify as "refractory to rituximab".

Sections affected by this modification: Synopsis, 5.1.1 Inclusion criteria

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 contraception and pregnancy testing requirements

Text was added in the inclusion criteria 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.

13.2.1.5 Modification 5 – modification of inclusion criterion related to laboratory requirements

The times of ULN requirement for blood total bilirubin during the evaluation of patient's eligibility with proven Gilbert-Meulengracht syndrome were changed considering the study patient population with Gilbert-Meulengracht disease and due to feedback from the investigators.

Considering the copanlisib safety profile and the fact that serum lipase level alone is sufficient to diagnose pancreatitis, amylase was removed from the inclusion criterion since lipase is reported to have a higher sensitivity compared to amylase.

Inclusion criterion was updated to clarify that INR should be ≤ 1.5 at Screening. The modification was done because previous language (INR ≤ 1.5 x ULN) allowed patients with INR of 1.8 to be eligible.

Section affected by this modification: 5.1.1 Inclusion criteria.

13.2.1.6 Modification 6 – 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.

This exclusion criterion was also added to the synopsis as one of the main criteria for exclusion.

Sections affected by this modification: Synopsis, 5.1.2 Exclusion criteria

13.2.1.7 Modification 7 – 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

13.2.1.8 Modification 8 – clarification of exclusion criterion related to proteinuria

Exclusion criterion was modified to clarify that laboratory method used to assess proteinuria is not limited to UPCR only.

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, 6.4 Dosage and administration, 7.1.1 Tabulated overview, 7.1.2.1 Screening period, 7.1.2.2 Treatment period, 7.5.3 Further safety, 7.5.3.1 Laboratory

13.2.1.9 Modification 9 – language on corticosteroid therapy clarified

It was clarified in the protocol that previous corticosteroid therapy must be stopped or reduced to the allowed dose **at least** 7 days prior to the screening tumor scan. 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

13.2.1.10 Modification 10 – modification of exclusion criterion related to evidence of resistance to PI3K inhibitors

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

13.2.1.11 Modification 11 – 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

13.2.1.12 Modification 12 – detailed instructions on copanlisib handling and PK blood sampling removed

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 required volume of blood samples for PK analysis was removed from the protocol. Detailed instructions will be provided in the Laboratory Manual.

The rationale for the text deletions was to avoid future protocol amendments in case this language would need updating and to avoid the duplication of information that is already included in the Pharmacy Manual, Laboratory Manual or in the IB.

Sections affected by this modification: 6.2 Identity of study treatment, 7.4 Pharmacokinetics/ pharmacodynamics

13.2.1.13 Modification 13 – updated guidance for management and monitoring of glucose increases

An updated guidance for the management of transient glucose increases was provided to ensure the patient safety. These changes were made based on updated clinical data and the feedback from the investigators.

Changes include:

- Management of transient glucose increases should be based on persistent post-infusion blood glucose results.
- Additional guidance regarding meal timing was provided.
- An updated guidance on dose modification for transient glucose increases was provided.
- Additional information regarding glucose monitoring at home was provided.
- The withdrawal criterion "*CTCAE Grade 4 symptomatic hyperglycemia or glucose intolerance*" was revised to align with a new guidance for the transient glucose increases management.Appendix 14.7 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 from 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 study treatment, 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, 7.5.3.6 Glucose measurements on infusion days, Appendix 14.7 The average glycemic index of common foods derived from multiple studies by different laboratories

13.2.1.14 Modification 14 – 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 study treatment,

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

13.2.1.15 Modification 15 – 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

13.2.1.16 Modification 16 – clarification of laboratory criteria for patients who switch to open-label treatment

The language was changed to clarify that certain laboratory parameters as outlined in the exclusion and inclusion criteria need to be met for Day 1 of the first open-label cycle. For Day 1 of subsequent open-label cycles, dosing criteria outlined in Table 6–2 will apply. The purpose of the modification is to document that patients retain certain minimal levels of organ function to maximize their safety when switching to open label treatment.

Sections affected by this modification: 6.4 Dosage and administration, 7.1.1 Tabulated overview, 7.1.2.2 Treatment period, 7.5.3 Further safety

13.2.1.17 Modification 17 – dose modification guidance of study treatment for NIP modified

Guidance regarding differentiation between NIP and other pneumonitis was added to the protocol. The addition was made to get an unbiased analysis of the safety profile of copanlisib with regards to pneumonitis developed due to a potential hypersensitivity reaction to the copanlisib infusion.

The dose modification guidance of study treatment for NIP was modified: the re-occurrence of CTCAE pneumonitis of grade 3 will lead to permanent discontinuation of the study drug. This change was made to provide with the guidance how to manage the re-occurrence of CTCAE pneumonitis event of grade 3 to ensure patient safety.

Section affected by this modification: 6.4.1.2 Non-hematological toxicity

13.2.1.18 Modification 18 – clarification of tumor evaluation 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.

Clarification was done that CT/MRI scans need to be re-submitted with the new PID in case of re-screening.

Modifications were also done to harmonize the language across the protocol and with other copanlisib protocols, e.g. tumor assessment in patients with WM was added as a separate section and was also explained in more detail in synopsis and study design sections.

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 (21) 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 (21). 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, 5.2.1 Withdrawal, 7.1.1 Tabulated overview, 7.1.2.3 Tumor assessments, 7.3.2 Radiological tumor assessments, 7.3.3 Tumor assessments in patients with WM, 14.1 Evaluation of tumor response.

13.2.1.19 Modification 19 – 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 study treatment

13.2.1.20 Modification 20 – clarification of AE reporting language

The statement was added that death should generally not be recorded as an AE but as the outcome of underlying AE(s) instead. If death is reported without any associated AE (s), it should be reported as SAE. The statement was added for increased clarity and to ensure consistency in how deaths should be reported.

It was also emphasized that disease progression should be **clearly** mentioned on the SAE form as an alternative explanation in case disease progression leads to signs and symptoms that meet the criteria for seriousness.

Sections affected by this modification: 7.5.1.3 Assessments and documentation of adverse events, 7.5.1.4 Reporting of serious adverse events

13.2.1.21 Modification 21 – 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

13.2.1.22 Modification 22 – 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

13.2.1.23 Modification 23 – 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

13.2.1.24 Modification 24 – 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 from study treatment, 11.2 Patient information and consent

13.2.1.25 Modification 25 – other clarifications and corrections

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

- The sentence regarding the institution of DMC for this study was modified for further clarity.

- 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 criteria apply to anemia, neutrophil count decreased and platelet count decreased of CTCAE grade ≥ 3, not only for events of CTCAE grade 3.
- The symbol "≥" was added to dose modification Table 6–4 to ensure that dose modification guidance is provided for anemia of CTCAE grade ≥ 3. A footnote was added to the same table clarifying that treatment with transfusion or growth factors is allowed at the investigator's discretion.
- Clarification was added that also doses scheduled for Days 1 after Cycle 1 Day 1 may be delayed by up to 2 days (in addition to doses scheduled on Days 8 and 15 or each cycle).
- 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.
- It was clarified in the timing of assessment section that for the assessments scheduled for the treatment period, deviations of -1 day and +2 days are acceptable unless otherwise specified in the protocol.
- It was clarified 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: 3 Investigator and other study personnel, 4 Study design 6.4 Dosage and administration, 6.4.1.1 Hematological toxicity, 6.9.2 Permitted concomitant therapy, 7.1.1 Tabulated overview, 7.1.2 Timing of assessments, 7.1.2.1 Screening period

13.2.2 Changes to the protocol text

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. 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 typing errors or omissions are not highlighted in this amendment.

13.2.2.1 Synopsis

Old text:

Diagnosis and main criteria for inclusion	[…] Prior therapy must include rituximab and alkylating agent(s). Prior exposure to idelalisib or other PI3K inhibitors is acceptable provided that there is no resistance (*modified by amendment 1*). Patients must be refractory to the last rituximab-based treatment ~~(~~no response or response lasting < 6 months~~)~~. […] 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) (*changed by amendment 1*). […]
Main criteria for exclusion	[…] Known lymphomatous involvement of the central nervous system. Type I or II diabetes mellitus with HbA1c > 8.5% ~~or fasting plasma glucose > 160 mg/dL~~ at Screening. […] • Progression (PD) after any response (PR/CR) or after stable disease (SD) within 6 months from the ~~end~~ of the therapy with a PI3K inhibitor. Patients who discontinued treatment due to other reason than disease progression, and did not exhibit any signs of PD, will be allowed to enroll in this study after discussion with the sponsor.
Methodology	[…] The final evaluation of treatment response (best response: ORR and CRR) will be done by central blinded review retrospective~~ly~~.

New text:

Diagnosis and main criteria for inclusion	[…] Prior therapy must include rituximab and alkylating agent(s). Prior exposure to idelalisib or other PI3K inhibitors is acceptable (except to copanlisib) provided that there is no resistance (*modified by amendment 1*). Patients must be refractory to the last rituximab-based treatment, defined as no response or response lasting < 6 months after completion of treatment. Time interval to assess refractoriness will be calculated between the end date (last day) of the last rituximab-containing regimen and the day of diagnosis confirmation of the subsequent relapse. […]. 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 (*changed by amendment 1*). […]
Main criteria for exclusion	Known lymphomatous involvement of the central nervous system. Uncontrolled arterial hypertension despite optimal medical management (per investigator's assessment). Type I or II diabetes mellitus with HbA1c > 8.5% at Screening. […] • Progression (PD) after any response (PR/CR) or after stable disease (SD) within 6 months from the start of the therapy with a PI3K inhibitor. Patients who discontinued treatment due to other reason than disease progression, and did not exhibit any signs of PD, will be allowed to enroll in this study after discussion with the sponsor. Prior treatment with copanlisib.
Methodology	[…] The final evaluation of treatment response (best response: ORR and CRR) will be done by central blinded review and for those not undergoing PD-confirmation in retrospective setting. 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. However, in cases when WM patients will develop disease progression confirmed radiologically by presenting with measurable lesion(s) without simultaneous increase in IgM, the imaging scans should be submitted for central review and PD confirmation. WM patients who have radiologically measurable lesion at Screening will continue having radiological assessments and, in addition, will have laboratory tests performed on the

	same days. Bone marrow biopsy will be mandatory at Screening. If the baseline biopsy is positive for lymphoma infiltration, it will be mandatory to perform it again to confirm the first complete response (CR).

13.2.2.2 List of abbreviations

New abbreviations were added:

BP	Blood pressure
DPP4	Dipeptidyl peptidase-4
FSH	Follicle stimulating hormone
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
SGLT-2	Sodium/glucose co-transporter 2
WOCBP	Woman of childbearing potential

13.2.2.3 Section 1.1.2 Clinical experience

Old text:

Copanlisib is currently under investigation in various trials enrolling cancer patients. As of ~~30 NOV~~ 201~~3~~, approximately ~~240~~ patients with advanced cancer have been treated with copanlisib in ~~five different~~ Phase 1 ~~studies~~ and ~~one~~ Phase 2 ~~study~~.

As of ~~30 NOV~~ 201~~3~~, 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. ~~The~~ MTD ~~of copanlisib,~~ when administered intravenously (IV) over 1 h, on Days 1, 8 and 15 of every 28 days ~~given~~ as a single agent~~, was determined to be 0.8 mg/kg, with a maximum~~ dose of 65 mg in order to control copanlisib exposure in obese patients.

~~Preliminary efficacy data are available from~~ the NHL expansion cohort of Study 12871~~.~~ ~~A~~ total of 6 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. ~~All 6 patients with FL reached a partial response (PR).~~ As of ~~30 NOV~~ 201~~3~~, ~~2 patients with FL were still on treatment, both having an ongoing PR since 978 and 507 days, respectively. Two patients had disease progression (PD) after 281 and 447 days of treatment, and 2 patients withdrew from the study due to treatment-related AEs (interstitial pneumonitis at the end of Cycle 2 and persisting mucositis at Cycle 8).~~

~~Preliminary analysis of the 9 NHL patients showed that the most common treatment-emergent adverse events (TEAEs), irrespective of relationship to study drug and grade, occurring in~~

~~> 20% of the patients, were hyperglycemia (89%), nausea (78%), diarrhea (67%), hypokalemia (56%), any infection, rash and cough (44% each), fatigue, vomiting, hypertension, pruritus, mucositis and constipation (33% each), thrombocytopenia, decreased appetite, dehydration, dizziness, anxiety and pneumonitis (22% each). The most common study drug-related TEAEs that occurred in > 20% of the patients were hyperglycemia (89%), nausea (78%), diarrhea, hypertension, mucositis and fatigue (33.3% each), pneumonitis, rash, pruritus and thrombocytopenia (22% each).~~

[…]

~~In the ongoing study 16349 (part A)~~, a total of ~~67~~ patients with various indolent and aggressive lymphomas were treated at a starting dose of 0.8 mg/kg. 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 iNHL, 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. ~~At~~ the cut-off date ~~of 04 NOV 2013~~ the median duration of treatment was 4 cycles in the indolent group. The objective response rate (ORR) was ~~47~~% in FL, 38% in CLL, 100% in SLL and 67% in MZL (*paragraph updated by amendment 1*).

~~As of 04 NOV 2013, t~~he most frequent TEAEs, regardless of relationship to study drug, occurring in > 20% of the whole study population were hyperglycemia (~~62.7~~%), hypertension (~~61.2~~%), ~~fatigue (44.8%),~~ diarrhea (40.~~3~~%), nausea (3~~4.3~~%), ~~neutrophil count decreased (31.3%),~~ anemia (2~~6.9~~%~~), and oral mucositis (20.9%).~~ The two most common study drug-related TEAEs were hyperglycemia (~~61.2~~%) and hypertension (5~~8.2~~%). ~~A~~ total of ~~50~~ patients ~~(19~~ with indolent, and ~~31~~ with aggressive lymphomas~~)~~ discontinued the study treatment. Altogether ~~25.4% of~~ patients stopped treatment because of AEs. No conspicuous cluster of AEs causing treatment discontinuation emerged. Overall 1~~3~~ out of ~~67~~ patients received treatment with short-acting insulin (*paragraph updated by amendment 1*).

New text:

Copanlisib is currently under investigation in various trials enrolling cancer patients. As of 01 FEB 2015, approximately 377 patients with advanced cancer have been treated with copanlisib in Phase 1and Phase 2 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 given 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%).

[…]

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 iNHL, 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 (*paragraph updated by amendment 1*).

The most frequent TEAEs, regardless of relationship to study drug, occurring in > 20% of the whole study population were hyperglycemia (59.3%), hypertension (56.8%), diarrhea (40.7%), fatigue (35.8%), nausea (32.1%), neutropenia (28.4%) and anemia (27.2%). The two most common study drug-related TEAEs were hyperglycemia (56.8%) and hypertension

(53.1%). At the time of the cut-off, a total of 75 patients (92.6%), 30 with indolent, and 45 with aggressive lymphomas, had discontinued the study treatment. Altogether 20 patients (24.7%) stopped treatment because of AEs. No conspicuous cluster of AEs causing treatment discontinuation emerged. Overall 17 out of 81 patients received treatment with short-acting insulin (*paragraph updated by amendment 1*).

13.2.2.4 Section 1.3 Benefit-risk assessment

Old text:

[…]

Copanlisib has showed activity in patients with iNHL. In the Phase I study 12871 all 6 patients with FL responded (please see Section 1.1.2). In the Phase II study 16349 (part A), response rates in patients with iNHL of various histologies were: ~~47~~% in FL, 67% in MZL, and 100% in SLL. Responses included complete remissions. Patients with iNHL were heavily pretreated, with 82% having received ≥ 3, and 36% ≥ 5 lines of treatment prior to study start (*updated by amendment 1*).

New text:

[…]

Copanlisib has showed activity in patients with iNHL. In the Phase I study 12871 all 6 patients with FL responded (please see Section 1.1.2). In the Phase II study 16349 (part A), response rates in patients with iNHL of various histologies were: 40% in FL, 67% in MZL, and 100% in SLL. Responses included complete remissions. Patients with iNHL were heavily pretreated, with 82% having received ≥ 3, and 36% ≥ 5 lines of treatment prior to study start (*updated by amendment 1*).

13.2.2.5 Section 3 Investigator and other study personnel

Data Monitoring Committee

Old text:

[…]

A Data Monitoring Committee (DMC) will be established ~~which will closely interact with the sponsor's Global Pharmacovigilance (GPV) department~~ in order to ~~assess all safety-relevant information.~~

Data Monitoring Committee

New text:

[…]

A Data Monitoring Committee (DMC) will be established for this study (according to a separate DMC charter) in order to ensure ongoing safety of study patients.

13.2.2.6 Section 4 Study design

Old text:

Design overview

[…]

The start of the treatment period is defined by first administration of study drug (copanlisib or placebo). Copanlisib will be administered IV over 1 h at starting dose of 60 mg on Days 1, 8 and 15 of each 28-day treatment cycle.

[…]

The final evaluation of treatment response (best response: objective tumor response rate [ORR] and complete response rate [CRR]) will be done by central blinded review retrospective~~ly~~.

Bone marrow biopsy will be mandatory at Screening. Biopsies taken up to 28 days prior to treatment start are acceptable. If the baseline biopsy is positive for lymphoma infiltration, it will be mandatory to perform it again to confirm the first complete response (CR).

New text:

Design overview

[…]

The start of the treatment period is defined by first administration of study drug (copanlisib or placebo). Copanlisib will be administered IV over approximately 1 h at starting dose of 60 mg on Days 1, 8 and 15 of each 28-day treatment cycle.

[…]

The final evaluation of treatment response (best response: objective tumor response rate [ORR] and complete response rate [CRR]) will be done by central blinded review and for those not undergoing PD-confirmation in retrospective setting.

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. However, in cases when WM patients will develop disease progression confirmed radiologically by presenting with measurable lesion(s) without simultaneous increase in IgM, the imaging scans should be submitted for central review and PD confirmation. WM patients who have radiologically measurable lesion at Screening will

continue having radiological assessments and, in addition, will have laboratory tests performed on the same days.

Bone marrow biopsy will be mandatory at Screening. Biopsies taken up to 28 days prior to treatment start are acceptable. If the baseline biopsy is positive for lymphoma infiltration, it will be mandatory to perform it again to confirm the first complete response (CR).

13.2.2.7 Section 5.1.1 Inclusion criteria

Old text:

[…]

4. Prior therapy must include rituximab and alkylating agent(s). Prior exposure to idelalisib or other PI3K inhibitors is acceptable provided that there is no resistance (*modified by amendment 1*).
5. Patients must be refractory to the last rituximab-based treatment ~~(~~no response or response lasting < 6 months~~)~~.

[…]

7. 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) (*changed by amendment 1*).

[…]

12. Women of childbearing potential and men must agree to use ~~adequate~~ contraception when sexually active. This applies ~~since~~ signing of the ICF ~~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 recommend method (or combination of methods) as per standard of care.~~

[…]

- 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).

[…]

- ~~Amylase and l~~ipase ≤ 1.5 x the ULN.

[…]

- International normalized ratio (INR) and partial thromboplastin time (PTT) ≤ 1.5 x ULN.

New text:

[…]

4. Prior therapy must include rituximab and alkylating agent(s). Prior exposure to idelalisib or other PI3K inhibitors is acceptable (except to copanlisib) provided that there is no resistance (*modified by amendment 1*).
5. Patients must be refractory to the last rituximab-based treatment, defined as no response or response lasting < 6 months after completion of treatment. Time interval to assess refractoriness will be calculated between the end date (last day) of the last rituximab-containing regimen and the day of diagnosis confirmation of the subsequent relapse.

[…]

7. 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 (*changed by amendment 1*).

[…]

12. 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 ICF and 3 months 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.

[…]

- Total bilirubin ≤ 1.5 x ULN
  (≤ 5 x ULN for patients with proven Gilbert-Meulengracht syndrome or
  ≤ 3 x ULN for patients with cholestasis due to compressive adenopathies of the hepatic hilum).

[…]

- Lipase ≤ 1.5 x the ULN.

[…]

- International normalized ratio (INR) ≤ 1.5 and
  partial thromboplastin time (PTT) ≤ 1.5 x ULN.

13.2.2.8 Section 5.1.2 Exclusion criteria

Old text:

[…]

14. Uncontrolled arterial hypertension ~~(systolic blood pressure > 150 mmHg **or** diastolic blood pressure > 90 mmHg~~ despite optimal medical management).
15. Type I or II diabetes mellitus with HbA1c > 8.5% ~~**or** fasting plasma glucose > 160 mg/dL~~ at Screening.

[…]

24. Proteinuria as ~~measured~~ by urine protein~~/~~creatinine ratio (UPCR) > 3.5 on a random urine sample.

[…]

39. 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 7 days before performing the screening CT/MRI ~~and again prior to the first study drug administration~~. If a patient is on chronic corticosteroid therapy, corticosteroids should be de-escalated to the maximum allowed dose before the Screening. Patients may be using topical or inhaled corticosteroids.

[…]

45. Documented evidence of resistance to a prior treatment with idelalisib or other PI3K inhibitors defined as (*exclusion criterion added by amendment 1*):
    - No response (response defined as PR or CR) at any time during therapy, **or**
    - Progression (PD) after any response (PR/CR) or after stable disease (SD) within 6 months from the ~~end~~ of the therapy with a PI3K inhibitor.

      Patients who discontinued treatment due to other reason than disease progression, and did not exhibit any signs of PD, will be allowed to enroll in this study after discussion with the sponsor.

New text:

[…]

14. Uncontrolled arterial hypertension despite optimal medical management (per investigator's assessment).
15. Type I or II diabetes mellitus with HbA1c > 8.5% at Screening.

[…]

24. 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.

[…]

39. 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.

[…]

45. Documented evidence of resistance to a prior treatment with idelalisib or other PI3K inhibitors defined as (*exclusion criterion added by amendment 1*):
    - No response (response defined as PR or CR) at any time during therapy, **or**
    - Progression (PD) after any response (PR/CR) or after stable disease (SD) within 6 months from the start of the therapy with a PI3K inhibitor.

      Patients who discontinued treatment due to other reason than disease progression, and did not exhibit any signs of PD, will be allowed to enroll in this study after discussion with the sponsor.
46. Prior treatment with copanlisib.

13.2.2.9 Section 5.2.1 Withdrawal

Old text:

[…]

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.

New text:

[…]

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. CT/MRI scans need to be resubmitted with the new PID.

13.2.2.10 Section 5.2.1.1 Withdrawal from study treatment

Old text:

[…]

- Patients who withdraw consent from treatment will still participate in the Active or Survival follow-up unless they object to follow-up data collection. ~~In this case the patient has to expressively inform the investigator and sign the Declaration of Objection to the Collection of Study Data after Withdrawal of Consent. The objection is also valid, if the declaration is not in place for any reason, but the investigator documented the objection in the files.~~

[…]

- ~~CTCAE Grade 4 symptomatic hyperglycemia or glucose intolerance (*modified by amendment 1*).~~

New text:

[…]

- Patients who withdraw consent from treatment will still participate in the Active or Survival follow-up unless they object to follow-up data collection (see Section 11.2).

[…]

- Persistent occurrence of post-infusion blood glucose > 400 mg/dL based on laboratory analysis which occurred at the lowest study drug dose level despite optimal glucose lowering therapy (after at least one cycle of treatment) with consultation of a diabetes specialist (e.g. diabetologist or endocrinologist).
  Definition of persistent occurrence is based on repeated post-infusion blood glucose laboratory analysis taken at different time during the whole cycle of treatment.

13.2.2.11 Section 6.2 Identity of study treatment

Old text:

Copanlisib

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. ~~Reconstitution and dilution should be performed according to separate handling instructions specified in the Pharmacy Manual (*reference added by amendment 1*).~~

~~The lyophilisate in each vial is to be reconstituted with 3.0 mL of normal saline solution, resulting in a concentration of 20 mg/mL of BAY 80-6946, and the extractable volume of not less than 3.0 mL for the starting dose (60 mg). For a dose modification of 45 mg (dose level -1) the volume to be extracted is 2.25 mL, and for a dose modification of 30 mg (dose level -2) the volume to be extracted is 1.5 mL. The required amount of reconstituted solution is to be further diluted with saline solution according to handling instructions. The resulting solution contains the excipients (lyophilisate) of mannitol, sodium hydroxide (NaOH) and citric acid in addition to active substance.~~

~~The diluted solution is physically and chemically stable for 24 h at room temperature. However, for microbiological consideration, diluted solution should be stored between 2°C (36°F) and 8°C (46°F) if not administered immediately.~~

~~R~~efer to IB for copanlisib for more details regarding drug properties and formulation (*modified by amendment 1*).

New text:

Copanlisib

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 (*modified by amendment 1*).

13.2.2.12 Section 6.4 Dosage and administration

Old text:

Study drug (copanlisib or placebo) is administered in a normal saline solution, intravenously, over 1 h. ~~No intravenous glucose preparations should be administered on the days of infusion.~~ See Pharmacy Manual for additional details (*modified by amendment 1*).

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 and pre-dose glucose levels are presented in Table 6-1 (*table added by amendment 1*).

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

Period	Fasting ≥ 8 h required before first glucose measurement	Pre-dose glucose levels	Fasting required before study drug infusion
Day 1 of cycle 1	Yes	≤125 mg/dL (non-diabetic patients) <160 mg/dL (diabetic patients)	~~No~~ [a]
Day 1 of subsequent cycles	Yes	<160 mg/dL (fasting) < 200 mg/dL (non-fasting) [c]	~~No~~ [b]
Days 8 and 15 of each cycle	No	<160 mg/dL (fasting) <200 mg/dL (non-fasting)	~~No~~ [b]

a: ~~Within 1 h before the start of study drug infusion patients may have a low carbohydrate breakfast (e.g. eggs, cheese, plain yoghurt, vegetables, meat).~~
b: ~~Patients may have a low carbohydrate breakfast (e.g. eggs, cheese, plain yoghurt, vegetables, meat) at any time after pre-dose glucose measurement.~~
c: In case of non-compliance with the fasting requirement.

The investigator will accurately document fasting/non-fasting for each glucose measurement done at the site. Fasting ~~for this purpose~~ refers to a ≥ 8 h fast. (*fasting requirements changed by amendment 1*).

From Cycle 1 Day 1 onwards, glucose measurements at the site may be done either by laboratory analysis or in capillary blood using a handheld glucose meter. If handheld glucose meters are chosen, the appropriate calibration of glucose meters will be documented.

Patients will continue study treatment until PD (per central independent blinded radiology review) or they meet the criteria described in Section 5.2.

[…]

If not previously done within 7 days, patients switching to open-label copanlisib must complete the following within 7 days prior to the first dose of open-label copanlisib: UPCR ~~measurement~~, GFR measurement, urinalysis, HbA1c, CBC, chemistry and coagulation panels ~~D~~dosing criteria outlined in Table 6-2 apply ~~also~~ for patients who switch to open-label treatment.

[…]

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 day of infusion, with the exception of blood glucose, which must be performed on the day of infusion. All laboratory results must be assessed by the investigator prior to administration of planned dose. On Day 1 of each subsequent cycle, the dose of study drug will be given only if the laboratory test criteria described in Table 6-2 are met.

[…]

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

- CTCAE Grade 3 neutrophil count decreased (ANC < 1,000/mm^3)
- CTCAE Grade 3 platelet count decreased (platelets < 50,000/mm^3)
- CTCAE Grade 3 anemia (hemoglobin < 8 g/dL)

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 study drugs is 5 days.

New text:

Study drug (copanlisib or placebo) is administered in a normal saline solution, intravenously, over approximately 1 h. See Pharmacy Manual for additional details (*modified by amendment 1*). 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 and pre-dose glucose levels are presented in Table 6-1 (*table added by amendment 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)	Fasting required before study drug infusion
Day 1 of cycle 1	Yes	≤125 mg/dL (non-diabetic patients) <160 mg/dL (diabetic patients)	Yes [a]
Day 1 of subsequent cycles	Yes	<160 mg/dL (fasting) < 200 mg/dL (non-fasting) [c]	Conditional [a, b, d]
Days 8 and 15 of each cycle	No	<160 mg/dL (fasting) <200 mg/dL (non-fasting)	Conditional [a, b, d]

a: Diabetic patients who take insulin treatment at any cycle visit: Timing and content of caloric intake on infusion days will be managed and monitored by the investigator. Consultation with treating physician or diabetes specialist 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 (see text below "Recommendations on meal timing on infusion days" for further details).
c: In case of non-compliance with the fasting requirement.
d: A low glycemic index meal may be taken at least 4 h before the start of the study drug infusion for patients who have their infusions scheduled at a later hour, or due to their age or medical condition when fasting prior to infusion is not viable.

The investigator will accurately document fasting/non-fasting for each glucose measurement done at the site.

- Fasting refers to a ≥ 8 h fast. (*fasting requirements changed by amendment 1*).
- 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 using a handheld glucose meter. If handheld glucose meters are chosen, the appropriate calibration of glucose meters will be documented.

Any capillary or plasma glucose levels > 250 mg/dL should be confirmed by repeated laboratory analysis.

Recommendations on meal timing on infusion days

Because of inhibitory effect on PI3K α-isoform, which is implicated in insulin metabolism, copanlisib infusions could be associated with temporarily increase in blood glucose. Addition of meal in close proximity to study drug infusion may exacerbate glucose increase. It is recommended that timing and content of caloric intake on infusion days is managed and monitored by the investigators. Consultation with treating physician or diabetes specialist (e.g. diabetologist or endocrinologist) is advised.

The investigator will review the glucose profile during and post the study drug infusions.

The investigator may manage the timing of post-infusion meals based on the glucose profile during prior infusion(s) to minimize glucose increases. This is in addition to glucose lowering medication. Low glycemic index meals (see Appendix 14.7) should be provided for patients who are kept in clinic for continued observation.

A low glycemic index diet is recommended for the first 48 h after study drug infusion. However, caloric restriction is not intended for the population under study.

All glucose measurements, oral glucose lowering medication and/or insulin administration, if applicable, and meal timing will be collected as part of the clinical source documentation.

Note: Caloric intake and timing recommendations for diabetic patients who require insulin treatment prior to the infusion at any cycle visit should be managed and monitored by the investigator based on consultation with treating physician or diabetes specialist.

- **On infusion days at any cycle:**

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

  Note: If patient needs to take a low glycemic meal, then glucose test should be taken prior to meal intake and at 1 h and 2 h after the meal (see Section 7.5.3.6).

- **Cycle 1 Day 1:**

  Fasting is required before start of infusion.

  A low glycemic index meal (see Appendix 14.7) may be taken 3 h after start of infusion.

- **Day 1 of each subsequent cycle after Cycle 1 Day 1:**

  Fasting is required before the first glucose measurement.

  After Cycle 1, a low glycemic index meal may be taken at least 4 h before the start of the study drug infusion for patients who have their infusions scheduled at a later hour, or due to their age or medical condition when fasting prior to infusion is not viable.

- **Day 8 and Day 15 of each cycle:**

  Fasting is not required before start of infusion.

  A low glycemic index meal may be taken at least 4 h before the start of the study drug infusion for patients who have their infusions scheduled at a later hour, or due to their age or medical condition when fasting prior to infusion is not viable.

Patients will continue study treatment until PD (per central independent blinded radiology review) or they meet the criteria described in Section 5.2.

[…]

If not previously done within 7 days, patients switching to open-label copanlisib must complete the following within 7 days prior to the first dose of open-label copanlisib: UPCR/24 h total urine protein quantification, GFR measurement, urinalysis, HbA1c, CBC, chemistry and coagulation panels. For Day 1 of the first open-label cycle, laboratory

parameters as outlined in inclusion criterion 13 and exclusion criteria 15 and 24 will apply. For Day 1 of subsequent open-label cycles, dosing criteria outlined in Table 6-2 will apply for patients who switch to open-label treatment.

[…]

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 day of infusion, with the exception of blood glucose, which must be performed on the day of infusion. All laboratory results must be assessed by the investigator and/or appropriate site personnel prior to administration of planned dose. On Day 1 of each subsequent cycle, the dose of study drug will be given only if the laboratory test criteria described in Table 6-2 are met.

[…]

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

- CTCAE Grade ≥ 3 neutrophil count decreased (ANC < 1,000/mm^3)
- CTCAE Grade ≥ 3 platelet count decreased (platelets < 50,000/mm^3)
- CTCAE Grade ≥ 3 anemia (hemoglobin < 8 g/dL)

Doses scheduled for Days 1 (after Cycle 1 Day 1), 8 and 15 may be delayed by up to 2 days. A delay of more than 2 days will be considered a missed dose. Missed doses will not be replaced. The minimum interval needed between two infusions of study drugs is 5 days.

13.2.2.13 Section 6.4.1 Dose modification

Old text:

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 trials: e.g., ~~hyperglycemia and arterial hypertension~~. Based on this knowledge the investigator may decide on the necessary dose modifications. If the dose is reduced or interrupted, the investigator's decision is to be clearly documented in the patient's records and in the eCRF.

New text:

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 trials: e.g., transient increases in glucose and blood pressure. Based on this knowledge the investigator may decide on the necessary dose modifications. If the dose is reduced or interrupted, the investigator's decision is to be clearly documented in the patient's records and in the eCRF.

13.2.2.14 Section 6.4.1.1 Hematological toxicity

Old text:

[…]

Table 6-4 Dose modification of study treatment for hematological toxicity

Note: This table should not be used to determine patient eligibility for infusion on days 1, 8 and 15. Please follow specific guidance given for laboratory test criteria on days 1, 8 and 15 (*note added by amendment 1*)

Hematological toxicity of CTCAE Grade (any of the following)	Study drug action (for all toxicities)
• Grade 4 thrombocytopenia (platelet < 25,000/mm^3) or Grade 3 (platelet < 50,000/mm^3) with bleeding. • Febrile neutropenia. • Grade 4 neutropenia (ANC < 500/mm^3).[a] • INR or PTT of Grade ≥ 3 with bleeding. • Grade 3 anemia (Hb < 8 g/dL).	Delay infusion until criteria displayed in Table 6-2 are met. 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 study treatment permanently. The lowest dose level is 30 mg.

[…]

[a]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.

New text:

[…]

Table 6-4 Dose modification of study treatment for hematological toxicity

Note: This table should not be used to determine patient eligibility for infusion on days 1, 8 and 15. Please follow specific guidance given for laboratory test criteria on days 1, 8 and 15 (*note added by amendment 1*)

Hematological toxicity of CTCAE Grade (any of the following)	Study drug action (for all toxicities)
• Grade 4 thrombocytopenia (platelet < 25,000/mm^3) or Grade 3 (platelet < 50,000/mm^3) with bleeding. • Febrile neutropenia. • Grade 4 neutropenia (ANC < 500/mm^3).[a] • INR or PTT of Grade ≥ 3 with bleeding. • Grade ≥ 3 anemia (Hb < 8 g/dL).	Delay infusion until criteria displayed in Table 6-2 are met.[c] 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 study treatment permanently. The lowest dose level is 30 mg.

[…]

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

13.2.2.15 Section 6.4.1.2 Non-hematological toxicity

Old text:

Dose modifications for non-hematologic toxicities except ~~hyperglycemia~~, dermatologic toxicity, NIP and arterial hypertension are outlined in Table 6-5.

Table 6-5 Dose modification of study treatment for non-hematological toxicity (except ~~hyperglycemia~~, dermatologic toxicity, non-infectious pneumonitis and arterial hypertension)

[…]

[…]

Non-infectious pneumonitis

In the event of NIP, an adjustment as described in Table 6-7 must be applied.

Table 6-7 Dose modification of study treatment for non-infectious pneumonitis (NIP)

	Study drug action	
Suspected or confirmed NIP of CTCAE	**For current course of therapy**	**Re-initiation of study drug (if recovered within 14 days)**
Grade 1	No change	Not applicable
Grade 2	Interruption	Decrease by one dose level[a]
Grade 2 re-occurrence	Permanent discontinuation	No
Grade 3	Interruption	Case by case decision (after consulting the sponsor)
Grade 4	Permanent discontinuation	No

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 meets criteria for further dose decrease, study treatment will be discontinued permanently.

Pneumonitis is to be reported as such only in the event of NIP.

~~Hyperglycemia~~ and arterial hypertension

~~a) Hyperglycemia~~

Section modified by amendment 1.

Patients who develop transient post-infusion ~~hyperglycemia (~~glucose ~~intolerance) of~~ > 250 mg/dL after study drug 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 ~~treatment~~ of ~~hyperglycemia~~ are given in Section 6.4.2.1.

~~A dose reduction of study drug by one dose level is mandatory in the event of asymptomatic hyperglycemia > 500 mg/dL. No further dose reductions will be allowed in the event of re-occurrence of asymptomatic hyperglycemia > 500 mg/dL and the treatment will be permanently discontinued.~~

~~If CTCAE Grade 4 glucose intolerance occurs, permanent discontinuation of the study drug is mandatory.~~

b) Arterial hypertension

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 study drug administrations may be reduced by 1 or 2 dose levels at the investigator's discretion. Guidelines for the treatment of ~~arterial hypertension~~ are given in Section 6.4.2.3. Patients with a ~~post-dose~~ blood pressure of CTCAE Grade 4~~, i.e., a post-dose blood pressure that may have life-threatening consequences (e.g., malignant arterial hypertension, transient or permanent neurologic deficit, hypertensive crisis), or patients who require urgent intervention,~~ must permanently discontinue the study drug.

New text:

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

Table 6-5 Dose modification of study treatment for non-hematological toxicity (except glucose increases, dermatologic toxicity, non-infectious pneumonitis and arterial hypertension)

[…]

[…]

Non-infectious pneumonitis

In the event of NIP, an adjustment as described in Table 6-7 must be applied.

Table 6-7 Dose modification of study treatment for non-infectious pneumonitis (NIP)

	Study drug action	
Suspected or confirmed NIP of CTCAE	**For current course of therapy**	**Re-initiation of study drug (if recovered within 14 days)**
Grade 1	No change	Not applicable
Grade 2	Interruption	Decrease by one dose level[a]
Grade 2 re-occurrence	Permanent discontinuation	No
Grade 3	Interruption	Case by case decision (after consulting the sponsor)
Grade 3 re-occurrence	Permanent discontinuation	No
Grade 4	Permanent discontinuation	No

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

Glucose increases and arterial hypertension

a) Glucose increases

Section modified by amendment 1.

Patients who develop transient post-infusion glucose > 250 mg/dL after study drug 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 > 400 mg/dL based on repeated laboratory analysis despite optimal glucose lowering therapy after 2 infusions of study drug will require dose reduction by one dose level.
- Further dose reduction is allowed as long as discontinuation criteria was 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 > 400 mg/dL based on laboratory analysis which occurred at the lowest study drug dose level despite optimal glucose

lowering therapy (after at least one cycle of treatment) with consultation of a diabetes specialist requires permanent discontinuation of the study treatment (see Section 5.2.1.1).

b) Arterial hypertension

The guidelines for dose modifications of study drug 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 study drug 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 blood pressure of CTCAE Grade 4 must permanently discontinue the study drug (see Section 5.2.1.1).

Table 6-8 Dose modification of study treatment 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 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.

13.2.2.16 Section 6.4.2.1 Management of transient post-infusion glucose increases that can occur with study treatment

Old text:

Management of ~~hyperglycemia~~ that can occur with study treatment

~~a)~~ Management of transient post-infusion ~~hyperglycemia~~

Section modified by amendment 1.

~~Only the use of rapid or short acting (regular) insulin is allowed for the treatment of transient hyperglycemia (glucose intolerance). The prophylactic administration of rapid or short acting (regular) insulin prior to study drug infusion is not permitted.~~

~~In the event of post-dose glucose > 250 mg/dL on the day of infusion, the administration of rapid or short acting (regular) insulin is recommended according the institution's insulin sliding scale regimen.~~

~~All patients (diabetic and non-diabetic) should be kept under close observation if the glucose level is > 250 mg/dL until the glucose level decreases to < 160 mg/dL at any cycle. In the event of rapid or short acting (regular) insulin administration at any cycle, a 3-h close observation time is required post-administration. Meals should be provided for patients who are kept for continued observation. A low dose carbohydrate diet is recommended for the first 48 h after study drug infusion. However, carbohydrate restriction is not meant as caloric restriction in the population under study.~~

Patients will be trained to measure their capillary blood glucose levels at home ~~starting at Screening and~~ will be provided with glucose meter and supplies (lancets, test strips and diary) to register measured values and record insulin administration~~, if applicable~~. The appropriate calibration of glucose meters will be documented.

~~Patients who might need treatment with rapid or short acting insulin not only on the day of infusion should be referred to the local diabetes center/endocrinologist, to be trained to self-administer rapid or short acting insulin and to be provided with insulin prescription and an insulin sliding scale regimen. Alternatively, the investigator will be free to adequately manage these patients in the same way as indicated above. A domiciliary support by specialized nurses (public or private) should be arranged for patients not able to co-operate (old age, no caregivers available) or who cannot be adequately trained to self-monitor home blood glucose or self-administer short acting insulin for any reason.~~

~~Monitoring of non-diabetic patients~~

~~Section modified by amendment 1.~~

~~All non-diabetic patients who experience hyperglycemia > 250 mg/dL or require insulin administration will be instructed to check blood glucose at home at least 3 times per full day for at least 72 h after the start of infusion. This includes fasting glucose (morning before breakfast) and 2 further random non-fasting measurements approximately 2 h after intake of food. If after the required 72 h the glucose values are not at goal (fasting glucose ≤ 125 mg/dL or random non-fasting glucose ≤ 160 mg/dL), this monitoring will continue until blood glucose values are at goal.~~

Monitoring of diabetic patients

Section clarified by amendment 1.

~~All diabetic patients will be instructed to check blood glucose at home at least 3 times per full day for at least 72 h after start of each infusion. This includes fasting glucose (morning before breakfast) and 2 further random non-fasting measurements approximately 2 h after intake of food. If after the required 72 h the glucose values are not at goal (fasting glucose < 160 mg/dL or random non-fasting glucose < 200 mg/dL), this monitoring will continue until blood glucose values are at goal, and the patient should be immediately referred to the local diabetes center/endocrinologist to adjust treatment.~~

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. In this situation, patients should add the study specific measurements to their routine, if applicable.

After the required 72 h, if blood glucose values are at goal (~~fasting glucose < 160 mg/dL or~~ random non-fasting glucose < 200 mg/dL) after each infusion, patients can then stop only the study specific measurements until the next day of infusion, but should keep their routine measurements unchanged and ongoing as usual.

Sites recruiting patients with diabetes should have the option to extend glucose monitoring overnight.

~~**b) Management of diabetic patients (non-transient hyperglycemia) for the duration of the study**~~

~~It is generally recommended that patients with a pre-existing or new-onset diagnosis of diabetes mellitus adhere to their regular medication schedule, and take their usual doses on the days of study drug infusion. Modifications are recommended if deemed necessary for changes in uptake of food.~~

~~To monitor non-transient hyperglycemia fasting glucose is recommended. Glucose measurement prior to the infusion on Day 1 of each cycle is needed for the management of non-transient hyperglycemia (*modified by amendment 1*). The following guideline applies:~~

- ~~The anti-diabetic regimen is to be continued if glucose values are at goal (fasting glucose < 160 mg/dL and random non-fasting glucose < 200 mg/dL).~~

~~If fasting glucose is ≥ 160 mg/dL or random non-fasting glucose is ≥ 200 mg/dL the patient should be immediately referred to the local diabetes center/endocrinologist to adjust treatment.~~

New text:

Management of <u>transient post-infusion glucose increases</u> that can occur with study treatment

Management of transient post-infusion <u>glucose increases on infusion days</u>

Section modified by amendment 1.

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

<u>The guidelines for management of transient post-infusion glucose increases on infusion days are given in Table 6-9.</u>

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 diabetes specialist is recommended	• Hydration if appropriate • When planning next infusion consider prophylaxis with oral glucose lowering medication
Symptomatic or persisting glucose increases > 250 mg/dL	• Hydration status should be clinically assessed • If clinical assessment is consistent with dehydration, fluids should be given as clinically appropriate (orally or IV). • Laboratory test confirming increase should be repeated. If the repeated glucose value is > 250 mg/dL and/or patient is symptomatic and/or the hydration status indicate the need for hydration, glucose lowering medication should be administered • Prompt input from a diabetes specialist 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 diabetes specialist 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

Glucose monitoring at home

At least 3 times per full day including fasting glucose (morning before breakfast) and 2 further measurements approximately 2 h after intake of food for at least 72 h after the start of infusion is required for:

- All diabetic patients regardless of glucose level on infusion day
- Non-diabetic patients who experience persisting glucose > 250 mg/dL or who require insulin administration post-infusion. Consultation with diabetes specialist is recommended.

Patients will be trained how to measure their capillary blood glucose levels at home. If applicable, patients will be provided with glucose meter and supplies (lancets, test strips and diary) to register measured values and record meal timing, oral glucose lowering medication and/or insulin administration. The appropriate calibration of glucose meters will be documented.

Monitoring of diabetic patients

Section clarified by amendment 1.

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. In this situation, patients should add the study specific measurements to their routine, if applicable. After the required 72 h, if blood glucose values are at goal (random non-fasting glucose < 200 mg/dL) after each infusion, patients can then stop only the study specific measurements until the next day of infusion, but should keep their routine measurements unchanged and ongoing as usual.

Sites recruiting patients with diabetes should have the option to extend glucose monitoring overnight.

13.2.2.17 Section 6.4.2.2 Management of hyperlipidemia

Old text:

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 ~~the patient would~~ be ~~required to be fasted for 11 h~~ prior to sampling. For patients who cannot adhere to ~~these~~ fasting requirements the evaluation of lipid-panels including triglycerides ~~and determination of treatment~~ is considered as not feasible.

New text:

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.

13.2.2.18 Section 6.4.2.3 Treatment of blood pressure increases associated with study treatment

Old text:

Treatment of ~~arterial hypertension~~ associated with study treatment

[…]

Topical nitrates should also be considered. Verapamil and diltiazem (non-dihydropyridine calcium channel blockers) should be ~~avoided~~ due to a potential CYP3A4 interaction. In general, it is advisable for sites to be prepared so that antihypertensive medication is readily available in case of need.

New text:

Treatment of blood pressure increases associated with study treatment

[…]

Topical nitrates should also be considered. Verapamil and diltiazem (non-dihydropyridine calcium channel blockers and moderate inhibitors of CYP 3A4) should be used with caution due to a potential CYP3A4 interaction. In general, it is advisable for sites to be prepared so that antihypertensive medication is readily available in case of need.

13.2.2.19 Section 6.9.1 Prohibited concomitant therapy

Old text:

[…]

- 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 7 days prior to the screening CT/MRI ~~and again prior to the first administration of study drug~~.

New text:

[…]

- 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.

13.2.2.20 Section 6.9.2 Permitted concomitant therapy

Old text:

[…]

- Patients taking narrow therapeutic index medications should be monitored proactively, if these medications cannot be avoided. These medications may include quinidine~~,~~ ~~cyclosporine~~ and digoxin.

New text:

[…]

- Patients taking narrow therapeutic index medications should be monitored proactively, if these medications cannot be avoided. These medications may include quinidine and digoxin.

13.2.2.21 Section 7.1.1 Tabulated overview

Old text:

	Screening maximum days before C1D1			Treatment *									EOT	SFU	Active follow-up [aa]	Survival follow-up [bb]
				Cycle 1					Cycle 2 and higher				Within (days) after			
Days	**-28**	**-14**	**-7**	**D1**	**D4**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22 [y]**	**7**	**30-35 [z]**		**every 3 months**
Acceptable deviation (in days)				-1 to +2 days					-1 to +2 days				Decision to stop	Last dose		±14 days

[…]

Serum pregnancy test (if applicable) [c]			X						X[c]							
UPCR			X													

[…]

Quality of life questionnaire (FLymSI-18) [q]				X					X				X	X		

[…]

* **NOTE**: Patients who experience PD on placebo treatment (per central independent blinded radiology review) can be offered open-label copanlisib upon discretion of the investigator and patient's consent. After individual patient unblinding, patients receiving placebo who switch to open-label copanlisib will have all study assessments and timing reset to the initial schedule of study evaluations (i.e. as if the patient was restarting the study at Cycle 1 Day 1). ~~If not previously done within 7 days, patients switching to open-label copanlisib must complete the following within 7 days prior to the first dose of open-label copanlisib: UPCR measurement, GFR measurement, urinalysis, HbA1c, CBC, chemistry and coagulation panels (see dosing criteria in Table 6-3) (*clarified by amendment 1*).~~

[…]

c After Cycle 1 serum pregnancy test is mandatory at every cycle ~~for France, Belgium, Canada and other~~ countries where it is required by local regulations.

[…]

i HbA1c at Screening, on Day 1 of every odd cycle (3, 5, 7, etc.) starting from Cycle 3 and at the EOT visit.

[…]

k 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), SCR, uric acid,

total bilirubin, creatine phosphokinase, ALT, AST, LDH, ALP, lipase, amylase (or pancreatic amylase, if total amylase is not routinely measured at the site), cholesterol (total and LDL) and triglycerides (*modified by amendment 1*). Total cholesterol, LDL and triglycerides will be tested only at Screening, on Day 1 of every 2nd cycle starting from Cycle 2, and at the EOT visit. On these dates patients must be fasting ~~for 11 h~~ prior to sampling. If a patient can't adhere to fasting requirements, the evaluation of lipid-panels including triglycerides is considered not feasible.

l On Cycle 1 Day 1, glucose will be measured at pre-dose and after the ~~start~~ of study drug infusion ~~(post infusion). For patients who had a low carbohydrate breakfast prior to the start of infusion, glucose monitoring will be up to 3 h post-infusion (1 h, 2 h and 3 h). For patients who did not have a low carbohydrate breakfast prior to infusion, monitoring will continue for up to 5 h post-infusion (1 h, 2 h and 5 h).~~ Additional measurements to be performed at the clinic as clinically indicated. On subsequent infusions, glucose will be measured prior to and after infusion. The pre-dose glucose sample on Day 1 of each cycle should be after an 8 h fasting. ~~On Cycle 1 Day 1, patient's fasting pre-dose glucose level should be ≤ 125 mg/dL (non-diabetic patients) or < 160 mg/dL (diabetic patients) before the infusion. Pre-dose glucose levels for subsequent infusions should be < 160 mg/dL (fasting) or < 200 mg/dL (non-fasting)~~. For fasting requirements, see Section 6.4 (*footnote changed by amendment 1*).

m Home glucose monitoring is required for all diabetic patients after each infusion. For non-diabetic patients home glucose measurement is required if patients ~~develop hyperglycemia~~ > 250 mg/dL or require insulin administration ~~after any~~ infusion. Measurements should be ~~taken at least 3 times per full day for at least 72 h after the start of infusion. This includes fasting glucose (morning before breakfast) and 2 further random non-fasting measurements approximately 2 h after intake of food. If after the required 72 h the glucose values are not at goal (fasting glucose ≤ 125 mg/dL/< 160 mg/dL or random non-fasting glucose ≤ 160 mg/dL/< 200 mg/dL for non-diabetic/diabetic patients, respectively), this monitoring will continue until blood glucose values are at goal.~~ Patients will be trained to measure their capillary blood glucose levels at home starting at Screening. On Cycle 1 Day 1, patients will be provided with glucose meter and supplies, (lancets, test strips and diary) to record glucose values and insulin ~~doses~~, if applicable (*footnote changed by amendment 1*). ~~For details see Section 6.4.2.1.~~

n Blood pressure will be measured every 5-10 min prior to infusion of study drug (no more than 4 measurements) until there are 2 consecutive results < 150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. ~~At Cycle 1 Day 1~~ blood pressure will be measured at 0 h (pre-dose), 30 min (mid-infusion), 60 min (end of infusion~~), 90 min,~~ 2 h~~, 3 h, 4 h and 6 h~~ after the ~~start~~ of infusion ~~(deviation ±5 min). From Cycle 1 Day 8 onwards a single blood pressure measurement is to be performed prior to each infusion, 30 min after the start of infusion and at the end of each infusion (deviation of ± 5 min is allowed)~~. The patient should rest for 5-10 min before blood pressure is recorded (*modified by amendment 1*).

[…]

p […]
During Active follow-up period patients will have radiological assessments at same intervals as during treatment (time window of ±14 days is allowed) until PD is documented or new anti-tumor treatment is administered (see Section 7.1.2.3 and Section 7.3.2) (*footnote changed by amendment 1*).

New text:

	Screening maximum days before C1D1			Treatment *									EOT	SFU	Active follow-up [aa]	Survival follow-up [bb]
				Cycle 1					Cycle 2 and higher				Within (days) after			
Days	**-28**	**-14**	**-7**	**D1**	**D4**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22 [y]**	**7**	**30-35 [z]**		**every 3 months**
Acceptable deviation (in days)				-1 to +2 days					-1 to +2 days				Decision to stop	Last dose		±14 days

[…]

Serum pregnancy test (if applicable) [c]			X						X[c]				X[c, ee]			
UPCR / 24 h total urine protein quantification [ee]			X													

[…]

Quality of life questionnaire (FLymSI-18) and PRO information sheet [q, ee]				X					X				X	X		

[…]

* **NOTE**: Patients who experience PD on placebo treatment (per central independent blinded radiology review) can be offered open-label copanlisib upon discretion of the investigator and patient's consent. After individual patient unblinding, patients receiving placebo who switch to open-label copanlisib will have all study assessments and timing reset to the initial schedule of study evaluations (i.e. as if the patient was restarting the study at Cycle 1 Day 1). For further information on laboratory requirements for patients who switch to open-label treatment, please see Section 7.1.2.2 (*clarified by amendment 1*).

[…]

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.

[…]

i HbA1c at Screening, on Day 1 of every odd cycle (3, 5, 7, etc.) starting from Cycle 3 and at the EOT visit. The testing is not required if the previous test was performed within 4 weeks preceding EOT visit.

[…]

k 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), SCR, uric acid, total bilirubin, creatine phosphokinase, ALT, AST, LDH, ALP, lipase, amylase (or pancreatic amylase, if total amylase is not routinely measured at the site), cholesterol (total and LDL) and triglycerides (*modified by amendment 1*). Total cholesterol, LDL and triglycerides will be tested only at Screening, on Day 1 of every 2nd cycle starting from Cycle 2, and at the EOT visit. On these dates patients must be fasting

prior to sampling according to local standards. If a patient can't adhere to fasting requirements, the evaluation of lipid-panels including triglycerides is considered not feasible.

l On Cycle 1 Day 1, glucose will be measured at pre-dose and post-dose after the end of study drug infusion (0), 1 h and 2 h. Additional measurements to be performed at the clinic as clinically indicated. On subsequent infusions, glucose will be measured prior to and 1 h after the end of infusion. Deviation of ± 5 min is allowed for glucose measurements, except for the pre-dose measurement. The pre-dose glucose sample on Day 1 of each cycle should be after an 8 h fasting. For details on fasting requirements and pre-dose glucose levels, see Section 6.4. Glucose is also measured as part of the chemistry panel (*footnote changed by amendment 1*).

m Home glucose monitoring is required for all diabetic patients after each infusion. For non-diabetic patients home glucose measurement is required if patients experience persisting glucose > 250 mg/dL or require insulin administration post-infusion. Measurements should be performed according to guidance provided in Section 6.4.2.1. Patients will be trained to measure their capillary blood glucose levels at home starting at Screening. On Cycle 1 Day 1, patients will be provided with glucose meter and supplies, (lancets, test strips and diary) to record glucose values, meal timing, oral glucose lowering medication and/or insulin administration, if applicable (*footnote changed by amendment 1*).

n Blood pressure will be measured every 5-10 min prior to infusion of study drug (no more than 4 measurements) until there are 2 consecutive results < 150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. On infusion days, blood pressure will be measured at 0 h (pre-dose), 30 min (mid-infusion), 60 min (end of infusion); and 1 h and 2 h after the end of infusion. Time window of ± 10 min is allowed for all blood pressure measurements except for 0 h (pre-dose). The patient should rest for 5-10 min before blood pressure is recorded (*modified by amendment 1*).

[…]

p […]
During Active follow-up period patients will have radiological assessments at same intervals as during treatment (time window of ±14 days is allowed) until PD is documented or new anti-tumor treatment is administered (see Section 7.1.2.3 and Section 7.3.2). For tumor assessments in patients with WM, see Section 7.3.3 (*footnote changed by amendment 1*).

13.2.2.22 Section 7.1.2 Timing of assessments

Old text:

[…]

All procedures during the treatment period should be done according to the relative days mentioned in this CSP. ~~D~~eviations of -1 day and +2 days are acceptable ~~with the exception of blood glucose (or capillary glucose sampling via glucose meter) and blood pressure measurement before study drug infusion~~ (*modified by amendment 1*).

New text:

[…]

All procedures during the treatment period should be done according to the relative days mentioned in this CSP. For assessments during the treatment period, deviations of -1 day and +2 days are acceptable unless otherwise specified in the protocol (*modified by amendment 1*).

13.2.2.23 Section 7.1.2.1 Screening period

Old text:

[…]

~~Less than~~ 28/14 days before the first administration of study drug:

[…]

~~Less than~~ 7 days before the first administration of study drug:

[…]

- UPCR ~~measurement~~ (see Section 7.5.3.1).
- GFR measurement (see Section 7.5.3.1 and Appendix 14.5).
- Blood tests for HbA1c, CBC, chemistry and coagulation panels (see Section 7.5.3.1). Patients must be fasting ~~for 11 h~~ prior to sampling. If a patient can't adhere to fasting requirements, the evaluation of lipid-panels including triglycerides is considered not feasible.

New text:

[…]

Within 28/14 days before the first administration of study drug:

[…]

Within 7 days before the first administration of study drug:

[…]

- UPCR/24 h total urine protein quantification (see Section 7.5.3.1).
- GFR measurement (see Section 7.5.3.1 and Appendix 14.5).

- Blood tests for HbA1c, CBC, chemistry and coagulation panels (see Section 7.5.3.1). Patients must be fasting prior to sampling <u>according to local standards</u>. If a patient can't adhere to fasting requirements, the evaluation of lipid-panels including triglycerides is considered not feasible.

13.2.2.24 Section 7.1.2.2 Treatment period

Old text:

[…]

If not previously done within 7 days, patients switching to open-label copanlisib must complete the following within 7 days prior to the first dose of open-label copanlisib: UPCR ~~measurement~~, GFR measurement, urinalysis, HbA1c, CBC, chemistry and coagulation panels. ~~D~~dosing criteria outlined in Table 6-2 apply ~~also~~ for patients who switch to open-label treatment (*clarified by amendment 1*).

New text:

[…]

If not previously done within 7 days, patients switching to open-label copanlisib must complete the following within 7 days prior to the first dose of open-label copanlisib: UPCR<u>/24 h total urine protein quantification</u>, GFR measurement, urinalysis, HbA1c, CBC, chemistry and coagulation panels. <u>For Day 1 of the first open-label cycle, laboratory parameters as outlined in inclusion criterion 13 and exclusion criteria 15 and 24 will apply. For Day 1 of subsequent open-label cycles, d</u>osing criteria outlined in Table 6-2 <u>will</u> apply for patients who switch to open-label treatment (*clarified by amendment 1*).

13.2.2.25 Section 7.1.2.2.1 Treatment – Cycle 1

Old text:

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. ~~After pre-dose glucose measurement and approximately within 1 h before the start of study drug infusion patients can have a low carbohydrate breakfast. Patient's fasting pre-dose glucose level should be ≤ 125 mg/dL (non-diabetic patients) or < 160 mg/dL (diabetic patients)~~ (*fasting requirements changed by amendment 1*) ~~(see also Section 6.4)~~.

[…]

- Glucose ~~measurement: on Cycle 1 Day 1, glucose~~ will be measured at pre-dose and after the ~~start~~ of study drug infusion ~~(post-infusion). For patients who had a low carbohydrate breakfast prior to the start of infusion, glucose monitoring will be up to 3 h post-infusion (1 h, 2 h and 3 h). For patients who did not have a low carbohydrate breakfast prior to infusion, monitoring will continue for up to 5 h post-infusion (1 h, 2 h and 5 h).~~ Additional measurements to be performed at the clinic as clinically indicated. ~~The pre-dose glucose sample on Cycle 1 Day 1 should be after an 8 h fasting (*changed by amendment 1*)~~ (see Section 6.4).

- Home blood glucose monitoring (*modified by amendment 1*):
  - ~~D~~iabetic patients~~: all patients~~.
  - Non-diabetic patients who experience ~~hyperglycemia~~ > 250 mg/dL or require insulin administration.
- Training on glucose self-monitoring with a glucose meter, if needed. Patients will be provided with glucose meter and supplies (lancets, test strips and diary) to record glucose values and insulin ~~doses~~, if applicable (*changed by amendment 1*).
- Blood pressure will be measured every 5-10 min prior to infusion of study drug (no more than 4 measurements) until there are 2 consecutive results < 150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. ~~On Cycle 1 Day 1 b~~blood pressure will be measured at 0 h (pre-dose), 30 min (mid-infusion), 60 min (end of infusion)~~, 90 min,~~ 2 h~~, 3 h, 4 h and 6 h~~ after the ~~start~~ of infusion ~~(deviation~~ of ± ~~5~~ min is allowed). The patient should rest for 5-10 min before blood pressure is recorded (*modified by amendment 1*).

Cycle 1 Day 4

- Review of blood glucose measurements, if applicable. Patients, who might need treatment with ~~insulin~~ not only on the day of infusion, ~~should~~ be referred to the local diabetes center/endocrinologist to be trained to self- administer insulin, and to be provided with ~~insulin~~ prescription and an insulin sliding scale regimen. Investigators will be free to manage ~~hyperglycemic~~ patients in the same way. If indicated, domiciliary support will be arranged.

Cycle 1 Day 8 and 15

[…]

- Glucose test prior to and after study drug ~~IV~~ infusion. Patients are not required to be fasting prior to pre-dose glucose measurement (*changed by amendment 1*) (see Section 6.4).
- Review of the home blood glucose measurements/insulin administration, if applicable. Provide glucose monitoring supplies if necessary (*changed by amendment 1*) (see Section 6.4.2.1).
- Home blood glucose monitoring:
  - ~~D~~iabetic patients~~: all patients~~.
  - Non-diabetic patients who experience ~~hyperglycemia~~ > 250 mg/dL or require insulin administration (*modified by amendment 1*).
- Blood pressure will be measured every 5-10 min prior to infusion of study drug (no more than 4 measurements) until there are 2 consecutive results < 150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention

or delaying the infusion of study drug. ~~From Cycle 1 Day 8 onwards a single b~~lood pressure ~~measurement is to be performed prior to each infusion, 30 min after the start of infusion and at the end of each infusion (deviation~~ of ± ~~5~~ min is allowed). The patient should rest for 5-10 min before blood pressure is recorded (*modified by amendment 1*).

[…]

Cycle 1 Day 22

[…]

- Review of the home blood glucose measurements/insulin administration, if applicable. Provide glucose monitoring supplies if necessary (*changed by amendment 1*) (see Section 6.4.2.1).

New text:

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 (*fasting requirements changed by amendment 1*).

[…]

- Glucose will be measured at pre-dose and post-dose after the end of study drug infusion (0), 1 h and 2 h (deviation of ± 5 min is allowed, except for the pre-dose measurement). Additional measurements to be performed at the clinic as clinically indicated.
  Note: If patient needs to take a low glycemic meal, then glucose test should be taken prior to meal intake and at 1 h and 2 h after the meal (see Section 6.4 and Section 7.5.3.6) (*changed by amendment 1*).
- Home blood glucose monitoring (*modified by amendment 1*):
  - All diabetic patients regardless of glucose level on infusion day.
  - Non-diabetic patients who experience persisting glucose > 250 mg/dL or who require insulin administration post-infusion.
- Training on glucose self-monitoring with a glucose meter, if needed. Patients will be provided with glucose meter and supplies (lancets, test strips and diary) to record glucose values, meal timing, oral glucose lowering medication and/or insulin administration, if applicable (see Section 6.4.2.1) (*changed by amendment 1*).
- Blood pressure will be measured every 5-10 min prior to infusion of study drug (no more than 4 measurements) until there are 2 consecutive results < 150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. Blood pressure will be measured at 0 h (pre-dose), 30 min (mid-infusion), 60 min (end of infusion); and 1 h and 2 h after the end of infusion. Time window of ± 10 min is allowed for all measurements except for 0 h

(pre-dose). The patient should rest for 5-10 min before blood pressure is recorded (*modified by amendment 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 and 15

[…]

- Glucose test prior to study drug infusion and 1 h after the end of study drug infusion (deviation of ± 5 min is allowed, except for the pre-dose measurement). Patients are not required to be fasting prior to pre-dose glucose measurement.
  Note: If patient needs to take a low glycemic meal, then glucose test should be taken prior to meal intake and at 1 h and 2 h after the meal (see Section 6.4 and Section 7.5.3.6) (*changed by amendment 1*).
- Review of the home blood glucose measurements/meal timing/oral glucose lowering medication/insulin administration, if applicable. Provide glucose monitoring supplies if necessary (*changed by amendment 1*) (see Section 6.4.2.1).
- Home blood glucose monitoring:
  - All diabetic patients regardless of glucose level on infusion day.
  - Non-diabetic patients who experience persisting glucose > 250 mg/dL or who require insulin administration post-infusion (*modified by amendment 1*).
- Blood pressure will be measured every 5-10 min prior to infusion of study drug (no more than 4 measurements) until there are 2 consecutive results < 150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. Blood pressure will be measured at 0 h (pre-dose), 30 min (mid-infusion), 60 min (end of infusion); and 1 h and 2 h after the end of infusion. Time window of ± 10 min is allowed for all measurements except for 0 h (pre-dose). The patient should rest for 5-10 min before blood pressure is recorded (*modified by amendment 1*).

[…]

Cycle 1 Day 22

[…]

- Review of the home blood glucose measurements/meal timing/oral glucose lowering medication/insulin administration, if applicable. Provide glucose monitoring supplies if necessary (*changed by amendment 1*) (see Section 6.4.2.1).

13.2.2.26 Section 7.1.2.2.2 Treatment – Cycle 2 and higher

Old text:

Cycle 2 and higher, Day 1

On Day 1 of each subsequent cycle, patients should be fasting for at least 8 h prior to the pre-dose glucose measurement. ~~After pre-dose glucose measurement patients can have a low carbohydrate breakfast. Patient's fasting pre-dose glucose level should be < 160 mg/dL (fasting) or, in case of non-compliance with fasting requirements, < 200 mg/dL (non-fasting)~~ (*added by amendment 1*) ~~(~~see ~~also~~ Section 6.4~~)~~.

[…]

Serum pregnancy test: after Cycle 1 serum pregnancy test is mandatory at every cycle for ~~France, Belgium, Canada and other~~ countries where it is required by local regulations.

[…]

- Blood tests for CBC, chemistry and coagulation panels (see Section 6.4 and Section 7.5.3.1). Total cholesterol, LDL and triglycerides will be determined on Day 1 of every 2nd cycle starting from Cycle 2. On these days patients must be fasting ~~for 11 h~~ prior to sampling. If a patient can't adhere to fasting requirements, the evaluation of lipid-panels including triglycerides is considered not feasible.
- […]
- Glucose test prior to and after study drug ~~IV~~ infusion. The pre-dose glucose sample on Day 1 of each cycle should be after an 8 h~~our~~ fasting (*changed by amendment 1*) (see Section 6.4).
- Review of the home blood glucose measurements/insulin administration, if applicable. Provide glucose monitoring supplies if necessary (*changed by amendment 1*) (see Section 6.4.2.1).
- Home blood glucose monitoring:
  - ~~D~~iabetic patients~~: all patients~~.
  - Non-diabetic patients who experience ~~hyperglycemia~~ > 250 mg/dL or require insulin administration (*modified by amendment 1*).
- Blood pressure will be measured every 5-10 min prior to infusion of study drug (no more than 4 measurements) until there are 2 consecutive results < 150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. ~~From Cycle 1 Day 8 onwards a single b~~lood

pressure ~~measurement is to be performed prior to each infusion, 30 min after the start of infusion and at the end of each infusion (deviation~~ of ± ~~5~~ min is allowed). The patient should rest for 5-10 min before blood pressure is recorded (*modified by amendment 1*).

[…]

Cycle 2 and higher, Day 8 and 15

[…]

- Glucose test prior to and after study drug ~~IV~~ infusion. Patients are not required to be fasting prior to pre-dose glucose measurement (*changed by amendment 1*) (see Section 6.4).
- Review of the home blood glucose measurements/insulin administration, if applicable. Provide glucose monitoring supplies if necessary (*changed by amendment 1*) (see Section 6.4.2.1).
- Home blood glucose monitoring:
  - ~~D~~iabetic patients~~: all patients~~.
  - Non-diabetic patients who experience ~~hyperglycemia~~ > 250 mg/dL or require insulin administration (*modified by amendment 1*).
- Blood pressure will be measured every 5-10 min prior to infusion of study drug (no more than 4 measurements) until there are 2 consecutive results < 150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. ~~From Cycle 1 Day 8 onwards a single b~~lood pressure ~~measurement is to be performed prior to each infusion, 30 min after the start of infusion and at the end of each infusion (deviation~~ of ± ~~5~~ min is allowed). The patient should rest for 5-10 min before blood pressure is recorded (*modified by amendment 1*).

New text:

Cycle 2 and higher, Day 1

On Day 1 of each subsequent cycle, patients should be fasting for at least 8 h prior to the pre-dose glucose measurement. <u>For details on fasting requirements and pre-dose glucose levels,</u> see Section 6.4 (*added by amendment 1*).

[…]

Serum pregnancy test <u>(if applicable)</u>: after Cycle 1 serum pregnancy test is mandatory at every cycle for countries where it is required by local regulations.

[…]

- Blood tests for CBC, chemistry and coagulation panels (see Section 6.4 and Section 7.5.3.1). Total cholesterol, LDL and triglycerides will be determined on Day 1 of every 2nd cycle starting from Cycle 2. On these days patients must be fasting prior

to sampling according to local standards. If a patient can't adhere to fasting requirements, the evaluation of lipid-panels including triglycerides is considered not feasible.

- […]
- Glucose test prior to study drug infusion and 1 h after the end of study drug infusion (deviation of ± 5 min is allowed, except for the pre-dose measurement). The pre-dose glucose sample on Day 1 of each cycle should be after an 8 h fasting
  Note: If patient needs to take a low glycemic meal, then glucose test should be taken prior to meal intake and at 1 h and 2 ho after the meal (see Section 6.4 and Section 7.5.3.6) (*changed by amendment 1*).
- Review of the home blood glucose measurements/meal timing/oral glucose lowering medication/insulin administration, if applicable. Provide glucose monitoring supplies if necessary (*changed by amendment 1*) (see Section 6.4.2.1).
- Home blood glucose monitoring:
  - All diabetic patients regardless of glucose level on infusion day.
  - Non-diabetic patients who experience persisting glucose > 250 mg/dL or who require insulin administration post-infusion (*modified by amendment 1*).
- Blood pressure will be measured every 5-10 min prior to infusion of study drug (no more than 4 measurements) until there are 2 consecutive results < 150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. Blood pressure will be measured at 0 h (pre-dose), 30 min (mid-infusion), 60 min (end of infusion); and 1 h and 2 h after the end of infusion. Time window of ± 10 min is allowed for all measurements except for 0 h (pre-dose). The patient should rest for 5-10 min before blood pressure is recorded (*modified by amendment 1*).

[…]

Cycle 2 and higher, Day 8 and 15

[…]

- Glucose test prior to study drug infusion and 1 h after the end of study drug infusion (deviation of ± 5 min is allowed, except for the pre-dose measurement). Patients are not required to be fasting prior to pre-dose glucose measurement
  Note: If patient needs to take a low glycemic meal, then glucose test should be taken prior to meal intake and at 1 h and 2 h after the meal (see Section 6.4 and Section 7.5.3.6) (*changed by amendment 1*).
- Review of the home blood glucose measurements/meal timing/oral glucose lowering medication/insulin administration, if applicable. Provide glucose monitoring supplies if necessary (*changed by amendment 1*) (see Section 6.4.2.1).
- Home blood glucose monitoring:

- All diabetic patients regardless of glucose level on infusion day.
- Non-diabetic patients who experience persisting glucose > 250 mg/dL or who require insulin administration post-infusion (*modified by amendment 1*).

- Blood pressure will be measured every 5-10 min prior to infusion of study drug (no more than 4 measurements) until there are 2 consecutive results < 150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. Blood pressure will be measured at 0 h (pre-dose), 30 min (mid-infusion), 60 min (end of infusion); and 1 h and 2 h after the end of infusion. Time window of ± 10 min is allowed for all measurements except for 0 h (pre-dose). The patient should rest for 5-10 min before blood pressure is recorded (*modified by amendment 1*).

13.2.2.27 Section 7.1.2.3 Tumor assessments

Old text:

[…]

- Serum quantitative IgM test.

New text:

[…]

- Serum quantitative IgM test.

For further details on tumor assessments in patients with WM, see Section 7.3.3.

13.2.2.28 Section 7.1.2.4 End-of-treatment visit

Old text:

[…]

- IVRS/IWRS transaction to register end of treatment.
- Toxicity/AE assessment (see Section 7.5.1.3).

[…]

- Blood tests for HbA1c, CBC, chemistry and coagulation panels (see Section 7.5.3.1). Patients must be fasting ~~for 11 h~~ prior to sampling. If a patient can't adhere to fasting requirements, the evaluation of lipid-panels including triglycerides is considered not feasible.

[…]

- Review of the home blood glucose measurements/insulin administration, if applicable (*modified by amendment 1*) (see Section 6.4.2.1).

New text:

[…]

- 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).

[…]

- Blood tests for HbA1c, CBC, chemistry and coagulation panels (see Section 7.5.3.1). Patients must be fasting prior to sampling according to local standards. If a patient can't 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.

[…]

- Review of the home blood glucose measurements/meal timing/oral glucose lowering medication/insulin administration, if applicable (*modified by amendment 1*) (see Section 6.4.2.1).

13.2.2.29 Section 7.3.2 Radiological tumor assessments

Old text:

[…]

The method chosen at the baseline must be the same throughout the study.

[…]

~~The response assessment will be done according to the Lugano Classification (21)~~. As long as the patient has not experienced PD, investigator's assessment is sufficient for case management. In the event of progression, radiological real-time confirmation by central independent blinded evaluation is required before a final decision to stop the treatment is made. In case of uncertain radiological disease progression the patient may stay on treatment at the investigator's discretion until progression is definitely confirmed on the subsequent tumor assessment. The final evaluation of treatment response (best response: ORR and CRR) will be done by central blinded review retrospective~~ly~~.

~~For patients with WM, response assessment will be performed according to the Owen criteria (22). However, CT scan will be done and collected for all patients according to the schedule specified in the protocol. According to this guidance, disease progression can be confirmed based on laboratory parameters. In such case when PD was assessed by an investigator based on laboratory parameters alone, no independent confirmation of PD by central independent blinded review is necessary. Site must notify the sponsor about disease progression and follow procedures outlined in the protocol for patients on study and control arm respectively. For patients with WM who had measurable disease at baseline and had PD~~

~~assessed based on CT scan, scans must be submitted for review to confirm disease progression by central blinded review.~~

Detailed instructions on tumor assessment are provided in Appendix 14.1.

[…]

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 meet the standard of care for imaging of lesions in the respective organ system(s). If IV (~~or~~ oral) contrast-enhanced CT is medically contraindicated, sites may acquire contrast-enhanced MRI of the neck, abdomen and pelvis, and an unenhanced CT of the chest above lung apices to the bottom of the adrenals. Chest CT is preferred. ~~I~~f a patient develops contra-indication to ~~any~~ contrast medium during the study, the case examinations should be continued without contrast. In certain countries MRI should be used based on local regulations.

New text:

[…]

The method chosen at the 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.

[…]

As long as the patient has not experienced PD, investigator's assessment is sufficient for case management. In the event of progression, radiological real-time confirmation by central independent blinded evaluation is required before a final decision to stop the treatment is made. In case of uncertain radiological disease progression the patient may stay on treatment at the investigator's discretion until progression is definitely confirmed on the subsequent tumor assessment. The final evaluation of treatment response (best response: ORR and CRR) will be done by central blinded review and for those not undergoing PD-confirmation in retrospective setting.

The response assessment will be done according to the Lugano Classification (21). For patients with WM, additional criteria apply (see Section 7.3.3).

Detailed instructions on tumor assessment are provided in Appendix 14.1.

[…]

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 IV (and oral, if indicated, per Imaging Manual) contrast-enhanced CT is medically contraindicated, sites may acquire contrast-enhanced MRI of the neck, abdomen and pelvis, and an unenhanced CT of the chest above lung apices to the bottom of the adrenals. Chest CT is preferred. Only if a patient develops contra-indication to both CT and MRI contrast medium during the treatment phase of the study, the case

examinations should be continued without contrast. In certain countries MRI should be used based on local regulations.

13.2.2.30 Section 7.3.3 Tumor assessments in patients with WM

New section was added:

WM patients who do not have radiologically measurable lesion at Screening will not have further radiological assessments as per protocol. Their tumor response will be measured only by laboratory/clinical tests, and response assessment will be done according to the Owen Criteria. If PD was assessed by an investigator based on laboratory parameters alone, no independent confirmation of PD by independent blinded review is necessary. However, in cases when WM patients will develop disease progression confirmed radiologically by presenting with measurable lesion(s) without simultaneous increase in IgM, the imaging scans should be submitted for central review and PD confirmation.

WM patients who have radiologically measurable lesion at Screening will continue having radiological assessments and, in addition, will have laboratory tests performed on the same days. CT/MRI scans will be done and collected according to the schedule specified in the protocol (see Section 7.1.2.3). For patients who have PD assessed based on CT/MRI, scans must be submitted for review to confirm disease progression by an independent blinded radiology review.

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

Detailed instructions on tumor assessment are provided in Appendix 14.1.

13.2.2.31 Section 7.4 Pharmacokinetics / pharmacodynamics

Old text:

[…]

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 ~~(5 mL at each sampling time point)~~ should be collected, processed, stored, and shipped according to procedures outlined in the Laboratory Manual.

New text:

[…]

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.

13.2.2.32 Section 7.5.1.3 Assessments and documentation of adverse events

Old text:

[…]

If any patient dies during the observation phase for AEs, the investigator will inform the sponsor and record the cause of death in detail within 24 h on an SAE form.

New text:

[…]

If any patient dies during the observation phase for AEs, the investigator will inform the sponsor and record the cause of death in detail within 24 h on an SAE form. "Death" should generally not be recorded as an AE on the AE page. Instead, "death" should be recorded as the outcome of underlying AE(s). If death is reported without any associated AE (s), it should be reported as SAE.

13.2.2.33 Section 7.5.1.4 Reporting of serious adverse events

Old text:

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".**

New text:

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 clearly mentioned on the SAE form as an "alternative explanation"**.

13.2.2.34 Section 7.5.3 Further safety

Old text:

[…]

If not previously done within 7 days, patients switching to open-label copanlisib must complete the following within 7 days prior to the first dose of open-label copanlisib: UPCR ~~measurement~~, GFR measurement, urinalysis, HbA1c, CBC, chemistry and coagulation panels. ~~Dosing criteria outlined in Table 6-2 apply also for patients who switch to open-label treatment~~ (*clarified by amendment 1*).

New text:

[…]

If not previously done within 7 days, patients switching to open-label copanlisib must complete the following within 7 days prior to the first dose of open-label copanlisib: UPCR/24 h total urine protein quantification, GFR measurement, urinalysis, HbA1c, CBC, chemistry and coagulation panels. For further information on laboratory requirements for patients who switch to open-label treatment, please see Section 7.1.2.2 (*clarified by amendment 1*).

13.2.2.35 Section 7.5.3.1 Laboratory

Old text:

All laboratory analyses will be performed locally. Dipsticks should be available for urinalysis (*modified by amendment 1*).

[…]

- Quantification of proteinuria by UPCR on a random urine sample preferably taken at mid-morning. This should be reported as the ratio of concentrations of total urine protein (in mg/dl) to urine creatinine (in mg/dl).

[…]

- 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).

New text:

All laboratory analyses will be performed locally according to the schedule summarized in the flow chart of Section 7.1.1. Dipsticks should be available for urinalysis (*modified by amendment 1*).

[…]

- Quantification of proteinuria by either a 24 h total urine protein quantification or by UPCR on a random urine sample preferably taken at 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.

[…]

- 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).
- Hemoglobin A1c.

13.2.2.36 Section 7.5.3.2.1 Complete physical examination

Old text:

[…]

- Skin (paleness, jaundice, redness/r~~u~~sh, acneiforme changes)

[…]

- Ears, nose, throat (presence of petechial bleeding~~s~~, gingival bleeding)

New text:

[…]

- Skin (paleness, jaundice, redness/rash, acneiforme changes) including clinical assessment of hydration status via hand extensor surface skin turgor

[…]

- Ears, nose, throat (presence of petechial bleeding, gingival bleeding) including inspection of oral mucosa for hydration status

13.2.2.37 Section 7.5.3.2.2 Brief physical examination

[…]

- Skin (paleness, jaundice, redness/r~~u~~sh, acneiforme changes)

[…]

- Throat (presence of petechial bleeding~~s~~, gingival bleeding)

New text:

[…]

- Skin (paleness, jaundice, redness/rash, acneiforme changes) including clinical assessment of hydration status via hand extensor surface skin turgor

[…]

- Throat (presence of petechial bleeding, gingival bleeding) including inspection of oral mucosa for hydration status

13.2.2.38 Section 7.5.3.3 Vital signs

Old text:

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 will be measured every 5-10 min prior to infusion of study drug (no more than 4 measurements) until there are 2 consecutive results < 150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. The patient should rest for 5-10 min before blood pressure is recorded (*modified by amendment 1*).

- ~~At Cycle 1 Day 1~~ blood pressure will be measured at 0 h (pre-dose), 30 min (mid-infusion), 60 min (end of infusion)~~, 90 min,~~ 2 h~~, 3 h, 4 h and 6 h~~ after the ~~start~~ of infusion ~~(deviation ±5 min)~~.
- From Cycle 1 Day 8 onwards a single blood pressure measurement is to be performed prior to each infusion, 30 min after the start of infusion and at the end of each infusion (deviation ±5 min) (*modified by amendment 1*).

New text:

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 every 5-10 min prior to infusion of study drug (no more than 4 measurements) until there are 2 consecutive results < 150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. The patient should rest for 5-10 min before blood pressure is recorded (*modified by amendment 1*).

- On infusion days: blood pressure will be measured at 0 h (pre-dose), 30 min (mid-infusion), 60 min (end of infusion); and 1 h and 2 h after the end of infusion.
- Note: time window of ± 10 min is allowed for all blood pressure measurements except for 0 h (pre-dose)

13.2.2.39 Section 7.5.3.6 Glucose measurement on infusion days

New section was added:

- On Cycle 1 Day 1: glucose will be measured at pre-dose and post-dose after the end of study drug infusion (0), 1 h and 2 h. Additional measurements to be performed at the clinic as clinically indicated.
- On subsequent infusion days: glucose will be measured prior to study drug infusion and 1 h after the end of study drug infusion.
- On all infusion days: time window of ± 5 min is allowed for glucose measurements, except for the pre-dose measurement. If patient needs to take a low glycemic meal, then glucose test should be taken prior to meal intake and at 1 h and 2 h after the meal.

13.2.2.40 Section 7.6.3 Electronic patient-reported outcomes evaluation

Old text:

ePRO devices will be implemented in this study. They will be used to complete the FLymSI-18 questionnaire (*modified by amendment 1*). A Site Manual will be provided to sites and each patient to help them understand how the ePRO devices work and how to use them correctly. If, for any reason, a device is not available at the site, or technical problems prevent it from working properly, ~~a paper PRO questionnaire may be used~~.

New text:

ePRO devices will be implemented in this study. They will be used to complete the FLymSI-18 questionnaire (*modified by amendment 1*). A Site Manual will be provided to sites and each patient to help them understand how the ePRO devices work and how to use them correctly. If, for any reason, a device is not available at the site, or technical problems prevent it from working properly, the FLymSI-18 questionnaire will not be completed at that visit.

13.2.2.41 Section 11.2 Patient information and consent

Old text:

[…]

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

Each patient will have ample time and opportunity to ask questions ~~and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.~~

Only if the patient voluntarily agrees to sign the ICF and has done so, may he/she enter the study.

New text:

[…]

The investigator will also mention that written approval of the IEC/IRB 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 ICF and has done so, may he/she enter the study.

13.2.2.42 Section 12 Reference list

Reference 38 was added.

38. Atkinson FS, Foster-Powell K, Brand-Miller JC. International Tables of Glycemic Index and Glycemic Load Values: 2008. Diabetes Care 2008;31:2281-2283.

13.2.2.43 Section 14.1 Evaluation of tumor response

Old text:

Tumor response will be evaluated according to Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification (21).

	Target lesions (nodal)	Target lesions (extranodal)	Non-target lesions	Spleen	New lesion	Bone marrow
[…]						
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)	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)	~~Lymphoma infiltration (new or % increased respect to baseline)~~

CR = complete response; IHC = Immunohistochemistry; LDi = longest diameter; PD = progressive disease; PPD = product of perpendicular diameters; PR = partial response; SD =stable disease; SDi = shortest diameter; SPD = sum of the product of the diameters

New text:

Tumor response will be evaluated according to Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification (21).

	Target lesions (nodal)	Target lesions (extranodal)	Non-target lesions	Spleen	New lesion	Bone marrow
[…]						
PD	Individual node/lesion: • LDi > 1.5 cm AND • Increase ≥ 50% in the PPD from nadir AND • Increase in LDi or SDi from nadir * ≥ 0.5 cm for lesions≤ 2 cm ≥ 1.0 cm for lesions > 2 cm		New or increased	• New splenomegaly: the splenic length must increase ≥ 2 cm from baseline length and be > 13 cm • Recurrent splenomegaly: the splenic length must increase ≥ 2 cm from nadir length and be > 13 cm • Progressive splenomegaly: the splenic length must increase by > 50% of the extent beyond normal at baseline (=value over 13 cm) and must increase ≥ 1 cm in total vertical length	Yes: • New node > 1.5 cm in any axis • New extranodal site > 1.0 cm in any axis (if < 1.0 cm in any axis its presence must be unequivocal and must be attributable to lymphoma)	New or recurrent involvement

CR = complete response; IHC = Immunohistochemistry; LDi = longest diameter; PD = progressive disease; PPD = product of perpendicular diameters; PR = partial response; SD =stable disease; SDi = shortest diameter; SPD = sum of the product of the diameters

* 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.

13.2.2.44 Section 14.7 The average glycemic index of common foods derived from multiple studies by different laboratories

New appendix was added:

Foods are categorized as having a low-glycemic index if the glucose reference index is ≤ 55. The summary table below contains glucose reference for common foods, please see reference 38 for additional information.

High-carbohydrate foods		Breakfast cereals		Fruit and fruit products		Vegetables	
White wheat bread*	75 ± 2	Cornflakes	81 ± 6	Apple, raw†	36 ± 2	Potato, boiled	78 ± 4
Whole wheat/whole meal bread	74 ± 2	Wheat flake biscuits	69 ± 2	Orange, raw†	43 ± 3	Potato, instant mash	87 ± 3
Specialty grain bread	53 ± 2	Porridge, rolled oats	55 ± 2	Banana, raw†	51 ± 3	Potato, french fries	63 ± 5
Unleavened wheat bread	70 ± 5	Instant oat porridge	79 ± 3	Pineapple, raw	59 ± 8	Carrots, boiled	39 ± 4
Wheat roti	62 ± 3	Rice porridge/congee	78 ± 9	Mango, raw†	51 ± 5	Sweet potato, boiled	63 ± 6
Chapatti	52 ± 4	Millet porridge	67 ± 5	Watermelon, raw	76 ± 4	Pumpkin, boiled	64 ± 7
Corn tortilla	46 ± 4	Muesli	57 ± 2	Dates, raw	42 ± 4	Plantain/green banana	55 ± 6
White rice, boiled*	73 ± 4			Peaches, canned†	43 ± 5	Taro, boiled	53 ± 2
Brown rice, boiled	68 ± 4			Strawberry jam/jelly	49 ± 3	Vegetable soup	48 ± 5
Barley	28 ± 2			Apple juice	41 ± 2		
Sweet corn	52 ± 5			Orange juice	50 ± 2		
Spaghetti, white	49 ± 2						
Spaghetti, whole meal	48 ± 5						
Rice noodles†	53 ± 7						
Udon noodles	55 ± 7						
Couscous†	65 ± 4						

Dairy products and alternatives		Legumes		Snack products		Sugars	
Milk, full fat	39 ± 3	Chickpeas	28 ± 9	Chocolate	40 ± 3	Fructose	15 ± 4
Milk, skim	37 ± 4	Kidney beans	24 ± 4	Popcorn	65 ± 5	Sucrose	65 ± 4
Ice cream	51 ± 3	Lentils	32 ± 5	Potato crisps	56 ± 3	Glucose	103 ± 3
Yogurt, fruit	41 ± 2	Soya beans	16 ± 1	Soft drink/soda	59 ± 3	Honey	61 ± 3
Soy milk	34 ± 4			Rice crackers/crisps	87 ± 2		
Rice milk	86 ± 7						

Data are means ± SEM. *Low-GI varieties were also identified. †Average of all available data.

GI = glycemic index.

Source: (38)

13.3 Amendment 4

Amendment 4 is a global amendment dated 21 JUL 2016.

13.3.1 Overview of changes

13.3.1.1 Modification 1 - clarification of bone marrow biopsy sample to be reviewed by central pathology

To align with other CHRONOS protocols, the statement was added when bone marrow biopsy samples must be sent to central pathology for review. Also it is at the investigator's discretion to perform a bone marrow biopsy if there is suspicion of bone marrow infiltration.

It was emphasized that the bone marrow biopsy is mandatory at screening, which is up to 28 days before the first study drug infusion.

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

13.3.1.2 Modification 2– 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.

13.3.1.3 Modification 3– clarification of inclusion criterion related to platelets

To clarify the requirements for platelet count in patients with confirmed lymphomatous bone marrow infiltration.

Section affected by this modification: 5.1.1 Inclusion criteria.

13.3.1.4 Modification 4 – exclusion of patients with Cytomegalovirus (CMV)

An additional exclusion criterion was added to exclude patients with positive CMV infection at baseline.

Sections affected by this modification: 5.1.2 Exclusion criteria, 7.1.1 Tabulated overview and 7.1.2.1 Screening period.

13.3.1.5 Modification 5 – clarification when a patient withdraws study treatment due to CMV infection

If a patient experiences reactivation of CMV infection and study drug is delayed up to 2 cycles, the patient should withdraw from study treatment. 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.

Section affected by this modification: 5.2.1.1 Withdrawal from study treatment.

13.3.1.6 Modification 6 – 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 6.4.2.6 was added to provide guidance for monitoring and prophylaxis of opportunistic infections in patients who are at risk for opportunistic infection development while on study treatment.

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.

Sections affected by this modification: 6.4.2.6 Guidance for monitoring and prophylaxis of opportunistic infection (OI) (new section), 7.1.1 Tabulated overview, 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, and 7.5.3.2.2 Brief physical examination.

13.3.1.7 Modification 7 – modification to management of hypertension

Dose modification guidance for the management of hypertension was clarified for incidence of grade 3 event.

Section affected by this modification: 6.4.1.2 Non-hematological toxicity.

13.3.1.8 Modification 8 – clarification of observation period for adverse events

AEs are to be documented upon signing the ICF until 30 days after the last dose of study drug. The period for TEAEs was clarified to be after start of study drug administration until 30 days after last study drug intake.

Sections affected by this modification: 7.1.1 Tabulated overview, 7.5.1.3 Assessments and documentation of adverse events and 8.3.2 Safety variables.

13.3.1.9 Modification 9 – modification to definition of complete response

In addition to a negative IHC confirmation for CR, a negative PCR is also acceptable.

Section affected by this modification: 14.1 Evaluation of tumor response.

13.3.1.10 Modification 10 – other clarifications and corrections

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

- Due to sponsor name change, sponsor information and sponsor logo were changed.
- Due to Study PPD change, the sponsor information was changed.

- The Safety follow-up visit window was clarified to be 30 days after last administration of study drug, with an additional +5 days allowed
- Minor updates were made to clarify that only ePRO devices would be used in this study.
- A minor inconsistency was corrected in Section 5.2.1 “Withdrawal” to clarify that baseline glucose test is not required for patient’s eligibility evaluation.
- 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.

Sections affected by this modification: Title Page, Synopsis, 3 Investigator and other study personnel, 4 Study Design, 5.2.1 Withdrawal, 7.1.1 Tabulated overview, 7.1.2.5.1 Safety follow-up, 7.5.1.3 Assessments and documentation of adverse events, 7.5.3.1 Laboratory, 7.6.3 Electronic patient-reported outcomes evaluation, and header on every page of the document.

13.3.2 Changes to the protocol text

13.3.2.1 Title page

Old text:

Sponsor:	Bayer ~~HealthCare~~ AG, D-51368 Leverkusen, Germany
Sponsor's PPD :	PPD ~~MD~~ ~~100 Bayer Blvd~~ ~~PO Box 915~~ ~~Whippany, NJ 07981, USA~~ ~~Telephone no.:~~ PPD

New text:

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 PPD :	PPD MD, PhD Bayer S.A. Rua Domingos Jorge, 1100, Predio 9301, 2º andar CEP 04779-900, Sao Paulo-SP, Brazil Telephone no.: PPD

13.3.2.2 Synopsis

Old text:

Methodology	[…] An End-of-treatment (EOT) visit will be performed within 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 (SFU) visit will take place 30~~–35~~ days after the last administration of study drug. […] Bone marrow biopsy will be mandatory at Screening. ~~If the baseline biopsy is positive for lymphoma infiltration, it will be mandatory to perform it again to confirm the first complete response (CR)~~ (*paragraph added to synopsis by amendment 3*).

New text:

Methodology	[…] An End-of-treatment (EOT) visit will be performed within 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 (SFU) visit will take place 30 days (window of +5 days allowed) after the last administration of study drug. […] Bone marrow biopsy will be mandatory at Screening. Bone marrow tissue biopsy will be done within 28 days before first study drug infusion and must be provided at screening. Bone marrow biopsy must be performed again to confirm the first complete response (CR) on patients with previous bone marrow infiltration at baseline, and may also be performed at the investigator discretion if there is clinical suspicion of bone marrow infiltration. All specimens must be sent to central pathology review (*paragraph added to synopsis by amendment 3*).

13.3.2.3 List of abbreviations

New abbreviations were added:

CD4	Cluster of differentiation 4
CD8	Cluster of differentiation 8
CMV	Cytomegalovirus
CRP	C-reactive protein
OI	Opportunistic Infection
PCR	Polymerase chain reaction

13.3.2.4 Section 1.1.2 Clinical experience

Old text:

Copanlisib is currently under investigation in various trials enrolling cancer patients. As of 01 FEB 201~~5~~, approximately ~~377~~ patients with advanced cancer have been treated with copanlisib in Phase 1~~and~~ Phase 2 clinical trials as a single agent or in combination with other agents.

New text:

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 1, Phase 2, and Phase 3 clinical trials (please refer to IB) as a single agent or in combination with other agents.

13.3.2.5 Section 3 Investigator and other study personnel

Old text:

Sponsor's PPD

Name: PPD ~~MD~~

Title: PPD ~~Oncology~~

Address: ~~100 Bayer Blvd~~

~~PO Box 915~~

~~Whippany, NJ 07981, USA~~

Telephone no.: PPD

New text:

Sponsor's PPD

Name: PPD MD, PhD
Title: PPD Oncology
Address: Rua Domingos Jorge, 1100, Predio 9301, 2º andar
CEP 04779-900, Sao Paulo-SP, Brazil
Telephone no.: PPD

13.3.2.6 Section 4 Study design

Old text:

An End-of-treatment (EOT) visit will be performed within 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 (SFU) visit will take place 30~~-35~~ days after the last administration of study drug.

[…]

Bone marrow biopsy will be mandatory at Screening. ~~Biopsies taken up to 28 days prior to treatment start are acceptable. If the baseline biopsy is positive for lymphoma infiltration, it will be mandatory to perform it again to confirm the first complete response (CR)~~.

New text:

An End-of-treatment (EOT) visit will be performed within 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 (SFU) visit will take place 30days (window of +5 days allowed) after the last administration of study drug.

[…]

Bone marrow biopsy will be mandatory at Screening. Bone marrow tissue biopsy will be performed within 28 days before first study drug infusion and must be provided at screening. Bone marrow biopsy must be performed again to confirm the first complete response (CR) on patients with bone marrow infiltration at baseline, and may also be performed at the investigator discretion if there is clinical suspicion of bone marrow infiltration. All specimens must be sent to central pathology review.

13.3.2.7 Section 5.1.1 Inclusion criteria

Old text:

[…]

13. Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements conducted within 7 days before start of study treatment:

[…]

- Platelet count ≥ 75,000/mm^3.

New text:

[…]

13. Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements conducted within 7 days before start of study treatment:

[…]

- 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.

13.3.2.8 Section 5.1.2 Exclusion criteria

Old text:

[…]

Excluded medical conditions

[…]

~~**Excluded previous therapies and medications**~~

New text:

[…]

Excluded medical conditions, previous therapies and medications

[…]

47. Positive cytomegalovirus (CMV) PCR test at baseline.

13.3.2.9 Section 5.2.1 Withdrawal

Old text:

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 ~~glucose and~~ HbA1c.

New text:

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.

13.3.2.10 Section 5.2.1.1 Withdrawal from study treatment

Old text:

- Delay in study drug administration due to toxicities for > 21 days (this does not include the required 1 week break), a delay of study drug dosing due to reasons other than toxicity is not included in this definition (*clarified by amendment 1*).

New text:

- Delay in study drug administration due to toxicities for > 21 days (this does not include the required 1 week break), a delay of study drug dosing due to reasons other than toxicity is not included in this definition (*clarified by amendment 1*). Except in case of delays due to reactivation of CMV where delay could be up to 2 cycles.

13.3.2.11 Section 6.4.1.2 Non-hematological toxicity

Old text:

Table 6-8 Dose modification of study treatment for arterial hypertension

Toxicity (CTCAE)	Study drug action	Recommendation
[…]		
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 skipped. Subsequent study drug administrations may be reduced by 1 dose level at the investigator's discretion.[b]
[…]		

New text:

Table 6-8 Dose modification of study treatment for arterial hypertension

Toxicity (CTCAE)	Study drug action	Recommendation
[…]		
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 skipped otherwise. Subsequent study drug administrations may be reduced by 1 dose level at the investigator's discretion.[b]
[…]		

13.3.2.12 Section 6.4.2.6 Guidance for monitoring and prophylaxis of opportunistic infection (OI)

New section was added:

6.4.2.6.1 Monitoring guidelines for OI

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

- Evaluation of any new onset or worsening of pulmonary symptoms (i.e. cough, dyspnea or fever) that includes an examination at each visit prior to infusion.
- Laboratory tests: cluster of differentiation 4 (CD4) for patients with signs of infection i.e. cough, dyspnea or fever, blood cultures when low ANC of CTCAE Grade 4, PCR for CMV (monthly for the first 6 months of study treatment and every 3 months thereafter).
    - 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 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 will include:

- CD4 and Cluster of differentiation 8 (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 scan)
    - Note: Treatment of opportunistic infections should be based on local SOC.

6.4.2.6.2 Prophylaxis of OI

Mandatory prophylactic therapy is not recommended in all patients:

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

Although not mandated in all patients, OI prophylaxis may be initiated at the discretion of the treating investigator's judgment of the benefit/risk ratio in any patient, irrespective of whether a high-risk feature is present, per local SOC. If so, drug name, indication, 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 local SOC in patients when high risk factors are identified (see protocol Section 6.4.2.6.1). For example: Bactrim or equivalent, Acyclovir or equivalent.

13.3.2.13 Section 7.1.1 Tabulated overview

Old text:

Table 7-1 Study flow chart

	Screening			Treatment *									EOT	SFU	Active follow-up [aa]	Survival follow-up [bb]
	maximum days before C1D1			Cycle 1					Cycle 2 and higher				Within (days) after			
Days	**-28**	**-14**	**-7**	**D1**	**D4**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22 [y]**	**7**	**30-~~35~~ [z]**		**every 3 months**
Acceptable deviation (in days)				-1 to +2 days					-1 to +2 days				Decision to stop	Last dose		±14 days
[…]																

[…]

d After Screening: AE assessment and concomitant medication review must be updated before each dose and ~~30-35 days after last dose~~. 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. 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 a complete review of body systems (*changed by amendment 1*).

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).

[…]

j CBC: Hemoglobin, hematocrit, RBC, WBC (with differential to include absolute neutrophil, lymphocyte, monocyte, basophil and eosinophil counts and platelet count). From Cycle 3 onwards, only hemoglobin, platelet and ANC counts will be performed on Day 8 and Day 15 prior to each infusion.

[…]

o ~~Bone marrow biopsy is mandatory at Screening (biopsy done up to 28 days prior to first dose can be used as baseline evaluation) and to confirm the first complete response, if positive at baseline. Biopsy will be performed as per local standard of care~~ (*clarified by amendment 1*).

[…]

z The post-treatment follow-up 30~~-35~~ days after the last administration of study drug can be conducted via telephone if the patient is no longer being actively seen at the clinic or has started another therapy. In this case, FLymSI-18 questionnaire does not need to be completed at the SFU evaluation (*modified by amendment 1*). Procedures marked with "(X)" are only to be performed, if clinically indicated.

[…]

New text:

Table 7-1 Study flow chart

	Screening maximum days before C1D1			Treatment *									EOT	SFU	Active follow-up [aa]	Survival follow-up [bb]
				Cycle 1					Cycle 2 and higher				Within (days) after			
Days	**-28**	**-14**	**-7**	**D1**	**D4**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22 [y]**	**7**	**30 + 5 days window[z]**		**every 3 months**
Acceptable deviation (in days)				-1 to +2 days					-1 to +2 days				Decision to stop	Last dose		±14 days
[…]																
CMV PCR test[ff, ii]	X			X[ff]					X[ff]							
[…]																
CD4 (for patients with signs of infection) and blood cultures when low ANC of CTCAE Grade 4 [gg, hh, ii]																
[…]																

] CD4 = Cluster of differentiation 4; CMV = cytomegalovirus; […] eCRF= Electronic case report form; […] OI = Opportunistic infection; PCR = polymerase chain reaction;

[…]

d After Screening: AE assessment and concomitant medication review must be updated before each dose and all AEs starting within 30 days after the last dose of study drug should be collected and recorded in eCRF. 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. 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 a complete review of body systems (*changed by amendment 1*), including lung examination.

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.

[…]

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

[…]

o Bone marrow biopsy must be performed within 28 days before first study drug infusion, and to confirm the first complete response if there is bone marrow infiltration at baseline, and also at the investigator discretion if there is clinical suspicion of bone marrow infiltration. All specimens must be sent to central pathology review(*clarified by amendment 1*).

[…]

z The post-treatment follow-up 30days (window of +5 days allowed) after the last administration of study drug can be conducted via telephone if the patient is no longer being actively seen at the clinic or has started another therapy. In this case, FLymSI-18 questionnaire does not need to be completed at the SFU evaluation(*modified by amendment 1*). Procedures marked with “(X)” are only to be performed, if clinically indicated.

[…]

ff Blood test for CMV. Should be performed in all patients prior to IV infusion of copanlisib. Every month for the first 6 months of treatment and every 3 months 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.

gg For patients with identified risk factors and those who developed OI on study treatment, 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 should be 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).

hh Blood cultures should be performed as per local SOC if the patient develops low ANC of CTCAE Grade 4. CD4 count should be performed for patients with signs of infection.

ii *Modified by amendment 4.*

13.3.2.14 Section 7.1.2.1 Screening period

Old text:

[…]

- Bone marrow biopsy: mandatory at Screening and to confirm the first complete response~~, if positive~~ at baseline. ~~Biopsy will be performed as per local standard of care~~ (*clarified by amendment 1*).

New text:

[…]

- Blood test for CMV infection. Patients who are CMV testpositive at baseline will not be eligible.

[…]

- Bone marrow biopsy: mandatory at Screening and to confirm the first complete response in patients with previous bone marrow infiltration at baseline. A bone marrow biopsy may also be performed at the investigator discretion if there is clinical suspicion of bone marrow infiltration. All specimens must be sent to central pathology review (*clarified by amendment 1*).

13.3.2.15 Section 7.1.2.2 Treatment period

Old text:

[…]

For Day 1 of subsequent open-label cycles, dosing criteria outlined in Table 6–2 will apply for patients who switch to open-label treatment (*clarified by amendment 1 and 3*).

New text:

[…]

For Day 1 of subsequent open-label cycles, dosing criteria outlined in Table 6–2 will apply for patients who switch to open-label treatment (*clarified by amendment 1 and 3*).

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

- Monitoring for OI (see Section 6.4.2.6):

  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:

  - 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, PCR for CMV (monthly for first 6 months of treatment and every 3 months thereafter)

  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.

13.3.2.16 Section 7.1.2.2.1 Treatment – Cycle 1

Old text:

Cycle 1 Day 1

[…]

- 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 AEs (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).

[…]

Cycle 1 Day 8

[…]

- 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 CBC and chemistry panel (excluding total cholesterol, LDL and triglycerides) (see Section 6.4 and Section 7.5.3.1).

[…]

Cycle 1 Day 15

[…]

- 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 CBC, chemistry and coagulation panels (excluding total cholesterol, LDL and triglycerides) (see Section 6.4 and Section 7.5.3.1).

[…]

Cycle 1 Day 22

[…]

- 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 CBC and chemistry panel (excluding total cholesterol, LDL and triglycerides) (see Section 7.5.3.1).

New text:

Cycle 1 Day 1

[…]

- 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 AEs (see Section 7.5.1.3).
- Monitoring for OI (see Section 6.4.2.6).
- 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).

[…]

Cycle 1 Day 8

[…]

- 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).
- Monitoring for OI (see Section 6.4.2.6).
- Blood tests for CBC and chemistry panel (excluding total cholesterol, LDL and triglycerides) (see Section 6.4 and Section 7.5.3.1).

[…]

Cycle 1 Day 15

[…]

- 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).
- Monitoring for OI (see Section 6.4.2.6).

- Blood tests for CBC, chemistry and coagulation panels (excluding total cholesterol, LDL and triglycerides) (see Section 6.4 and Section 7.5.3.1).

[…]

Cycle 1 Day 22

[…]

- 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).
- Monitoring for OI (see Section 6.4.2.6).
- Blood tests for CBC and chemistry panel (excluding total cholesterol, LDL and triglycerides) (see Section 7.5.3.1).

13.3.2.17 Section 7.1.2.2.2 Treatment – Cycle 2 and higher

Old text:

Cycle 2 and higher, Day 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 AE related to its administration (e.g. allergic reaction).

[…]

Cycle 2 and higher, Day 8

[…]

- 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).
- On Cycle 2, blood tests for CBC and chemistry panel (excluding total cholesterol, LDL and triglycerides) will be performed. From Cycle 3 onwards, only hemoglobin, platelet and ANC counts will be performed prior to each infusion (see Section 6.4 and Section 7.5.3.1).

[…]

Cycle 2 and higher, Day 15

[…]

- 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).
- *12-lead ECG removed by amendment 1*.

New text:

Cycle 2 and higher, Day 1

[…]

- Toxicity/AE assessment (see Section 7.5.1.3).
- Monitoring for OI (see Section 6.4.2.6).
- 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).

[…]

Cycle 2 and higher, Day 8

[…]

- 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).
- Monitoring for OI (see Section 6.4.2.6).
- On Cycle 2, blood tests for CBC and chemistry panel (excluding total cholesterol, LDL and triglycerides) will be performed. From Cycle 3 onwards, only hemoglobin, platelet and ANC counts will be performed prior to each infusion (see Section 6.4 and Section 7.5.3.1).

[…]

Cycle 2 and higher, Day 15

[…]

- 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).
- Monitoring for OI (see Section 6.4.2.6).
- *12-lead ECG removed by amendment 1*.

13.3.2.18 Section 7.1.2.3 Tumor assessments

Old text:

~~Bone marrow biopsy will be mandatory at baseline and if positive at Screening, will be repeated for confirmation of the first CR.~~ Biopsy will be performed as per local standard of care.

New text:

Bone marrow biopsy is mandatory at baseline and to confirm the first CR if there is bone marrow infiltration at baseline. It may also be performed at the investigator discretion if there is clinical suspicion of bone marrow infiltration. All specimens must be sent to central pathology review. Biopsy will be performed as per local standard of care.

13.3.2.19 Section 7.1.2.5.1 Safety follow-up

Old text:

If a patient discontinues study treatment at any time during the study for any reason (except death or lost to follow-up) SFU visit will take place 30~~–35~~ days after the last administration of study drug.

New text:

If a patient discontinues study treatment at any time during the study for any reason (except death or lost to follow-up) SFU visit will take place 30 days (window of +5 days allowed) after the last administration of study drug.

13.3.2.20 Section 7.5.1.3 Assessments and documentation of adverse events

Old text:

The observation phase for AEs will start with signing the ICF and ~~will~~ end ~~in general with the SFU visit~~ 30~~–35~~ days after the last dose of study drug. 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.

New text:

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 the condition is unlikely to resolve due to the patient's underlying disease.

13.3.2.21 Section 7.5.3.1 Laboratory

Old text:

All laboratory analyses will be performed locally according to the schedule summarized in the flow chart of Section 7.1.1. Dipsticks should be available for urinalysis (*modified by amendment 1 and 3*).

- Complete blood count (CBC): hemoglobin, hematocrit, red blood cell count (RBC), and white blood cell count (WBC) with differential to include absolute neutrophil, lymphocyte, monocyte, basophil and eosinophil counts, and platelet count.

[…]

- ~~•~~ Hemoglobin A1c (*bullet point added by amendment 3*).

New text:

All laboratory analyses will be performed locally according to the schedule summarized in the flow chart of Section 7.1.1. Dipsticks should be available for urinalysis (*modified by amendment 1 and 3*).

- Complete blood count (CBC): hemoglobin, hematocrit, red blood cell count (RBC), and white blood cell count (WBC) with differential to include absolute neutrophil, lymphocyte, monocyte, basophil and eosinophil counts, and platelet count. Differential blood count in percentage can be provided when absolute count is not available per SOC of the local lab.

[…]

- Hemoglobin A1c (*bullet point added by amendment 3*).
- CD4 (for patients with signs of infection), blood cultures when low ANC of CTCAE Grade 4, PCR for CMV.

  For patients with identified risk factors and those who developed opportunistic infections, additional laboratory assessments will include:

  - CD4, CD8 count and ratio, CRP, blood cultures.

13.3.2.22 Section 7.5.3.2.1 Complete physical examination

Old text:

[…]

- Lungs

New text:

[…]

- Lungs: Evaluation of new onset or worsening of pulmonary symptoms, and lung examination.

13.3.2.23 Section 7.5.3.2.2 Brief physical examination

Old text:

[…]

- Lungs

New text:

[…]

- Lungs: Evaluation of new onset or worsening of pulmonary symptoms, and lung examination

13.3.2.24 Section 7.6.3 Electronic patient-reported outcomes evaluation

Old text:

ePRO devices will be implemented in this study. ~~They~~ will be used to complete the FLymSI-18 questionnaire (*modified by amendment 1*). A Site Manual will be provided to sites and each patient ~~to help them understand~~ how the ePRO device~~s~~ work and how to use ~~them~~ correctly. If, for any reason, a device is not available at the site, or technical problems prevent it from working properly, the FLymSI-18 questionnaire will not be completed at that visit (*changed by amendment 3*).

New text:

ePRO devices will be implemented in this study. It will be used to complete the FLymSI-18 questionnaire (*modified by amendment 1*). A Site Manual will be provided to sites and each patient will be trained how the ePRO device works and how to use it correctly. If, for any reason, a device is not available at the site, or technical problems prevent it from working properly, the FLymSI-18 questionnaire will not be completed at that visit (*changed by amendment 3*).

13.3.2.25 Section 8.3.2 Safety variables

Old text:

[…]

TEAE is defined as any event arising or worsening after start of study drug administration until 30~~-35~~ days after the last study drug intake (end of Safety follow-up).

New text:

[…]

TEAE 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).

13.3.2.26 Section 14.1 Evaluation of tumor response

Old text:

[…]

	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

[…]

New text:

[…]

	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 and/or PCR negative

[…]

13.4 Amendment 5

Amendment 5 is a global amendment dated 31 MAR 2017.

13.4.1 Overview of changes

13.4.1.1 Modification 1 - study design revised

Following sponsor's decision to stop enrollment due to lack of feasibility to complete this study in reasonable time frame, the study design is modified from randomized, double-blind, placebo controlled study design to open label, single arm study. After unblinding all patients will be given an opportunity to continue treatment with copanlisib.

Sections affected by this modification: Synopsis; Section 1.2 Rationale of the study; Section 1.3 Benefit-risk assessment; Section 4. Study design; Section 5.2.1 Withdrawal; Section 6.1 Treatments to be administered; Section 6.2 Identity of study treatment; Section 6.3 Treatment assignment; Section 6.4 Dosage and administration; Section 6.5 Blinding; Section 6.7 Treatment compliance; Section 7.1.2.2 Treatment period; Section 7.1.2.4 End-of-treatment visit; Section 7.1.2.5 Follow-up periods; Section 7.1.2.5.1 Safety follow-up; Section 7.3.1 Primary efficacy variable; Section 7.4 Pharmacokinetics / pharmacodynamics; Section 7.5.3 Further safety; Section 10. Premature termination of the study; Section 11.2 Patient information and consent; Appendix 14.6 Quality of life questionnaire: NCCN-FACT FLymSI-18

13.4.1.2 Modification 2 – statistical methods and efficacy variables revised

Following sponsor's decision to stop enrollment, limited number of patients will be included in the analyses, as a consequence the statistical analyses in this study will be focused on descriptive statistics without any hypothesis testing.

The primary efficacy variable is changed from PFS to ORR. The following secondary efficacy variables are removed: Time to progression, Time to deterioration in disease-related symptoms – physical (DRS-P) of at least 3 points and Time to improvement in DRS-P of at least 3 points.

Sections affected by this modification: Synopsis; Section 2. Study objectives; Section 4. Study design; Section 7.1.1 Tabulated overview; Section 7.6.2 Quality of life questionnaire; Section 7.6.3 Electronic patient-reported outcomes evaluation; Section 8.1 General considerations; Section 8.2 Analysis sets; Section 8.3.1 Efficacy variables; Section 8.3.1.1 Primary efficacy variable; Section 8.3.1.2 Secondary efficacy variables; Section 8.3.1.3 Other efficacy variables; Section 8.4.1 Population characteristics; Section 8.4.2 Efficacy; Section 8.4.2.1 Primary efficacy analysis; Section 8.4.2.2 Secondary efficacy analysis; Section 8.4.2.3 Confirmatory statistical testing strategy; Section 8.4.2.4 Subgroup analyses; Section 8.4.3 Safety; Section 8.6 Determination of sample size; Section 9.3 Data processing

13.4.1.3 Modification 3 - Central image evaluation revised

Following sponsor's decision to stop enrollment, limited number of patients will be included in the efficacy analyses and the primary efficacy endpoint is changed from PFS to ORR. The efficacy analyses will be done based on investigator's assessment of tumor response. Therefore, language on central image evaluation is modified by removing central image review.

Sections affected by this modification: Synopsis; Section 3. Investigator and other study personnel; Section 4. Study design; Section 5.2.1.1 Withdrawal from study treatment; Section 6.4 Dosage and administration; Section 7.1.2.5.2 Active follow-up; Section 7.3.2 Radiological tumor assessments; Section 7.3.3 Tumor assessments in patients with WM

13.4.1.4 Modification 4 - Change in frequency of tumor assessment

Text is modified to allow sites to determine the frequency of radiological tumor assessment and serum tests (for LPL/WM patients only) based on local standard of care, but no less than every 16 weeks. This change is made for easier site compliance, and the requirement for determination of no less than every 16 weeks is implemented with the consideration of biological characteristics of indolent lymphoma.

Section affected by this modification: Synopsis; Section 4. Study design; Section 7.1.1 Tabulated overview; Section 7.1.2.3 Tumor assessments; Section 7.3.2 Radiological tumor assessments

13.4.1.5 Modification 5 – Survival follow-up revised

The frequency of survival follow up is changed from every 3 months to every 6 month. This change is implemented with the consideration of biological characteristics of indolent lymphoma.

Sections affected by this modification: Synopsis; Section 4. Study design; Section 5.2.1.2 Withdrawal from follow-up period; Section 7.1.1 Tabulated overview; Section 7.1.2.5.3 Survival follow-up

13.4.1.6 Modification 6 – Bone marrow biopsy revised

Due to the change of study design language on bone marrow biopsy is modified. Bone marrow biopsy will be performed as per local standard of care. This was done to reduce the burden on patients and sites. In addition, as a result the overall number of samples to be shipped and processed will be reduced.

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

13.4.1.7 Modification 7 – laboratory evaluations revised

Frequency of HbA1C and total cholesterol, LDL and triglycerides are changed to be tested at Screening and EOT.

Sections affected by this modification: Section 7.1.1 Tabulated overview; Section 7.1.2.2.2 Treatment – Cycle 2 and higher

13.4.1.8 Modification 8 – ECG and MUGA scan or echocardiogram evaluations revised

Frequency of 12-lead ECG and MUGA scan or echocardiogram are changed to Screening, EOT and clinically indicated, to avoid overtesting. The patient will have the ECG and/or MUGA or echocardiogram if clinically indicated to ensure patients' safety.

Sections affected by this modification: Section 7.1.1 Tabulated overview; Section 7.1.2.2.1 Treatment – Cycle 1; Section 7.1.2.2.2 Treatment – Cycle 2 and higher

13.4.1.9 Modification 9 – change in the visits during treatment period

Visit on Cycle 1 Day 4 and Cycle 1 Day 22 are no longer required. The safety assessment will be done in the following visit. The visits without study drug infusions are removed for easier patients' compliance.

Sections affected by this modification: Section 7.1.1 Tabulated overview; Section 7.1.2.2.1 Treatment – Cycle 1; Section 7.1.2.2.2 Treatment – Cycle 2 and higher

13.4.1.10 Modification 10 – administrative information updated and other clarification

- The study PPD changed. Therefore the contact details are updated.
- The sponsor's medically responsible person changed. Therefore the signature page was updated.
- Whole blood collection for biomarker is removed, because it was already collected when the patient was screened.
- Revision of list of references
- Revision of list of abbreviations

Sections affected by this modification: Title Page; Signature of the sponsor's medically responsible person; List of abbreviations; Section 3. Investigator and other study personnel; Section 7.1.1 Tabulated overview; Section 7.1.2.2.1 Treatment – Cycle 1; Section 7.6.1 Biomarker investigations; Section 12. Reference list

13.4.2 Changes to the protocol text

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. 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 typing errors or omissions are not highlighted in this amendment.

13.4.2.1 Title Page

Old text:

[..]

Clinical study phase:	III	Date:	~~21 JUL 2016~~
EudraCT no.:	2014-000925-19	Version no.:	~~4.0~~

[…]

Sponsor's PPD :

PPD ~~MD, PhD~~

~~Bayer S.A.~~

~~Rua Domingos Jorge, 1100, Predio 9301, 2º andar~~

~~CEP 04779-900, Sao Paulo-SP, Brazil~~

Telephone no.: PPD

[…]

New text:

[..]

Clinical study phase:	III	Date:	31 MAR 2017
EudraCT no.:	2014-000925-19	Version no.:	5.0

[…]

Sponsor's PPD :

PPD MD

PPD , Bayer Center,

No.27 Dong San Huan North Road,

Chaoyang District, Beijing, China, 100020

Telephone no.: PPD

[…]

13.4.2.2 Signature of the sponsor's medically responsible person

Old text:

Name: PPD MD Role: PPD (PPD

Date: ..... Signature: .....

New text:

Name: PPD MD Role: PPD (PPD

Date: ..... Signature: .....

13.4.2.3 Synopsis

Old text:

[…]	
Study objectives	The primary objective of this study is: • To investigate ~~whether copanlisib as monotherapy is superior to placebo~~ in ~~prolonging progression-free survival (PFS) in~~ patients with rituximab-refractory iNHL who have received two or more prior lines of treatment, have been exposed to rituximab and alkylating agent(s), and have progressed within six months of the end of the last previous rituximab-containing regimen. The secondary objectives of this study are to evaluate: • Efficacy including ~~tumor~~ response~~, time to progression~~ and overall survival. • ~~The following characteristics of disease-related symptoms: time to deterioration and time to improvement.~~ • Safety. The other objectives of this study are to evaluate: • ~~PFS2 in placebo-treated patients who switched to open-label copanlisib treatment.~~ • Pharmacokinetics. • Biomarkers. • ~~Quality of life.~~
[…]	
Duration of treatment	Treatment will be continued until disease progression (PD) (per ~~central independent blinded radiology review~~) as defined in the Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. unacceptable toxicity, or until another criterion is met for withdrawal from the study treatment. For patients with Waldenström macroglobulinemia (WM), response assessment will be done according to the Response Assessment in Waldenström macroglobulinemia: update from the VIth International Workshop.
Reference drug	Not applicable. ~~This is a placebo-controlled study.~~
[…]	
Study design	A randomized, double-blind, two-arm Phase III study to evaluate the efficacy and safety of copanlisib as monotherapy in comparison to placebo in patients with rituximab-refractory iNHL. ~~Approximately 189 patients (144 FL and 45 other iNHL) who meet the~~

	~~eligibility criteria will be randomly assigned in a 2:1 ratio to one of the double-blinded treatment arms: copanlisib monotherapy or placebo, respectively (*changed by amendment 1*).~~ ~~Patients will be stratified at randomization based on NHL histology (FL histology vs. other iNHL histology), the time between last course of systemic anticancer therapy and most recent progression (≤ 6 months vs. > 6 months) and prior treatment with PI3K inhibitors (yes vs. no) (*changed by amendment 1*).~~ ~~Patients who experience PD on placebo treatment (per central independent blinded radiology review) can be offered open-label copanlisib upon discretion of the investigator and patient's consent. After~~ individual patient unblinding, patients receiving placebo who switch to ~~open-label~~ copanlisib will have all study assessments ~~and timing~~ reset to the initial schedule of study evaluations (i.e. as if the patient was ~~restarting~~ the study at Cycle 1 Day 1).
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 deterioration and time to improvement in disease-related symptoms – physical (DRS-P) of at least 3 points of lymphoma as measured by the FLymSI-18 questionnaire (*changed by amendment 1*).~~ ~~Other efficacy variables are PFS2, FLymSI-18 subscale, total score analyses and time to onset of physical symptoms of lymphoma based on DRS-P, and ECOG performance status (*changed by amendment 1*).~~ 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 the copanlisib treatment arm~~ will receive 60 mg copanlisib IV infusion on Days 1, 8 and 15 of each 28-day treatment cycle. ~~Patients randomized to the placebo arm will receive placebo IV infusion on Days 1, 8 and 15 of each 28-day treatment cycle.~~ Treatment will be continued until PD ~~(per central independent blinded radiology review)~~ unacceptable toxicity, or until another criterion is met for withdrawal from the study treatment. […] 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 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 radiological assessments ~~by central independent blinded review~~ as outlined in this protocol from the day of ~~randomization~~ 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 treatment period as well as during the Active follow-up

	period tumor assessments with the same modality will be performed ~~every 12 weeks during Year 1, every 16 weeks during Year 2, and every 24 weeks during Year 3.~~ 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. ~~As long as the patient has not experienced PD, investigator's assessment is sufficient for case management. In the event of progression, radiological real-time confirmation by central independent blinded evaluation is required before a final decision to stop the treatment is made. The final~~ evaluation of treatment response (best response: ORR and CRR) will be done by ~~central blinded review and for those not undergoing PD confirmation in retrospective setting~~ 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. However, in cases when WM patients will develop disease progression confirmed radiologically by presenting with measurable lesion(s) without simultaneous increase in IgM~~, the imaging scans should be submitted for central review and PD confirmation.~~ WM patients who have radiologically measurable lesion at Screening will continue having radiological assessments and, in addition, will have laboratory tests performed on the same days. Bone marrow biopsy will be mandatory at Screening. Bone marrow tissue biopsy will be done within 28 days before first study drug infusion and must be provided at screening. Bone marrow biopsy must be performed again to confirm the first complete response (CR) on patients with previous bone marrow infiltration at baseline, and may also be performed at the investigator discretion if there is clinical suspicion of bone marrow infiltration. ~~All specimens must be sent to central pathology review .~~
Type of control	~~Inactive control: placebo.~~
Number of patients	~~Approximately 237 patients will be screened for enrollment to this study. Approximately 189 patients who meet the eligibility criteria will be randomized – the copanlisib monotherapy arm will consist of approximately 126 patients and placebo arm of approximately 63 patients.~~
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	~~Primary efficacy analysis:~~ ~~The primary efficacy variable is PFS as assessed by central review. It will be evaluated whether PFS in the copanlisib group is higher compared to PFS in the placebo group for the total study population and separately for the FL subgroup. All efficacy analyses will be performed when approximately 82 centrally evaluated PFS events are observed in the FL subgroup.~~ ~~The study-wise alpha of 1% will initially be split, according to the test strategy for this study: with 80% * 1% = 0.8% assigned to the one-sided PFS test in the FL subgroup, and 20% * 1% = 0.2% to the one-sided PFS~~

	~~test in the total study population.~~ ~~The following null hypothesis will be tested:~~ ~~$H_{0, PFS}$: $S_{Copanlisib}(t) = S_{Placebo}(t)$ for all time points $t \geq 0$~~ ~~The alternative hypothesis will be:~~ ~~$H_{1,PFS}$: $S_{Copanlisib}(t) > S_{Placebo}(t)$ for at least one time point $t \geq 0$, and~~ ~~$S_{Copanlisib}(t) \geq S_{Placebo}(t)$ for all time points $t \geq 0$,~~ ~~where $S_{Copanlisib}$ denotes the survival function of the copanlisib group and $S_{Placebo}$ denotes the survival function of the placebo group in the total study population or the FL subgroup, respectively.~~ ~~The following decision rule to test the null hypothesis will be applied:~~ ~~According to the size of this study it is justified to assume that under $H_{0, PFS}$ the one-sided log-rank test is a sufficiently close approximation to the normal distribution. If the z-value from the one-sided log-rank test (for the difference $S_{Copanlisib} - S_{Placebo}$, stratified by the same factors as used for randomization) is larger than the respective critical quantile from the normal distribution (for FL subgroup: $z_{0.992} = 2.409$, for the total study population: $z_{0.998} = 2.878$), the null hypothesis will be rejected in favor of the alternative hypothesis.~~ ~~Additional analyses of the primary efficacy variable:~~ ~~Kaplan-Meier estimates of median times to PFS (including 98% confidence interval) and Kaplan-Meier curves for the total study population and the FL subgroup will be presented for each treatment group.~~ ~~The hazard ratio (including 98% confidence interval) will be derived for the total study population and separately for the FL subgroup from a Cox proportional hazards models that are stratified by the same factors as used for the primary efficacy analysis.~~ ~~The censoring mechanism of patients 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 statistical analysis plan (SAP).~~

New text:

[…]	
Study objectives	The primary objective of this study is: • To investigate objective tumor response rate (ORR) assessed in all patients with rituximab-refractory iNHL who have received two or more prior lines of treatment, have been exposed to rituximab and alkylating agent(s), and have progressed within six month of the end of the last previous rituximab-containing regimen. The secondary objectives of this study are to evaluate: • Efficacy including complete response rate and overall survival. • Safety. The other objectives of this study are to evaluate: • Pharmacokinetics. • Biomarkers.
[…]	
Duration of treatment	Treatment will be continued until disease progression (PD) (per investigator's assessment) as defined in the Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. unacceptable toxicity, or until another criterion is met for withdrawal from the study treatment. For patients with Waldenström macroglobulinemia (WM), response assessment will be done according to the Response Assessment in Waldenström macroglobulinemia: update from the VIth International Workshop.
Reference drug	Not applicable.
[…]	

Study design	A randomized, double-blind, two-arm Phase III study to evaluate the efficacy and safety of copanlisib as monotherapy in comparison to placebo in patients with rituximab-refractory iNHL. Following sponsor's decision to stop enrollment due to lack of feasibility to complete this study in reasonable time frame, the study design is modified to reflect an open label study. After unblinding all patients will be given an opportunity to continue treatment with copanlisib. Patients who are on copanlisib treatment at the time of unblinding will continue copanlisib treatment. Patients who are on placebo at the time of unblinding will be offered to switch to copanlisib treatment after unblinding procedures are completed. After individual patient unblinding, patients receiving placebo, who switch to copanlisib will have all study assessments reset to the initial schedule of study evaluations (i.e. as if the patient was restarted the study at Cycle 1 Day 1).
Methodology	[…] The patients in the Active follow-up will have radiological assessments as outlined in this protocol from the day of start of study treatment 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 least at 6-month intervals during the Survival follow-up period (up to 3 years after the last patient started study treatment), except for patients who object to follow-up data collection. […] During the treatment period as well as during the Active follow-up period tumor assessments with the same modality will be performed per local SOC but not less than every 16 weeks. 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 evaluation of treatment response (best response: ORR and CRR) will be done by the investigator. […] Bone marrow biopsy will be mandatory at Screening. Bone marrow tissue biopsy will be done within 28 days before first study drug infusion and must be provided at screening. Bone marrow biopsy must be performed again to confirm the first complete response (CR) on patients with previous bone marrow infiltration at baseline, and may also be performed at the investigator discretion if there is clinical suspicion of bone marrow infiltration. Bone marrow biopsy will be performed per local standard of care.
Type of control	Not applicable.
Number of patients	Following sponsor's decision to stop the study no further patients will be enrolled. All patients enrolled in the study by the time the protocol amendment 5 is approved will be unblinded.

Primary variable	The primary efficacy analysis is ORR, which is defined as the proportion of patients who have a best response rating over the whole duration of the study of complete response (CR) or partial response (PR) according to the Lugano Classification (21), 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 (22).
Plan for statistical analysis	Due to the decision of stopping enrollment as protocol amendment 5 becomes effective, limited number of patients will be included in the analyses. Therefore, the statistical analyses included in this study will be focused on descriptive statistics without any hypothesis testing. Two sets of analyses will be performed at the timing when all treated patients completed at least 6 cycles of study treatment: 1) unblinding cutoff: analyze all data available before the unblinding (details in section 6.5); 2) final analysis: analyze all data available until all treated patients complete at least 6 cycles of study treatment.

13.4.2.4 List of abbreviations

Old text:

[…]

~~ePRO~~	~~Electronic patient-reported outcome~~
[…]	
~~FWB~~	~~Functional and well-being (subscale)~~
[…]	
~~H_0~~	~~Null hypothesis~~
~~H_1~~	~~Alternative hypothesis~~
~~Hb~~	~~Hemoglobin~~
[…]	
~~ImpDRSP~~	~~Improvement in disease-related symptoms – physical~~
[…]	
~~ITF~~	~~Investigator's trial file~~
[…]	
~~NaOH~~	~~Sodium hydroxide~~
[…]	
~~SAC~~	~~Statistical Analysis Center~~
[…]	
~~SUV~~	~~Standardized uptake value~~
[…]	
~~TMF~~	~~Trial master file~~
~~TSE~~	~~Treatment side effects (subscale)~~
~~TTP~~	~~Time to progression~~

[…]

New text: no new abbreviations were added.

13.4.2.5 Section 1.2 Rationale of the study

Old text:

[…]

~~In order to provide a scientifically rigorous answer about copanlisib single agent activity, the randomized study is the most appropriate approach. Because no standard of care is available for the selected patient population, placebo is an appropriate choice of control in this randomized study. To minimize risk, following parameters are included in this study design (*added by amendment 1*):~~

- ~~2:1 randomization.~~
- ~~Exclusion of patients with bulky disease.~~
- ~~Opportunity for patients in the control arm to switch to active treatment after progression will ensure that all patients with radiologically confirmed PD will be treated with copanlisib.~~

~~Considering the pre-clinical profile of copanlisib and the evidence of clinical activity emerging from Phase I study 12871 and the ongoing Phase II study 16349, it is expected that copanlisib will improve progression-free survival (PFS) in patients with rituximab-refractory iNHL who have received two or more prior lines of treatment (*changed by amendment 1*).~~

New text:

[…]

Following sponsor's decision to stop enrollment due to lack of feasibility to complete this study in reasonable time frame, the study design is modified to reflect an open label study. All patients on study treatment will be offered to continue treatment with copanlisib after unblinding procedures are completed.

13.4.2.6 Section 1.3 Benefit-risk assessment

Old text:

[…]

Hyperglycemia and hypertension, the most frequently observed and expected toxicities with copanlisib, have been manageable. Toxicities will be carefully monitored during the course of the study with a detailed and tailored program of management. ~~A Data Monitoring Committee (DMC) will be instituted to maximize the safety of the patients participating in the study.~~

~~Because of the slowly progressing nature of the disease, the low symptom burden, and the opportunity to receive open-label copanlisib following PD on placebo, the patients assigned to the placebo arm will not be exposed to undue risk.~~

[…]

New text: no new text was added.

13.4.2.7 Section 2. Study objectives

Old text:

The primary objective of this study is:

- To investigate ~~whether copanlisib as monotherapy is superior to placebo~~ in ~~prolonging progression-free survival (PFS)~~ in patients with rituximab-refractory iNHL who have received two or more prior lines of treatment, have been exposed to rituximab and alkylating agent(s), and have progressed within six months of the end of the last previous rituximab-containing regimen (*changed by amendment 1*).

The secondary objectives of this study are to evaluate:

- Efficacy including ~~tumor~~ response~~, time to progression~~ and overall survival (*modified by amendment 1*).
- ~~The following characteristics of disease-related symptoms: time to deterioration and time to improvement (changed by amendment 1).~~
- Safety.

The other objectives of this study are to evaluate:

- ~~PFS2 in placebo-treated patients who switched to open-label copanlisib treatment (added by amendment 1).~~
- Pharmacokinetics.
- Biomarkers.
- ~~Quality of life.~~

New text:

The primary objective of this study is:

- To investigate objective tumor response rate (ORR) assessed in all patients with rituximab-refractory iNHL who have received two or more prior lines of treatment, have been exposed to rituximab and alkylating agent(s), and have progressed within six month of the end of the last previous rituximab-containing regimen.

The secondary objectives of this study are to evaluate:

- Efficacy including complete response rate and overall survival.
- Safety.

The other objectives of this study are to evaluate:

- Pharmacokinetics.
- Biomarkers.

13.4.2.8 Section 3. Investigator and other study personnel

Old text:

Sponsor's PPD

Name: PPD ~~MD, PhD~~
~~Title:~~ PPD ~~Oncology~~
~~Address: Rua Domingos Jorge, 1100, Predio 9301, 2º andar~~
~~CEP 04779-900, Sao Paulo-SP, Brazil~~
Telephone no.: PPD

[…]

Data Monitoring Committee

[…]

The DMC will include at least three members, including an independent Statistician and Oncologist. Safety review meetings will be held ~~periodically~~ as per separate DMC charter. ~~Enrollment to the study will continue throughout the scheduled meetings of the DMC.~~

[…]

Central radiological evaluation

~~Radiological evaluation of computed tomography/magnetic resonance imaging (CT/MRI) scans will be performed centrally.~~

[…]

New text:

Sponsor's PPD

Name: PPD MD
PPD Bayer Center,
No.27 Dong San Huan North Road,
Chaoyang District, Beijing, China, 100020
Telephone no.: PPD

[…]

Central radiological evaluation

After study stopped for enrollment and all patients will be unblinded and offered an open label study treatment, there will be no central radiological evaluation.

13.4.2.9 Section 4. Study design

Old text:

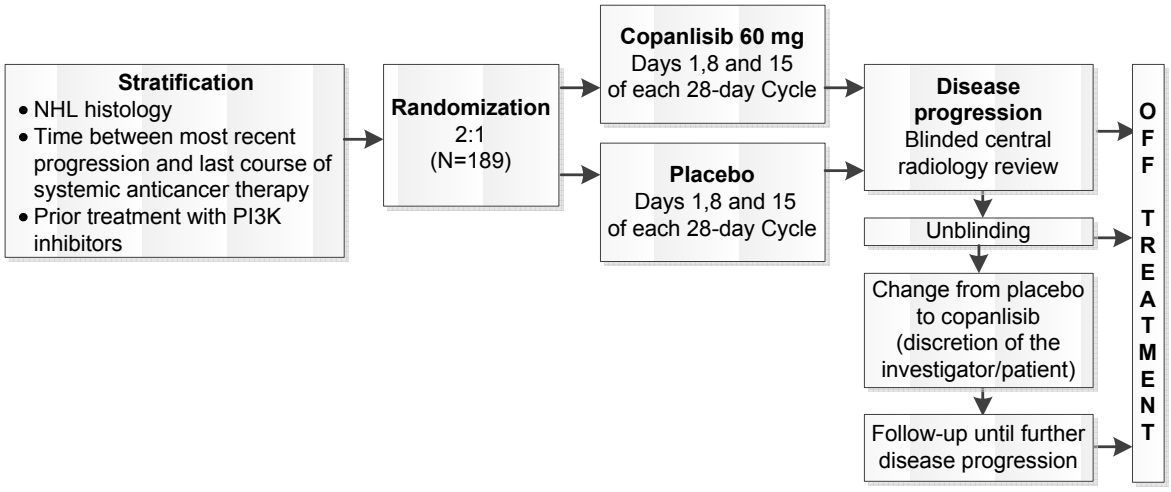
Design overview

[…]

The start of the study period is defined by signing of the informed consent form (ICF). ~~Assuming a 20% screen failure rate, approximately 237 patients will be screened for enrollment to this study. Approximately 189 patients who meet the eligibility criteria (see Section 5.1) will be randomly assigned in a 2:1 ratio to one of the double-blinded treatment arms: copanlisib monotherapy or placebo. The copanlisib monotherapy arm will consist of approximately 126 patients and placebo arm of approximately 63 patients. Patients will be stratified at randomization based on NHL histology (FL histology vs. other iNHL histology), the time between last course of systemic anticancer therapy and most recent progression (≤ 6 months vs. > 6 months) and prior treatment with PI3K inhibitors (yes vs. no) (see Section 6.3). The study is planned to include approximately 144 patients with FL histology and 45 patients with other iNHL histologies (*paragraph changed by amendment 1*).~~

A graphical presentation of the ~~overall~~ study design is shown in Figure 4–2.

~~**Figure 4–2 Overall study design**~~



~~NHL = Non-Hodgkin's lymphoma, PI3K = Phosphatidylinositol 3-kinase.~~

Figure modified by amendment 1

The start of the treatment period is defined by first administration of study drug (copanlisib ~~or placebo~~). Copanlisib will be administered IV over approximately 1 h at starting dose of 60 mg on Days 1, 8 and 15 of each 28-day treatment cycle. ~~Patients in the placebo arm will receive a placebo IV infusion at the same schedule~~. Treatment will be continued until PD (per ~~central~~

~~independent blinded radiology review~~) as defined in the Lugano Classification (21), unacceptable toxicity, or until another criterion is met for withdrawal from the study treatment (see Section 5.2). For patients with WM, response assessment will be done according to the Owen criteria (22).

~~Patients who experience PD on placebo treatment (per central independent blinded radiology review) can be offered open-label copanlisib upon discretion of the investigator and patient's consent.~~ After individual patient unblinding, patients receiving placebo who switch to ~~open-label~~ copanlisib will have all study assessments ~~and timing~~ reset to the initial schedule of study evaluations (i.e. as if the patient was ~~restarting~~ the study at Cycle 1 Day 1).~~These patients~~ will be treated until ~~further~~ disease progression (per ~~central review)~~ unacceptable toxicity, or until another criterion is met for withdrawal from the study treatment (see Section 5.2).

[…]

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 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 radiological assessments by ~~central independent blinded review~~ as outlined in this protocol from the day of ~~randomization~~ 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.

[…] The method chosen at the baseline must be the same throughout the study. During the treatment period as well as during the Active follow-up period tumor assessments with the same modality will be performed ~~every 12 weeks during Year 1, every 16 weeks during Year 2, and every 24 weeks during Year 3 (*modified by amendment 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 (21), and for patients with WM, according to the Owen criteria (22). Detailed instructions on tumor assessment are provided in Appendix 14.1. ~~As long as the patient has not experienced PD, investigator's assessment is sufficient for case management. In the event of progression, radiological real-time confirmation by central independent blinded evaluation is required before a final decision to stop the treatment is made. The final evaluation of treatment response (best response: objective tumor response rate [ORR] and complete response rate [CRR]) will be done by central blinded review and for those not undergoing PD confirmation in retrospective setting (*modified by amendment 3*).~~

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. However, in cases when WM patients ~~will~~ develop ~~disease progression confirmed radiologically by presenting with measurable lesion(s)~~ without simultaneous increase in IgM~~, the imaging scans should be submitted for central review and PD confirmation.~~ WM patients who have radiologically measurable lesion at Screening will continue having radiological assessments and, in addition, will have laboratory tests performed on the same days.

Bone marrow biopsy will be mandatory at Screening. Bone marrow tissue biopsy will be performed within 28 days before first study drug infusion and must be provided at screening. Bone marrow biopsy must be performed again to confirm the first complete response (CR) on patients with bone marrow infiltration at baseline, and may also be performed at the investigator discretion if there is clinical suspicion of bone marrow infiltration. ~~All specimens must be sent to central pathology review (*paragraph modified by amendment 4*).~~

~~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).

[…]

~~Health-related quality of life (QoL) will be assessed using the FLymSI-18 questionnaire. This questionnaire is to be completed according to schedule specified in Section 7.6.2.~~

Primary 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). All efficacy analyses will be performed when approximately 82 centrally evaluated PFS events are observed in the FL subgroup (*changed by amendment 1*).~~

Justification of the design

The pre-clinical profile of copanlisib and preliminary efficacy data from Phase I study 12871 and Phase II study 16349 suggest that copanlisib may improve PFS in patients with rituximab-refractory iNHL who have received two or more prior lines of treatment and have been exposed to rituximab and alkylating agent(s). The purpose of this study is to demonstrate efficacy and safety of treatment with copanlisib in patients where treatment is indicated, with ~~a controlled randomized study with PFS~~ as the primary endpoint.

~~The use of placebo as a comparator in this study is justified for the following reasons:~~

- ~~No standard of care is available for the defined patient population.~~
- ~~Published data indicates multiple options of chemotherapy combinations or single agent therapy used in these patients based on data from, often small, single arm studies.~~
- ~~No randomized study has confirmed efficacy or safety of these therapeutic options, including for those agents where regulatory approval was granted (bendamustine, idelalisib). Potential control agents have limited data on PFS.~~
- ~~The natural course of disease in patients with rituximab-refractory iNHL is not known.~~
- ~~Use of placebo can minimize investigator bias in assessing treatment effects beyond tumor shrinkage. This is particularly important when assessing duration endpoints.~~

- ~~This study is designed to show significant improvement in PFS for study drug vs. control (132% improvement in median PFS).~~
- ~~2:1 randomization will assure that the majority of patients will be treated with copanlisib from onset.~~
- ~~Exclusion of patients with bulky disease.~~
- ~~Available opportunity for patients in the control arm to switch to active treatment after progression will ensure that all patients with radiologically confirmed PD will be treated with copanlisib. Additional exploratory efficacy endpoint is PFS2, which will assess PFS for patients on placebo arm who switched to receive therapy with copanlisib.~~

~~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 expected rarity of patients eligible for enrollment.~~

End of study

[…]

~~However, as the primary endpoint of this study is event-based, the end of the study as a whole will only be reached when this endpoint has been achieved in patients in all participating centers (EU and non-EU).~~

[…]

New text:

Design overview

[…]

The start of the study period is defined by signing of the informed consent form (ICF).

Approximately 189 patients (of approx. 237 screened) will meet the eligibility criteria (see Section 5.1) and will be randomly assigned in a 2:1 ratio to one of the double-blinded treatment arms: copanlisib monotherapy (approx. 126 patients) or placebo (approx. 63 patients). Patients will be stratified at randomization based on NHL histology (FL histology: approx. 144 patients; iNHL histology: approx. 45 patients) , the time between last course of systemic anticancer therapy and most recent progression and prior treatment with PI3K inhibitors (see Section 6.3).

Following sponsor's decision to stop enrollment due to lack of feasibility to complete this study in reasonable time frame, the study design is modified to reflect an open label study. All

patients on study treatment will be offered to continue treatment with copanlisib after unblinding procedures are completed (see Section 6.5).

A graphical presentation of the study design valid as of amendment 5 is shown in Figure 4–2.

Figure 4–2 Overall study design as of amendment 5

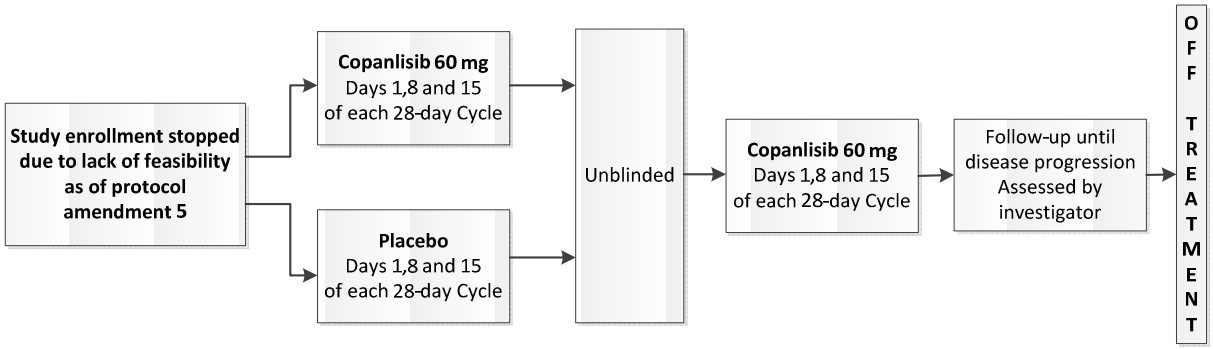


Figure modified by amendment 1 and replaced by amendment 5.

The start of the treatment period is defined by first administration of study drug (copanlisib). Copanlisib will be administered IV over approximately 1 h at starting dose of 60 mg on Days 1, 8 and 15 of each 28-day treatment cycle. Treatment will be continued until PD (per investigator's assessment) as defined in the Lugano Classification (21), unacceptable toxicity, or until another criterion is met for withdrawal from the study treatment (see Section 5.2). For patients with WM, response assessment will be done according to the Owen criteria (22).

All patients after unblinding procedures are completed will be offered an opportunity to continue this clinical study and receive active treatment with copanlisib. Patients who are on copanlisib treatment at the time of unblinding will continue copanlisib treatment. Patients who are on placebo at the time of unblinding will switch to copanlisib treatment after unblinding procedures are completed. After individual patient unblinding, patients receiving placebo, who switch to copanlisib will have all study assessments reset to the initial schedule of study evaluations (i.e. as if the patient was restarted the study at Cycle 1 Day 1). Patients will be treated until disease progression (per investigator's assessment), unacceptable toxicity, or until another criterion is met for withdrawal from the study treatment (see Section 5.2).

[…]

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 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 radiological assessments by investigator as outlined in this protocol from the day of start of study treatment 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 sponsor's GPV department.

All patients will be followed off-study for overall survival at least at 6-month intervals during the Survival follow-up period (up to 3 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".

[…] The method chosen at the baseline must be the same throughout the study. During the treatment period as well as during the Active follow-up period tumor assessments with the same modality will be performed, and the schedule of tumor assessment will be performed per local standard of care of the institution but not less than every 16 weeks. 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 (21), and for patients with WM, according to the Owen criteria (22). Detailed instructions on tumor assessment are provided in Appendix 14.1. All the efficacy analyses will be done based on investigator's assessment of tumor response.

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. However, in cases when WM patients who develop extramedullary disease without simultaneous increase in IgM will have radiological assessment to confirm disease progression (per investigator's assessment). 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. Bone marrow tissue biopsy will be performed within 28 days before first study drug infusion and must be provided at screening. Bone marrow biopsy must be performed again to confirm the first complete response (CR) on patients with bone marrow infiltration at baseline, and may also be performed at the investigator discretion if there is clinical suspicion of bone marrow infiltration. Bone marrow biopsy will be performed as per local standard of care.

All collected tumor tissue samples will be utilized 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).

[…]

Primary variable

Due to the decision of stopping enrollment, limited number of patients will be included in the analyses. Therefore, the statistical analyses included in this study will be focused on descriptive statistics.

The primary efficacy variable of this study will be objective tumor response rate (ORR), which is defined as the proportion of patients who have a best response rating up to the dates of data cutoffs (for dates of data cutoffs, see details in section 8.1) of complete response (CR) or partial response (PR) according to the Lugano Classification (21), 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 (22).

Justification of the design

The pre-clinical profile of copanlisib and preliminary efficacy data from Phase I study 12871 and Phase II study 16349 suggest that copanlisib may improve PFS in patients with rituximab-refractory iNHL who have received two or more prior lines of treatment and have been exposed to rituximab and alkylating agent(s). The purpose of this study is to demonstrate efficacy and safety of treatment with copanlisib in patients where treatment is indicated, with ORR as the primary endpoint.

[…]

13.4.2.10 Section 5.2.1 Withdrawal

Old text:

A patient who, for any reason (e.g. failure to satisfy the selection criteria), terminates the study before randomization is regarded a "screening failure".

A patient who discontinues study participation prematurely for any reason is defined as a "dropout" if the patient has already ~~been randomized~~.

~~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 re-screening will start again by signing a new informed consent form and being assigned a new PID.~~

~~All initial screening laboratory tests will need to be taken within 7 days prior to planned Cycle 1 Day 1. 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 which are 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 re-testing cannot be completed within 7 days of the Cycle 1 Day 1, all blood and urinary tests that are required to be within 7 days of Cycle 1 Day 1 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. CT/MRI scans need to be re-submitted with the new PID (*sentence added by amendment 3*).~~

~~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 (*modified by amendment 4*).~~

New text:

A patient who, for any reason (e.g. failure to satisfy the selection criteria), terminates the study before randomization is regarded a "screening failure".

A patient who discontinues study participation prematurely for any reason is defined as a "dropout" if the patient has already entered treatment.

13.4.2.11 Section 5.2.1.1 Withdrawal from study treatment

Old text:

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

- […]
- Disease progression (PD) as defined in the Lugano Classification (21), and for patients with WM, according to the Owen criteria (22) (*changed by amendment 1*). Detailed instructions on tumor assessment are provided in Appendix 14.1. ~~Radiological PD must be assessed by central independent blinded review before unblinding of study treatment (copanlisib or placebo). The result of PD per central review instead of investigational site image assessment will be used to unblind the patient. Patients who have received placebo can be offered open-label copanlisib upon discretion of the investigator and patient's consent.~~

[…]

New text: no new text was added.

13.4.2.12 Section 5.2.1.2 Withdrawal from follow-up period

Old text:

[…]

All patients will be contacted at least every ~~3~~ months to determine survival status during the Survival follow-up period (up to 3 years after the last patient started study treatment).

[…]

New text:

[…]

All patients will be contacted at least every 6 months to determine survival status during the Survival follow-up period (up to 3 years after the last patient started study treatment).

[…]

13.4.2.13 Section 6.1 Treatments to be administered

Old text:

The following treatments will be administered in this study:

- Copanlisib (BAY 80-6946) solution for IV infusion (study drug/investigational medicinal product)
- ~~*Placebo solution for IV infusion*~~

~~Patients randomized to the copanlisib treatment arm~~ will receive copanlisib IV infusion at a starting dose of 60 mg as single agent on Days 1, 8 and 15 of each 28-day treatment cycle.

~~Patients randomized to the placebo arm will receive placebo IV infusion on Days 1, 8 and 15 of each 28-day treatment cycle.~~

In the event of toxicities, dose reductions to 45 mg and further to 30 mg are allowed. The dose modifications will follow the pre-defined dose levels outlined in Section 6.4.1. ~~Dummy dose modifications are used if toxicities occur in the placebo arm.~~

[…]

New text:

The following treatments will be administered in this study:

- Copanlisib (BAY 80-6946) solution for IV infusion (study drug/investigational medicinal product)
- *Placebo solution for IV infusion removed by amendment 5*

Eligible patients will receive copanlisib IV infusion at a starting dose of 60 mg as single agent on Days 1, 8 and 15 of each 28-day treatment cycle.

[…]

13.4.2.14 Section 6.2 Identity of study treatment

Old text:

~~All~~ study ~~drugs~~ will be labeled according to the requirements of local law and legislation. 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 ware of the ingredients. Lists linking all numbering levels will be maintained by the sponsor's clinical supplies QA 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 study file.

[…]

~~**Placebo**~~

~~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 drugs, please refer to Section 6.5.~~

New text:

The study drug will be labeled according to the requirements of local law and legislation. 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 the study drug, 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 ware of the ingredients. Lists linking all numbering levels will be maintained by the sponsor's clinical supplies QA group.

A complete record of batch numbers and expiry dates of study treatment as well as the label will be maintained in the sponsor study file.

[…]

13.4.2.15 Section 6.3 Treatment assignment

Old text:

~~At the end of the Screening period, eligible patients will be randomly assigned in a 2:1 ratio to one of the double-blinded treatment arms: copanlisib monotherapy or placebo, respectively (*modified by amendment 1*). The randomization must be performed within 48 h before the first dose of study drug.~~

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

~~IVRS/IWRS will stratify patients according to three factors based on baseline characteristics (*modified by amendment 1*):~~

- ~~NHL histology, with categories:~~
  - ~~FL histology~~
  - ~~Other NHL histology, and~~
- ~~Time between last course of systemic anticancer therapy and most recent progression, with categories:~~
  - ~~≤ 6 months~~
  - ~~> 6 months, and~~
- ~~Prior treatment with PI3K inhibitors (*added by amendment 1*):~~
  - ~~Yes~~
  - ~~No~~

~~Resulting from the combination of these three stratification factors, patients will be randomized into 8 different strata (*modified by amendment 1*).~~

~~The IVRS/IWRS procedure is described in detail in a separate IVRS/IWRS instruction manual that will be maintained in the trial master file (TMF), and in each center's investigator's trial file (ITF).~~

~~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 (SAC) for the DMC and its meetings, the Bioanalytics group and the Pharmacokinetic Evaluator in order to perform the PK analysis.~~

~~Unblinding of the treatment assignment of a patient 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 (see Section 6.5).~~

New text:

With protocol amendment 5 there will be no randomization. All patients who are on study will be offered the opportunity to continue treatment with copanlisib.

The IXRS/IWRS will remain open in order to manage study drug.

13.4.2.16 Section 6.4 Dosage and administration

Old text:

Study drug (copanlisib ~~or placebo~~) is administered 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.

[…]

Recommendations on meal timing on infusion days

[…]

~~Patients will continue study treatment until PD (per central independent blinded radiology review) or they meet the criteria described in Section 5.2. Patients who experience PD on placebo treatment can be offered open-label copanlisib upon discretion of the investigator and patient's consent. After individual patient unblinding, patients receiving placebo who switch to open-label copanlisib will have all study assessments and timing reset to the initial schedule of study evaluations (i.e. as if the patient was restarting the study at Cycle 1 Day 1). If not previously done within 7 days, patients switching to open-label copanlisib must complete the following within 7 days prior to the first dose of open-label copanlisib: UPCR/24 h total urine protein quantification, GFR measurement, urinalysis, HbA1c, CBC, chemistry and coagulation panels. For Day 1 of the first open-label cycle, laboratory parameters as outlined in inclusion criterion 13 and exclusion criteria 15 and 24 will apply. For Day 1 of subsequent open-label cycles, dosing criteria outlined in Table 6–2 will apply for patients who switch to open-label treatment (*modified by amendment 3*). These patients will be treated until further disease progression (per central review) unacceptable toxicity, or until another criterion is met for withdrawal from the study treatment (see Section 5.2) (*changed by amendment 1*).~~

[…]

New text: no new text was added.

13.4.2.17 Section 6.5 Blinding

Old text:

~~Patients will be randomized to receive copanlisib or placebo in a double-blind fashion such 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 supplied by the investigator when the patient qualifies for study treatment.~~

~~The appearance of the packaging for copanlisib and placebo will be identical in order to preserve blinding. Both will be packaged in a drug pack labeled with a unique drug pack~~

~~number which will be pre-printed. The study drug pack number will be assigned to the patient through the IVRS/IWRS.~~

~~Because copanlisib solution may have a yellowish color while the placebo solution is colorless, measures will be taken to preserve the blind. This includes an unblinded, study-independent pharmacist (or qualified person) who will handle the preparation of the study drug, and unblinded monitors, separate from the blinded monitoring team, to conduct the monitoring of the pharmacy and drug supplies. Additional details will be described in the Pharmacy Manual (*paragraph changed by amendment 1*.)~~

~~In compliance with applicable regulations, in the event of a SUSARs (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 treatment assignment of a patient 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.~~

New text:

Not applicable.

After individual patient unblinding, patients receiving active study drug will continue copanlisib treatment as scheduled. Patients receiving placebo will be offered to switch to copanlisib upon discretion of the investigator and patient's consent.

13.4.2.18 Section 6.6 Drug logistics and accountability

Old text:

[…]

Study drug supply and predictive re-supply will be managed through the IVRS/IWRS. After a patient is ~~randomized~~ to ~~a~~ treatment ~~group~~, the amount of study drug supply needed at the study site for each ~~randomized~~ patient will be calculated. Re-supply of study drug will be performed automatically at regular intervals through the IVRS/IWRS based on the expected dosing of the study drug. When a patient is permanently withdrawn from treatment, the study site must notify the Sponsor ~~or the CRO~~ through the IVRS/IWRS.

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

New text:

Study drug supply and predictive re-supply will be managed through the IVRS/IWRS. After a patient is assigned to treatment, the amount of study drug supply needed at the study site for each patient will be calculated. Re-supply of study drug will be performed automatically at regular intervals through the IVRS/IWRS based on the expected dosing of the study drug. After closure of the study enrollment, the IxRS will continue to supply copanlisib treatment for all patients who remain in the study. When a patient is permanently withdrawn from treatment, the study site must notify the Sponsor through the IVRS/IWRS.

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

13.4.2.19 Section 6.7 Treatment compliance

Old text:

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

New text: no new text was added.

13.4.2.20 Section 7.1.1 Tabulated overview

Old text: see next page

Table 7-1 Study flow chart

	Screening			Treatment *									EOT	SFU	Active follow-up [aa]	Survival follow-up [bb]
	maximum days before C1D1			Cycle 1					Cycle 2 and higher				Within (days) after			
Days	**-28**	**-14**	**-7**	**D1**	~~**D4**~~	**D8**	**D15**	~~**D22**~~	**D1**	**D8**	**D15**	~~**D22**~~ [y]	**7**	**30 + 5** days window[z]		**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)	X[cc,dd]															
Check in- and exclusion criteria		X	X	X												
Medical history [a]		X														
IVRS/IWRS transaction [b, dd]	X			X[b]					X				X			
HBsAg, HBcAb, HCV IgG	X															
CMV PCR test [ff,ii]	X			X[ff]					X[ff]							
Serum pregnancy test (if applicable) [c]			X						X[c]				X[c, ee]			
UPCR / 24 h total urine protein quantification [ee]			X													
GFR [dd]			X						X							
Safety																
Toxicity / AE assessment [d]		X		X		X	X	X	X	X	X		X	X	(X)[d]	
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, dd]						X	X	X		X	X			(X)		
12-lead ECG [g, dd]	X			~~X~~					~~X~~[g]				X[g]			
MUGA scan or echocardiogram [h, dd]	X[h]								~~X~~[h]				X[h]			
HbA1c [i]			X						~~X~~[i]				X			
Complete blood count [j]			X			X[x]	X[x]	X	X[x]	C2 only[x]	C2 only[x]		X	(X)		
Hemoglobin, ANC and platelet counts (C3->)										X[x]	X[x]					
Chemistry panel [k]			X[k]			X[x]	X[x]	X	X[k,x]	C2 only[x]	C2 only[x]		X[k]	(X)		
Coagulation panel: PT, INR and PTT			X				X[x]		X[x]				X	(X)		
CD4 (for patients with signs of infection) and blood cultures when low ANC of CTCAE Grade 4 [gg, hh,ii]																

Table 7-1 Study flow chart

	Screening			Treatment *									EOT	SFU	Active follow-up [aa]	Survival follow-up [bb]
	maximum days before C1D1			Cycle 1					Cycle 2 and higher				Within (days) after			
Days	**-28**	**-14**	**-7**	**D1**	**~~D4~~**	**D8**	**D15**	**~~D22~~**	**D1**	**D8**	**D15**	**~~D22~~ [y]**	**7**	**30 + 5** days window[z]		**every ~~3~~ months**
Acceptable deviation (in days)				-1 to +2 days					-1 to +2 days				Decision to stop	Last dose		±14 days
Urinalysis (dipstick)			X						X				X			
Glucose [l]				X		X	X		X	X	X					
Home glucose monitoring [m, dd]			X	X	~~X~~	X	X	X	X	X	X		X			
Blood pressure [n]				X		X	X		X	X	X					
Efficacy																
Bone marrow biopsy [o]	X											~~X~~[o]				
CT/MRI and tumor evaluations [p]	X[p]											~~X~~[p]	X[p]		X[p]	
~~Quality of life questionnaire (FLymSI-18) and PRO information sheet~~ [q, ee]				~~X~~					~~X~~				~~X~~	~~X~~		
Pharmacokinetic sampling [r, dd]						X										
Biomarkers																
Tumor tissue for central pathology and biomarkers [s, dd]	X												(X)			
Plasma for tumor genetics [t, dd]				X									X			
Plasma for non-genetic biomarker analysis [u dd]				X		X	X		C2 only	C2 only	C2 only		X			
~~Whole blood for biomarkers~~ [y]				~~X~~												
Study drug administration																
Copanlisib or placebo IV infusion				X		X	X		X	X	X					
Survival status, new anticancer therapy																X
For LPL/WM patients only																
Serum protein electrophoresis [w]		X[w]										~~X~~[w]	(X)[w]			
Immunofixation [w]		X[w]										~~X~~[w]	(X)[w]			
Serum quantitative IgM test [w]		X[w]										~~X~~[w]	(X)[w]			
Serum beta-2-microglobulin [dd]		X[w]														
Serum or plasma viscosity [w]		X[w]							(X)[w]				(X)[w]			

AE = Adverse event; ALP = Alkaline phosphatase; ALT = Alanine aminotransferase; ANC = Absolute neutrophil count; AST = Aspartate aminotransferase; BUN = Blood urea nitrogen; CBC = Complete blood count; CD4 = Cluster of differentiation 4; CMV = cytomegalovirus; CT = Computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; D = Day; ECG = Electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = End of treatment; eCRF= Electronic case report form; ~~ePRO = Electronic patient-reported outcome;~~ FL = Follicular lymphoma; FLIPI = Follicular Lymphoma International Prognostic Index; FLymSI-18 = NCCN-FACT Lymphoma Symptom Index-18; GFR = Glomerular filtration rate; h = Hour(s); HbA1c = Glycated hemoglobin; HBcAb = Hepatitis B core antibody; HBsAg = Hepatitis B surface antigen; HCV = Hepatitis C virus; IgG = Immunoglobulin G; IgM = Immunoglobulin M; iNHL = Indolent non-Hodgkin's lymphoma; 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; min = Minute(s); MRI = Magnetic resonance imaging; MUGA = Multiple gated acquisition; NYHA = New York Heart Association; OI = Opportunistic infection; PCR = polymerase chain reaction; PD = Disease progression; PK = Pharmacokinetic(s); ~~PRO = Patient-reported outcome;~~ PT = Prothrombin time; PTT = Partial thromboplastin time; RBC = Red blood cell count; SAE = Serious adverse event; SCR = Serum creatinine; SFU = Safety follow-up; UPCR = Urine protein to creatinine ratio; WBC = White blood cell count.

* **NOTE**: ~~Patients who experience PD on placebo treatment (per central independent blinded radiology review) can be offered open-label copanlisib upon discretion of the investigator and patient's consent.~~ After individual patient unblinding, patients receiving placebo who switch to ~~open-label~~ copanlisib will have all study assessments ~~and timing~~ reset to the initial schedule of study evaluations (i.e. as if the patient was restarting the study at Cycle 1 Day 1). For further information on laboratory requirements for patients who switch to open-label treatment, please see Section 7.1.2.2.

[…]

b IVRS/IWRS transaction to register the patient in the system will be at Screening (*modified by amendment 1*). IVRS/IWRS ~~randomization~~ transaction will take place within 48 h before the first dose of study drug. 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.

[…]

g 12-lead ECG (including QTcB and QTcF evaluation) will be performed at Screening (within 28 days before 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)~~ At the EOT visit, a 12-lead ECG is necessary only if not recorded within the previous 4 weeks.

h MUGA scan or echocardiogram to measure LVEF at Screening (within 28 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 visit~~ (if not previously done within 4 weeks). The method chosen at Screening must be the same throughout the whole study.

i HbA1c at Screening~~, on Day 1 of every odd cycle (3, 5, 7, etc.) starting from Cycle 3~~ and at the EOT visit. The testing is not required if the previous test was performed within 4 weeks preceding EOT visit.

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

k 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), SCR, uric acid, total bilirubin, creatine phosphokinase, ALT, AST, LDH, ALP, lipase, amylase (or pancreatic amylase, if total amylase is not routinely measured at the site), cholesterol (total and LDL) and triglycerides. Total cholesterol, LDL and triglycerides will be tested only at Screening~~, on Day 1 of every 2nd cycle starting from Cycle 2,~~ and at the EOT visit. On these dates patients must be fasting prior to sampling according to local standards. If a patient can't adhere to fasting requirements, the evaluation of lipid-panels including triglycerides is considered not feasible.

[…]

o Bone marrow biopsy must be performed within 28 days before first study drug infusion, and to confirm the first complete response if there is bone marrow infiltration at baseline, and also at the investigator discretion if there is clinical suspicion of bone marrow infiltration~~. All specimens must be sent to central pathology review~~.

p 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 be stopped or reduced to the allowed dose (less than 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 the baseline must be the same throughout the study. During treatment, tumor scans will be done with the same modality~~ every 12 weeks during Year 1, every 16 weeks during Year 2, and every 24 weeksduring Year 3~~. Time points for assessments are calculated from Cycle 1 Day 1. Tumor assessments must be performed within 14 days after the last dose (Day 15) and before the next dose (Day 1 of the subsequent cycle) starting from Cycle 3. 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. During Active follow-up period patients will have radiological assessments at same intervals as during treatment ~~(time window of ±14 days is allowed)~~ until PD is documented or new anti-tumor treatment is administered (see Section 7.1.2.3 and Section 7.3.2). For tumor assessments in patients with WM, see Section 7.3.3.

q ~~FLymSI-18 questionnaire is to be completed on Cycle 1 Day 1 and every cycle thereafter (i.e. on Day 1 of Cycles 2, 3, 4 etc.), at the EOT visit and at the SFU visit in both treatment arms. Questionnaire should be self-administered by the patient via an ePRO at the start of the visit before the patient sees the physician. A PRO information sheet will be provided and completed by the study personnel at each visit at which the FLymSI-18 questionnaire is to be administered, regardless of whether or not the FLymSI-18 questionnaire is completed by the patient (*clarified by amendment 1*).~~

[…]

v ~~Whole blood for biomarkers will be collected on Cycle 1 Day 1 prior to drug administration (only from patients who provide a separate consent for genetic research) (*modified by amendment 1*).~~

[…]

y ~~After Cycle 1, there are no mandatory procedures on Day 22 of subsequent cycles. Tumor assessments and related procedures marked for Day 22 will be done according to schedule specified in Section 7.1.2.3 (*changed by amendment 1*).~~

z The post-treatment follow-up 30 days (window of +5 days allowed) after the last administration of study drug can be conducted via telephone if the patient is no longer being actively seen at the clinic or has started another therapy. ~~In this case, FLymSI-18 questionnaire does not need to be completed at the SFU evaluation (*modified by amendments 1and 4*).~~ Procedures marked with "(X)" are only to be performed, if clinically indicated.

[…]

bb 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 at least every ~~3~~ months (± 14 days), until death or until the end of the trial (up to 3 years after the last patient started study treatment), whichever comes first. Information to be recorded: date of contact, survival status, the first new anticancer regimen including response (if applicable), and date and cause of death (if applicable).

[…]

New text:

Table 7-1 Study flow chart

	Screening maximum days before C1D1			**Treatment ***						**EOT**	**SFU**	**Active follow-up [aa]**	**Survival follow-up [bb]**
				Cycle 1			**Cycle 2 and higher**			Within (days) after			
Days	**-28**	**-14**	**-7**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**7**	**30 + 5** days window[z]		**every 6 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) [ii]	X[cc,dd]												
[…]													

[…]

g 12-lead ECG (including QTcB and QTcF evaluation) will be performed at Screening (within 28 days before Cycle 1 Day 1), EOT and as clinically indicated. At the EOT visit, a 12-lead ECG is necessary only if not recorded within the previous 4 weeks.

h MUGA scan or echocardiogram to measure LVEF at Screening (within 28 days before Cycle 1 Day 1), EOT and as clinically indicated (if not previously done within 4 weeks). The method chosen at Screening must be the same throughout the whole study.

[…]

j CBC: Hemoglobin, hematocrit, RBC, WBC (with differential to include absolute neutrophil, lymphocyte, monocyte, basophil and eosinophil counts and platelet count). From Cycle 2 onwards, only hemoglobin, platelet and ANC counts will be performed on Day 8 and Day 15 prior to each infusion. Differential blood count in percentage can be provided when absolute count is not available per standard of care of the local lab.

[…]

o Bone marrow biopsy must be performed within 28 days before first study drug infusion, and to confirm the first complete response if there is bone marrow infiltration at baseline, and also at the investigator discretion if there is clinical suspicion of bone marrow infiltration. Bone marrow biopsy will be performed as per local standard of care.

p 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 be stopped or reduced to the allowed dose (less than 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 the baseline must be the same throughout the study. During treatment, tumor scans will be done with the same modality, and the schedule of tumor assessment will be done per local standard of care of the institution but no less than 16 weeks). Time points for assessments are calculated from Cycle 1 Day 1. Tumor assessments must be performed within 14 days after the last dose (Day 15) and before the next dose (Day 1 of the subsequent cycle) starting from Cycle 3. 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. During Active follow-up period patients will have radiological assessments at same intervals as during treatment until PD is documented or new anti-tumor treatment is administered (see Section 7.1.2.3 and Section 7.3.2). For tumor assessments in patients with WM, see Section 7.3.3.

q *Footnote removed by amendment 5.*

[…]

V *Footnote removed by amendment 5*

[…]

Y *Footnote removed by amendment 5*

[…]

bb 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 at least every 6 months (± 14 days), until death or until the end of the trial (up to 3 years after the last patient started study treatment), whichever comes first. Information to be recorded: date of contact, survival status, the first new anticancer regimen including response (if applicable), and date and cause of death (if applicable).

[…]

jj As of amendment 5, all patients will be reconsented and need to voluntarily agree to sign the ICF and have to do so, to continue in the study (*added by amendment 5*).

13.4.2.21 Section 7.1.2.1 Screening period

Old text:

[…]

Within 28 days before the first administration of study drug (*clarified by amendment 3*):

- […]
- Bone marrow biopsy: mandatory at Screening and to confirm the first complete response in patients with previous bone marrow infiltration at baseline. A bone marrow biopsy may also be performed at the investigator discretion if there is clinical suspicion of bone marrow infiltration. ~~All specimens must be sent to central pathology review.~~

[…]

New text:

[…]

Within 28 days before the first administration of study drug (*clarified by amendment 3*):

- […]
- Blood test for CMV infection per local SOC. Patients who are CMV testpositive at baseline will not be eligible.
- […]
- Bone marrow biopsy: mandatory at Screening and to confirm the first complete response in patients with previous bone marrow infiltration at baseline. A bone marrow biopsy may also be performed at the investigator discretion if there is clinical suspicion of bone marrow infiltration. Bone marrow biopsy will be performed as per local standard of care.

[…]

13.4.2.22 Section 7.1.2.2 Treatment period

Old text:

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 randomization will take place within 48 h before the first dose of study drug.

~~The following assessments should be performed both in patients on double-blinded study treatment (copanlisib or placebo) as well as those who are randomized to placebo and change to copanlisib.~~ After individual patient unblinding, patients receiving placebo who switch to

~~open-label~~ copanlisib will have all study assessments ~~and timing~~ reset to the initial schedule of study evaluations (i.e. as if the patient was ~~restarting~~ the study at Cycle 1 Day 1). ~~If not previously done within 7 days, patients switching to open-label copanlisib must complete the following within 7 days prior to the first dose of open-label copanlisib: UPCR/24 h total urine protein quantification, GFR measurement, urinalysis, HbA1c, CBC, chemistry and coagulation panels. For Day 1 of the first open-label cycle, laboratory parameters as outlined in inclusion criterion 13 and exclusion criteria 15 and 24 will apply.~~ For Day 1 of subsequent ~~open-label~~ cycles, dosing criteria outlined in Table 6–2 will apply for patients ~~who switch to~~ open-label treatment.

[…]

New text:

After all screening assessments have been completed and the patient's eligibility has been confirmed and documented, the patient will be assigned to treatment via IVRS/IWRS. The randomization will take place within 48 h before the first dose of study drug.

After individual patient unblinding, patients receiving placebo, who switch to copanlisib will have all study assessments reset to the initial schedule of study evaluations (i.e. as if the patient was restarted the study at Cycle 1 Day 1). ~~1315~~For Day 1 of subsequent cycles, dosing criteria outlined in Table 6–2 will apply for patients receiving open-label treatment.

[…]

13.4.2.23 Section 7.1.2.2.1 Treatment – Cycle 1

Old text:

[…]

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

- ~~Quality of life (QoL) questionnaire (FLymSI-18): Patient completes the questionnaire at the start of a visit, before the patient sees the physician. To be completed by electronic patient-reported outcome (ePRO) device. A PRO information sheet will be provided and completed by the study personnel at each visit at which the FLymSI-18 questionnaire is to be administered, regardless of whether or not the FLymSI-18 questionnaire is completed by the patient (*clarified by amendment 1*) (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 will take place within 48 h before the first dose of study drug.
- […]

- ~~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) (*modified by amendment 1*) (see Section 7.5.3.4).~~
- […]
- Collection of blood for biomarker analyses prior to infusion (see Section 7.6.1):
  - Plasma for tumor genetics (*modified by amendment 1*).
  - Plasma for non-genetic biomarker analysis.
  - ~~*Whole blood for genetic biomarker analysis* (only from patients who provide a separate consent for genetic research).~~
- […]

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 (*modified by amendment 3*).~~

[…]

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).~~

~~Monitoring for OI (see Section 6.4.2.6) (*added by amendment 4*).~~

- ~~Blood tests for CBC and chemistry panel (excluding total cholesterol, LDL and triglycerides) (see Section 7.5.3.1).~~
- ~~Review of the home blood glucose measurements/meal timing/oral glucose lowering medication/insulin administration, if applicable. Provide glucose monitoring supplies if necessary (*changed by amendment 1 and 3*) (see Section 6.4.2.1).~~

New text:

[…]

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

- *QoL questionnaire removed by amendment 5.*
- 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 transaction will take place within 48 h before the first dose of study drug.
- […]
- *12-lead ECG removed by amendment 5.*
- […]
- Collection of blood for biomarker analyses prior to infusion (see Section 7.6.1):
  - Plasma for tumor genetics (*modified by amendment 1*).
  - Plasma for non-genetic biomarker analysis.
  - *Whole blood for genetic biomarker analysis removed by amendment 5.*
- […]

Cycle 1 Day 4 removed by amendment 5

[…]

Cycle 1 Day 22 removed by amendment 5

13.4.2.24 Section 7.1.2.2.2 Treatment – Cycle 2 and higher

Old text:

Cycle 2 and higher, Day 1

On Day 1 of each subsequent cycle, 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 (*added by amendment 1 and modified by amendment 3*).

- ~~QoL questionnaire (FLymSI-18) on Day 1 of each cycle (i.e. on Day 1 of Cycles 2, 3, 4 etc.): Patient completes the questionnaire at the start of a visit, before the patient sees the physician (*clarified by amendment 1*). To be completed by ePRO device (see Section 7.6.2).~~
- […]
- ~~12-lead ECG including QTcB and QTcF evaluation 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) (*modified by amendment 1*) (see Section 7.5.3.4).~~
- ~~MUGA scan or echocardiogram to measure LVEF within 7 days prior to dosing on Day 1 of every 3rd cycle (3, 6, 9 etc.). The method chosen at Screening must be the same throughout the whole study (see Section 7.5.3.5).~~
- ~~Blood test for HbA1c will be done on Day 1 of every odd cycle (3, 5, 7 etc.) starting from Cycle 3.~~
- Blood tests for CBC, chemistry and coagulation panels (see Section 6.4 and Section 7.5.3.1).~~ Total cholesterol, LDL and triglycerides will be determined on Day 1 of every 2nd cycle starting from Cycle 2. On these days patients must be fasting prior to sampling according to local standards (*changed by amendment 3*). If a patient can't adhere to fasting requirements, the evaluation of lipid panels including triglycerides is considered not feasible.~~
- […]

Cycle 2 and higher, Day 8

- […]
- On Cycle 2, blood tests for CBC and chemistry panel (excluding total cholesterol, LDL and triglycerides) will be performed. From Cycle ~~3~~ onwards, only hemoglobin, platelet and ANC counts will be performed prior to each infusion (see Section 6.4 and Section 7.5.3.1).
- […]

Cycle 2 and higher, Day 15

- […]
- On Cycle 2, blood tests for CBC and chemistry panel (excluding total cholesterol, LDL and triglycerides) will be performed. From Cycle ~~3~~ onwards, only hemoglobin, platelet and ANC counts will be performed prior to each infusion (see Section 6.4 and Section 7.5.3.1).
- […]

Cycle 2 and higher, Day 22

~~After Cycle 1, there are no mandatory procedures on Day 22 of subsequent cycles. Tumor assessments and related procedures marked for Day 22 will be done according to schedule specified in Section 7.1.2.3 (*paragraph added by amendment 1*).~~

New text:

Cycle 2 and higher, Day 1

On Day 1 of each subsequent cycle, 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 (*added by amendment 1 and modified by amendment 3*).

- *QoL questionnaire removed by amendment 5.*
- […]
- *12-lead ECG removed by amendment 5.*
- *MUGA scan or echocardiogram removed by amendment 5.*
- *Blood test for HbA1c removed by amendment 5.*
- Blood tests for CBC, chemistry and coagulation panels (see Section 6.4 and Section 7.5.3.1).
- […]

Cycle 2 and higher, Day 8

- […]
- On Cycle 2, blood tests for CBC and chemistry panel (excluding total cholesterol, LDL and triglycerides) will be performed. From Cycle 2 onwards, only hemoglobin, platelet and ANC counts will be performed prior to each infusion (see Section 6.4 and Section 7.5.3.1).
- […]

Cycle 2 and higher, Day 15

- […]
- On Cycle 2, blood tests for CBC and chemistry panel (excluding total cholesterol, LDL and triglycerides) will be performed. From Cycle 2 onwards, only hemoglobin, platelet and ANC counts will be performed prior to each infusion (see Section 6.4 and Section 7.5.3.1).
- […]

Cycle 2 and higher, Day 22 removed by amendment 5

13.4.2.25 Section 7.1.2.3 Tumor assessments

Old text:

Radiological tumor evaluations (IV [and oral, if indicated, per Imaging Manual] contrast-enhanced CT/MRI scans of neck, chest, abdomen and pelvis) will be performed during the treatment period as well as during the Active follow-up period ~~at the following intervals.~~ Time points for assessments are calculated from Cycle 1 Day 1.The method chosen at the baseline must be the same throughout the study (see also Section 7.3.2):

- ~~Year 1: every 12 weeks~~
- ~~Year 2: every 16 weeks~~
- ~~Year 3: every 24 weeks~~

During treatment, tumor assessments must be performed within 14 days after the last dose (Day 15) and before the next dose (Day 1 of the subsequent cycle~~) starting from Cycle 3.~~

During Active follow-up, tumor assessments will be done until PD is documented or new anti-tumor treatment is administered. ~~Time window of ±14 days is allowed for scheduling the visit for response assessment.~~

Bone marrow biopsy is mandatory at baseline and to confirm the first CR if there is bone marrow infiltration at baseline. It may also be performed at the investigator discretion if there is clinical suspicion of bone marrow infiltration. ~~All specimens must be sent to central pathology review.~~ Biopsy will be performed as per local standard of care.

[...]

New text:

Radiological tumor evaluations (IV [and oral, if indicated, per Imaging Manual] contrast-enhanced CT/MRI scans of neck, chest, abdomen and pelvis) will be performed during the treatment period as well as during the Active follow-up period, the frequency of tumor assessment will be determined by investigator per local standard of care of the institution but not less than every 16 weeks. Time points for assessments are calculated from Cycle 1 Day 1.The method chosen at the baseline must be the same throughout the study (see also Section 7.3.2):

[…]

13.4.2.26 Section 7.1.2.4 End-of-treatment visit

Old text:

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:

- ~~QoL questionnaire (FLymSI-18): Patient completes the questionnaire at the start of a visit, before the patient sees the physician (*clarified by amendment 1*). To be completed by ePRO device (see Section 7.6.2).~~
- […]

New text:

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:

- *QoL questionnaire removed by amendment 5.*
- […]

13.4.2.27 Section 7.1.2.5 Follow-up periods

Old text:

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).

New text: no new text was added.

13.4.2.28 Section 7.1.2.5.1 Safety follow-up

Old text:

If a patient discontinues study treatment at any time during the study for any reason (except death or lost to follow-up) SFU visit will take place 30 days (window of +5 days allowed) after the last administration of study drug. This visit includes:

- ~~QoL questionnaire (FLymSI-18): Patient completes the questionnaire at the start of a visit, before the patient sees the physician (*clarified by amendment 1*). To be completed by ePRO device (see Section 7.6.2).~~
- […]

If a patient has begun treatment with another anticancer 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 SFU evaluation.~~

New text:

If a patient discontinues study treatment at any time during the study for any reason (except death or lost to follow-up) SFU visit will take place 30 days (window of +5 days allowed) after the last administration of study drug. This visit includes:

- *QoL questionnaire removed by amendment 5.*

[…]

13.4.2.29 Section 7.1.2.5.2 Active follow-up

Old text:

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 radiological assessments ~~(also by central independent blinded review)~~ as outlined in this CSP from the day of ~~randomization~~ until PD is documented or new anti-tumor treatment is administered (see Section 7.1.2.3).

[…]

New text:

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 radiological assessments as outlined in this CSP from the day of start of treatment until PD is documented or new anti-tumor treatment is administered (see Section 7.1.2.3).

[…]

13.4.2.30 Section 7.1.2.5.3 Survival follow-up

Old text:

All patients will be followed off study for overall survival at least at ~~3~~-month intervals during the Survival follow-up period (up to 3 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.

[…]

New text:

All patients will be followed off study for overall survival at least at 6-month intervals during the Survival follow-up period (up to 3 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.

[…]

13.4.2.31 Section 7.3.1 Primary efficacy variable

Old text:

~~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 the other efficacy variables to be analyzed for this study please refer to Section 8.3.1.

New text:

The primary efficacy variable of this study is objective tumor response rate (ORR), which is defined as the proportion of patients who have a best response rating over the whole duration of the study up to the dates of data cutoffs (for dates of data cutoffs, see details in section 8.1) of complete response (CR) or partial response (PR) according to the Lugano Classification (21), 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 (22).

For the other efficacy variables to be analyzed for this study please refer to Section 8.3.1.

13.4.2.32 Section 7.3.2 Radiological tumor assessments

Old text:

Radiological tumor assessments with IV (and oral, if indicated, per Imaging Manual) contrast-enhanced CT/MRI will include neck, chest, abdomen and pelvis, and will be evaluated locally at the study site~~ and by the central independent blinded review~~.

[…]

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 12 weeks during Year 1,~~ every 16 weeks~~ during Year 2, and every 24 weeks during Year 3~~ (see Section 7.1.2.3). 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.

[…]

As long as the patient has not experienced PD, investigator's assessment is sufficient for case management. ~~In the event of progression, radiological real-time confirmation by central independent blinded evaluation is required before a final decision to stop the treatment is made.~~ In case of uncertain radiological disease progression the patient may stay on treatment at the investigator's discretion until progression is definitely confirmed on the subsequent tumor assessment.~~ The final evaluation of treatment response (best response: ORR and CRR) will be done by central blinded review and for those not undergoing PD-confirmation in retrospective setting (*modified by amendment 3*).~~

[…]

~~Patients who experience PD on placebo treatment (per central independent blinded radiology review) can be offered open-label copanlisib upon discretion of the investigator and patient's consent. After individual patient unblinding, patients receiving placebo who switch to open-label copanlisib will have tumor assessments reset to the initial schedule as if the patient was restarting the study at Cycle 1 Day 1. For further instructions please refer to the Imaging Manual.~~

[…]

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

~~The independent reviewers will be experienced radiologists, who will not have been involved in the clinical part of the study and are considered independent from the study. They will be blinded to patient data (excluding those which are specified in the Independent Review Charter, e.g. for bone marrow biopsy).~~ The primary efficacy variable will be analyzed based

on the assessment ~~of the central image evaluation, as outlined in the Imaging Manual (or charter).~~

New text:

[…]

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, per local standard of care of the institution but no less than every 16 weeks (see Section 7.1.2.3). 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.

For patients switching from placebo to copanlisib therapy after unblinding procedures completed CT/MRI scans are not required if the patient had radiological tumor evaluation performed and documented in eCRF within 4 weeks preceeding the start date of copanlisib treatment.

If the patients on placebo treatment had symptoms/signs of clinical progressive disease prior to switching to copanlisib treatment, it is recommended to have radiological tumor assessments before starting copanlisib therapy unless CT/MRI scans performed within 4 weeks prior to a scheduled date of the first copanlisib infusion. For patients who previously received placebo and will be treated with copanlisib the tumor assessments should be continued as the initial schedule. For further instructions please refer to the Imaging Manual.

[…]

The primary efficacy variable will be analyzed based on the assessment by the investigator.

13.4.2.33 Section 7.3.3 Tumor assessments in patients with WM

Old text:

WM patients who do not have radiologically measurable lesion at Screening will not have further radiological assessments as per protocol. Their tumor response will be measured only by laboratory/clinical tests, and response assessment will be done according to the Owen Criteria. ~~If PD was assessed by an investigator based on laboratory parameters alone, no independent confirmation of PD by independent blinded review is necessary.~~ However, in cases when WM patients will develop ~~disease progression confirmed radiologically by presenting with measurable lesion(s)~~ without simultaneous increase in IgM~~,~~ the ~~imaging scans~~ should be ~~submitted for central review and PD confirmation.~~

WM patients who have radiologically measurable lesion at Screening will continue having radiological assessments and, in addition, will have laboratory tests performed on the same days. CT/MRI scans will be done and collected according to the schedule specified in the protocol (see Section 7.1.2.3). ~~For patients who have PD assessed based on CT/MRI, scans must be submitted for review to confirm disease progression by an independent blinded radiology review.~~

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

[…]

New text:

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. However, in cases when WM patients will develop extramedullary disease without simultaneous increase in IgM the radiological assessment should be performed to confirm disease progression (per investigator's assessment).

[…]

13.4.2.34 Section 7.4 Pharmacokinetics / pharmacodynamics

Old text:

[…]

~~Patients who experience PD on placebo treatment (per blinded central independent blinded radiology review) can be offered open-label copanlisib upon discretion of the investigator and patient's consent.~~ After individual patient unblinding, patients receiving placebo who switch to ~~open-label~~ copanlisib will have PK assessments reset to the initial schedule as if the patient was restarting the study at Cycle 1 Day 1.

[…]

New text: no new text was added.

13.4.2.35 Section 7.5.3 Further safety

Old text:

~~The following assessments should be performed both in patients on double-blinded study treatment (copanlisib or placebo) as well as those who are randomized to placebo and change to copanlisib. After individual patient unblinding, patients receiving placebo who switch to~~

~~open-label copanlisib will have all study assessments and timing reset to the initial schedule of study evaluations (i.e. as if the patient was restarting the study at Cycle 1 Day 1). If not previously done within 7 days, patients switching to open-label copanlisib must complete the following within 7 days prior to the first dose of open-label copanlisib: UPCR/24 h total urine protein quantification, GFR measurement, urinalysis, HbA1c, CBC, chemistry and coagulation panels. For further information on laboratory requirements for patients who switch to open-label treatment, please see Section 7.1.2.2 (*clarified by amendment 1 and modified by amendment 3*).~~

New text: no new text was added.

13.4.2.36 Section 7.6.1 Biomarker investigations

Old text:

[…]

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

~~Patients who experience PD on placebo treatment (per blinded central independent blinded radiology review) can be offered open-label copanlisib upon discretion of the investigator and patient's consent.~~

After individual patient unblinding, patients receiving placebo who switch to ~~open-label~~ copanlisib will have biomarker plasma sampling analogous to the initial schedule as if the patient was restarting the study at Cycle 1 Day 1.

[…]

New text:.

~~Whole blood removed by amenmdnet 5~~

After individual patient unblinding, patients receiving placebo who switch to copanlisib upon discretion of the investigator and patient's consent will have biomarker plasma sampling analogous to the initial schedule as if the patient was restarting the study at Cycle 1 Day 1.

13.4.2.37 Section 7.6.2 Quality of life questionnaire

Old text (section removed):

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

~~The main purpose of the symptom assessment in this study is to describe any differences between the treatment groups in the time to deterioration and in time to improvement in disease-related symptoms – physical (DRS-P) at least 3 points (*changed by amendment 1*).~~

~~In this study physical symptoms of lymphoma will be assessed using the NCCN-FACT Lymphoma Symptom Index-18 (FLymSI-18), version 4 (see Appendix 14.6) (NCCN-FACT: National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy).~~

~~The FLymSI-18 is a validated instrument that was developed to assess symptoms of lymphoma, symptoms of treatment of lymphoma, and health related QoL of patients with lymphoma. The instrument was developed in accordance with recent Food and Drug administration (FDA) guidance for the development of instruments for PROs.~~

~~The instrument contains 18 items, each of which utilizes a Likert scale with 5 possible responses ranging from 0 "Not at all" to 4 "Very much". Nine items reflect DRS-P, and the responses to the items are summed to calculate a DRS-P subscale score. Four items represent disease-related symptoms – emotional (DRS-E), and the responses to those items may be used to calculate a DRS-E subscale score. Three items represent treatment side effects, and the responses to these items may be summed to calculate a treatment side-effect (TSE) subscale score. Finally, two items represent function and well-being (FWB), and responses to those items may be summed to calculate a FWB subscale score. The questionnaire allows for calculation of total score and four subscales: DRS-P, DRS-E, TSE and FWB (26, 27).~~

~~The FLymSI-18 questionnaire is to be completed on Cycle 1 Day 1 and every cycle thereafter (i.e. on Day 1 of Cycles 2, 3, 4 etc.), at the EOT visit and at the SFU visit (see flowchart in Table 7–1).~~

~~Patients who experience PD on placebo treatment (per central independent blinded radiology review) can be offered open-label copanlisib upon discretion of the investigator and patient's consent. After individual patient unblinding, patients receiving placebo who switch to open-label copanlisib will have symptom assessments reset to the initial schedule as if the patient was restarting the study at Cycle 1 Day 1.~~

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

~~A patient-reported outcome (PRO) information sheet will be provided and completed by the study personnel at each visit at which the FLymSI-18 questionnaire is to be administered (*modified by amendment 1*), regardless of whether or not the FLymSI-18 questionnaire is completed by the patient. This is to document information such as questionnaire completion, date of completion, and reasons for non-completed questionnaires.~~

New text: no new text was added.

13.4.2.38 Section 7.6.3 Electronic patient-reported outcomes evaluation

Old text (section removed):

~~ePRO devices will be implemented in this study. It will be used to complete the FLymSI-18 questionnaire (*modified by amendment 1*). A Site Manual will be provided to sites and each patient will be trained how the ePRO device works and how to use it correctly. If, for any reason, a device is not available at the site, or technical problems prevent it from working properly, the FLymSI-18 questionnaire will not be completed at that visit (*changed by amendment 3 and modified by amendment 4*).~~

New text: no new text was added.

13.4.2.39 Section 8.1 General considerations

Old text: no text was removed.

New text:

[…]

Due to the decision of stopping enrollment as protocol amendment 5 becomes effective, limited number of patients will be included in the analyses. Therefore, the statistical analyses included in this study will be focused on descriptive statistics without any hypothesis testing.

Two sets of analyses will be performed at the timing when all treated patients completed at least 6 cycles of study treatment.

3) unblinding cutoff: analyze all data available before the unblinding (details in section 6.5);
4) final analysis: analyze all data available until all treated patients complete at least 6 cycles of study treatment.

The data cutoffs and treatment groups included for each analysis are summarized in the following table.

Table 8-1 Analysis data cutoffs and treatment group overview

	Analysis cutoff on the date of unblinding	Final analysis cutoff[4]
Patients randomized to Copanlisib[1]	✓	✓
Placebo Patients: Period 1 (before their PD) [2]	✓	Not shown
Placebo Patients: Period 2 (after PD period 2) [2]	Not shown	✓
Placebo Patients: switching to Copanlisib per protocol amend 5[3]	NA	✓

[1] All patients randomized/assgined into Copanlisib arm
[2] Patients randomized into Placebo arm, with at least one tumor response assessment until date of unblinding
[3] Includes patients switched from Placebo to Copanlisib before their first tumor response assessment
[4] When all treated patients complete at least 6 cycles of study treatment

13.4.2.40 Section 8.2 Analysis sets

Old text:

The statistical analysis sets are defined as follows:

- Full analysis set (FAS): all patients ~~randomized.~~ Following the intent to treat (ITT) principle, the treatment the patient is ~~randomized~~ to will be used in the analysis (as ~~randomized~~ rather than as treated).
- Safety analysis set (SAF): all ~~FAS~~ patients with at least one intake of study drug.

[…]

New text:

The statistical analysis sets are defined as follows:

- Full analysis set (FAS): all patients assigned to treatment. Following the intent to treat (ITT) principle, the treatment the patient is assigned to will be used in the analysis (as assgined rather than as treated).
- Safety analysis set (SAF): all patients with at least one intake of study drug. The SAF will be analyzed as treated.

[…]

13.4.2.41 Section 8.3.1 Efficacy variables

Old text:

~~Disease progression (PD) in the context of statistical efficacy evaluation is considered to be radiological progression, as assessed by central review. 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).~~

If PD ~~is~~ reported after a switch to ~~open-label~~ copanlisib treatment in placebo patients (see Section 6.4), this information is not used for calculation of primary or secondary efficacy variables.

New text:

[…]

If PD was reported after a switch to copanlisib treatment in placebo patients (see Section 6.4), this information is not used for calculation of primary or secondary efficacy variables.

13.4.2.42 Section 8.3.1.1 Primary efficacy variable

Old text:

~~**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). 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.~~

New text:

Objective tumor response rate (ORR) assessed in all patients, which is defined as the proportion of patients who have a best response rating up to the dates of data cutoffs (for dates of data cutoffs, see details in section 8.1) of complete response (CR) or partial response (PR) according to the Lugano Classification (21), 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 (22). Detailed instructions on tumor assessment are provided in Appendix 14.1. In addition to the ORR by treatment group, and period, a listing will be provided for all patients with their best response, histology type along with other important demographic and disease characteristics information.

13.4.2.43 Section 8.3.1.2 Secondary efficacy variables

Old text:

~~**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 the time of analysis of PFS) of complete response (CR) or partial response (PR) according to the Lugano Classification (21), 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 (22) (*changed by amendment 1*). Detailed instructions on tumor assessment are provided in Appendix 14.1.~~

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 (*modified by amendment 1*). 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 (in days) 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.~~

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 disease-related symptoms – physical (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. Due to the symptom-related inclusion criteria (i.e. ECOG performance status ≤ 1), a worsening of symptoms can potentially occur in all patients. Therefore all patients will be included into this analysis (*modified by amendment 1*).~~

~~**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 subjects evaluated for improvement), plus 1 day (*paragraph added by amendment 1*).~~

~~Further sensitivity analyses for the DRS-P 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 (*two previous sentences modified by amendment 1*). 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.~~

New text:

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 (*modified by amendment 1*). Patients without PD or death at the time of analysis will be considered as responders till at the date of their last tumor evaluation. DOR will be summarized by descriptive statistics. Further details will be included in the SAP.

Complete response rate (CRR), defined as the proportion of patients who have a best response up to the dates of data cutoffs (for dates of data cutoffs, see details in section 8.1) of complete response (CR) according to the Lugano Classification (3), and for patients with WM, a response rating of CR according to the Owen criteria (4).

Overall survival (OS), defined as the time (in days) from assignment to study drug 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.

13.4.2.44 Section 8.3.1.3 Other efficacy variables

Old text (section removed):

- ~~PFS2 defined as the time (in days) from first PD after start of study treatment to second PD (both assessed by central review) or death from any cause (if no progression is documented). PFS2 will be evaluated only in placebo-treated patients who switched to open-label copanlisib treatment after first PD (*added by amendment 1*).~~
- ~~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.~~
- ~~ECOG performance status.~~

New text: no new text was added.

13.4.2.45 Section 8.4.1 Population characteristics

Old text:

Demographics and baseline characteristics will be summarized by treatment and total population, using descriptive statistics and frequency tables as appropriate. ~~In addition, the same summaries will be provided separately by FL and other iNHL subgroups (*modified by amendment 1*).~~

New text: no new text was added.

13.4.2.46 Section 8.4.2 Efficacy

Old text:

~~All efficacy analyses will be performed when approximately 82 centrally evaluated PFS events are observed in the FL subgroup (see Section 8.6) (*changed by amendment 1*). Evaluations from central blinded review.~~ will be used for the primary efficacy analyses of primary and secondary variables containing radiological tumor assessments.

~~The study-wise alpha of 1% will initially be split, according to the test strategy for this study (see Figure 8–1): with 80% * 1% = 0.8% assigned to the one-sided PFS test in the FL subgroup, and 20% * 1% = 0.2% to the one-sided PFS test in the total study population (*paragraph added by amendment 1*).~~

New text:

Evaluations by investigators will be used for the primary efficacy analyses of primary and secondary variables containing radiological tumor assessments.

For variables other than OS, the data collected after switching from placebo to copanlisib will be summarized separately using descriptive statistics and frequency tables. Further details will be included in the SAP.

13.4.2.47 Section 8.4.2.1 Primary efficacy analysis

Old text (section removed):

~~The primary efficacy variable is PFS as assessed by central review (for definition see Section 8.3.1.1). It will be evaluated whether PFS in the copanlisib group is higher compared to PFS in the placebo group for the total study population and separately for the FL subgroup.~~

~~The following null hypothesis will be tested:~~

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

~~The alternative hypothesis will be:~~

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

~~$S_{Copanlisib}(t) \geq S_{Placebo}(t)$ for all time points $t \geq 0$,~~

~~where $S_{Copanlisib}$ denotes the survival function of the copanlisib group and $S_{Placebo}$ denotes the survival function of the placebo group in the total study population or the FL subgroup, respectively.~~

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

~~According to the size of this study it is justified to assume that under $H_{0, PFS}$ the one-sided log-rank test (28) is a sufficiently close approximation to the normal distribution. If the z-value from the one-sided log-rank test (for the difference $S_{Copanlisib} - S_{Placebo}$, stratified by the same factors as used for randomization: FL vs. other iNHL histology [in the test for total study population only], the time between last course of systemic anticancer therapy and most recent progression [≤ 6 months vs. > 6 months] and previous treatment with PI3K inhibitors [yes vs. no]) is larger than the respective critical quantile from the normal distribution (for FL subgroup: $z_{0.992} = 2.409$, for the total study population: $z_{0.998} = 2.878$), the null hypothesis will be rejected in favor of the alternative hypothesis.~~

~~Additional analyses of the primary efficacy variable~~

~~Kaplan-Meier estimates of median times to PFS (including 98% confidence interval) and Kaplan-Meier curves for the total study population and the FL subgroup will be presented for each treatment group (*~~changed by amendment 1~~*).~~

~~The hazard ratio (including 98% confidence interval) will be derived for the total study population and separately for the FL subgroup from Cox proportional hazards models that are stratified by the same factors as used for the primary efficacy analysis (*~~changed by amendment 1~~*).~~

~~The censoring mechanism of patients 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.~~

New text: no new text was added.

13.4.2.48 Section 8.4.2.2 Secondary efficacy analysis

Old text (section removed):

~~Depending on study success in the primary efficacy variable in the FL subgroup the secondary efficacy variables ORR, time to deterioration and time to improvement in DRS-P subscale of FLymSI-18 of at least 3 points will be tested hierarchically in the FL subgroup according to the multiple testing strategy outlined in Figure 8–1.~~

~~If the study shows success in all secondary endpoints in the FL subgroup and in the primary efficacy endpoint for the total study population, then the secondary efficacy endpoints ORR, time to deterioration and time to improvement in DRS-P subscale of FLymSI-18 of at least 3 points will also be tested hierarchically in the total study population.~~

~~Despite the initial split of study-wise alpha for the primary efficacy tests of PFS, the applied multiple test strategy includes the chance of so-called re-tests at full study-wise alpha-level of 1% in certain cases. The details are described in Section 8.4.2.3 below.~~

~~The ORR will be analyzed using the Cochran-Mantel-Haenszel test (29), stratified for the same stratification factors as used for PFS. The null hypothesis is defined as:~~

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

~~The alternative hypothesis will be:~~

~~$H_{1, ORR}$: $ORR_{Copanlisib} > ORR_{Placebo}$~~

~~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 twice the available significance level for the respective test and the estimated difference $ORR_{Copanlisib} - ORR_{Placebo}$ (comparing copanlisib vs. placebo) 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 according to the testing strategy.~~

~~OS, CRR, TTP as well as DOR will not be included into the confirmatory testing strategy but analyzed supportively only.~~

~~OS will be analyzed using stratified log-rank tests similar to that for the primary variable, PFS. In addition, statistical methods to include the time after change to copanlisib by placebo patients in an analysis of OS will be investigated. Further details will be included in the SAP.~~

~~For variables other than OS, the data collected after the change from placebo to copanlisib will be summarized separately using descriptive statistics and frequency tables. Further details will be included in the SAP.~~

~~TTP, DOR, time to deterioration and time to improvement in DRS-P of at least 3 points will be analyzed using stratified log-rank tests similar to that for the primary variable, PFS.~~

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

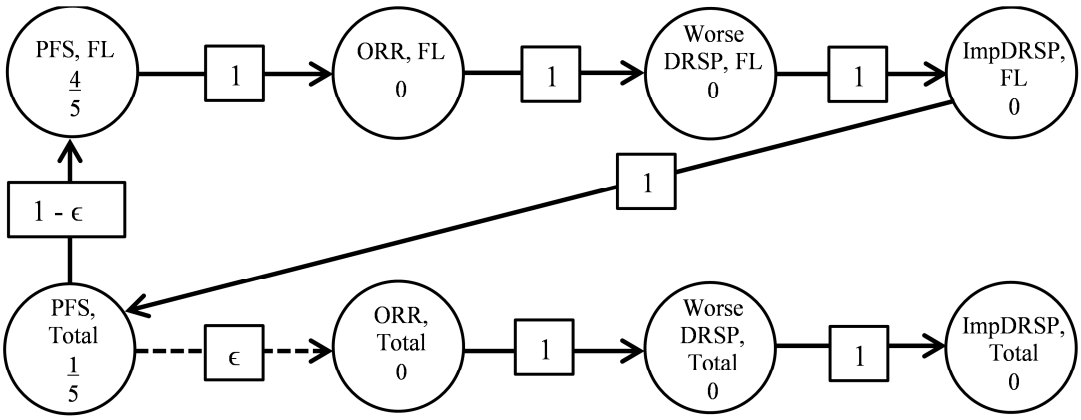
New text: no new text was added.

13.4.2.49 Section 8.4.2.3 Confirmatory statistical testing strategy

Old text (section removed):

~~A graphical summary of the testing strategy is displayed in Figure 8–1, using methodology as outlined in "A graphical approach to sequentially rejective multiple test procedures" (30). Package "gMCP"(Graph Based Multiple Test Procedures) for the statistical software R has been used for display (31, 32).~~

~~Figure 8–1 Confirmatory statistical testing strategy (*figure added by amendment 1*)~~



~~FL = follicular lymphoma; ImpDRSP = improvement in disease-related symptoms – physical; ORR = objective tumor response rate; PFS = progression-free survival; total = total study population; WorseDRSP = worsening of disease-related symptoms – physical.~~

~~Note: This design involving ϵ is a technical construct to potentially allow propagation of alpha to secondary endpoints in the total study population, in case all FL secondary endpoints can be rejected. The amount ϵ will be close to zero, and will be exactly defined in the SAP.~~

~~PFS is tested in parallel in the FL subgroup (tested at significance level of 0.8%), and in the total study population (tested at significance level of 0.2%).~~

~~The secondary endpoints in the FL subgroup and in the total study population, respectively, will only be tested if the test for the primary endpoint PFS is successful in the respective (sub-) population. A sequentially rejective multiple test procedure (30) will be used for the secondary efficacy endpoints in order to control the study-wise alpha level of 1%.~~

~~Tests on primary endpoint PFS in the FL subgroup and total study population~~

~~*Section added by amendment 1.*~~

~~As the study is powered to show a success in the FL subgroup, the multiple testing strategy also reflects the priority of the FL subgroup by propagating alpha-level first to the FL subgroup. After a successful test in the FL subgroup, the alpha-level of 0.8% will be propagated to the secondary endpoints in the FL subgroup.~~

~~In case of a successful test of PFS in the total study population, the respective alpha-level of 0.2% will be propagated to the test hierarchy in the FL subgroup except for an amount ε (with ε close to zero). The remaining proportion ε of available alpha of 0.2% will be propagated to the secondary endpoints in the total study population.~~

~~Test hierarchy in secondary endpoints~~

~~Section added by amendment 1.~~

~~The secondary endpoints are tested hierarchically both within the FL subgroup and the total study population.~~

~~Within each (sub-) group, ORR is tested first, followed by worsening in DRS-P, followed by improvement in DRS-P according to the pre-defined test sequence.~~

~~If both the primary and all secondary efficacy endpoints within the FL subgroup are tested successfully, the respective alpha-level is then finally propagated to the test sequence in the total study population. This means that for all practical purposes, the secondary endpoints for the total study population are only tested if all tests in the FL subgroup and the primary efficacy endpoint PFS in the total study population were successful.~~

~~Potential for re-tests~~

~~Section added by amendment 1.~~

~~Therefore, re-tests at (practically) the full study-wise alpha level of 1% could occur, if either:~~

1. ~~PFS test in the total study population is successful: Then the FL-related test hierarchy, starting from PFS in FL subgroup, can be re-tested at full alpha-level (except for the small ε part), or~~
2. ~~Primary as well as all secondary assessments in the FL subgroup are successful: In this case, PFS and secondary efficacy hierarchy in the total study population can be tested at full alpha.~~

~~Other efficacy evaluations~~

~~PFS2 will be descriptively evaluated using Kaplan-Meier estimates for quantiles, including 98% two-sided confidence intervals (*added by amendment 1*).~~

~~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 both in the total study population and the FL subgroup based on AUC. Total FLymSI-18 and subscales will be evaluated descriptively. Further details on PRO data analysis will be provided in the SAP.~~

~~ECOG performance status will be summarized using descriptive statistics for the original score, as well as for the change from baseline score by treatment group in the total study population and in the FL subgroup.~~

New text: no new text was added.

13.4.2.50 Section 8.4.2.4 Subgroup analyses

Old text (section removed):

~~Countries will be combined into regions as US vs. Europe vs. rest of world in order to defined 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.~~

~~As an efficacious result in the confirmatory multiple testing strategy in the FL subgroup could dominate the result for the total population, a pre-defined consistency assessment across iNHL subtypes will be pre-specified in the SAP.~~

New text: no new text was added.

13.4.2.51 Section 8.4.3 Safety

Old text:

Safety variables will be summarized by means of descriptive statistics and/or frequency tables as appropriate. Summaries will be given by treatment group and total. ~~Summaries will be provided for the total study population and separately for the FL subgroup (*modified by amendment 1*).~~

[…]

New text:

Safety variables will be summarized by means of descriptive statistics and/or frequency tables as appropriate. Summaries will be given by treatment group and total. As clarified in section 8.1, safety data analyses will be provided based on two sets of data, unblinding cutoff and final data cutoff.

[…]

13.4.2.52 Section 8.6 Determination of sample size

Old text:

~~Sample size estimation is based on the evaluation of the primary efficacy variable, PFS, in the primary subgroup of follicular lymphoma (FL). Study recruitment will be closed as soon as the required number of evaluable FL patients is reached.~~

~~Copanlisib versus placebo treatment groups will be compared. The stratification factor NHL histology (FL vs. other iNHL) will be used to derive two subgroups of patients. Superiority of the copanlisib arm over the placebo arm will be tested for the total study population and separately for the FL subgroup. A study-wise alpha level of 1% will be used to show superiority in the FL subgroup and/or the total study population.~~

~~For the placebo arm, a median PFS of 6 months is assumed, whereas the copanlisib arm will be considered to have a median PFS of 14 months.~~

~~The study is planned to detect a 132% increase in median PFS in copanlisib versus placebo comparison (i.e. to detect a hazard ratio of 0.43), using a stratified log-rank test.~~

~~Study-wise alpha level of 1% will be split in terms of the test strategy planned (see Figure 8–1), performing the one-sided primary efficacy test (and successive test hierarchy) with an initial alpha level of 0.8% for FL subgroup, and an initial alpha of 0.2% for the one-sided efficacy test in PFS for the total study population. Depending on the outcome of the primary efficacy tests, respective alpha will be propagated to further hypotheses in accordance with the planned test procedure.~~

~~Randomization ratio will be 2:1 between copanlisib group and placebo group, respectively.~~

~~Sample size justification for primary efficacy test on PFS in FL patients~~

~~Section modified by amendment 1.~~

~~Using the software PASS 11 and with the above assumptions (especially alpha level of 0.8%), it was determined that this study can be evaluated after approximately 82 PFS events are observed in the FL subgroup to achieve a statistical power of 90% of observing a significant result in the primary efficacy test in the FL subgroup.~~

~~In case a re-test in the test strategy is possible, because the test of PFS in the total study population was significant at the 0.2% level, the power of showing success in PFS for FL patients would increase to 91.4%, which is not considered as an excessive overpowering.~~

~~To determine the number of FL patients required to reach this number of events, a drop-out rate of 20% (equally distributed among treatment arms and time), and an accrual time of 12 months (including 6 month ramp-up phase for study site openings) with a maximum of 10 month follow-up for last recruited patient was assumed.~~

~~PASS 11 calculations (assuming exponential distribution of events) resulted in a required number of patients per group: approximately 96 patients in the copanlisib monotherapy arm and approximately 48 patients in the placebo arm (total of 144 FL patients) for the study.~~

~~Sample size assumptions for other iNHL patients~~

~~Section added by amendment 1.~~

~~Recruitment will be open to several types of iNHL patients. The size of the other iNHL subgroup is expected to reach between 20% and 25% of overall patients. Inclusion of these patients in addition to FL subgroup was encouraged by advice from EMA Scientific Advice Working Party to seek significance in FL subgroup, but to not exclude other subtypes. Assuming 23% of patients in the total population have other iNHL histologies, we expect ~45 other iNHL patients to also be included into the study.~~

~~The total study population will thus comprise approximately189 recruited patients.~~

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

~~Section added by amendment 1.~~

~~Under comparable assumptions as for the FL subjects (but using alpha level of 0.2%), the power to detect a difference in PFS for the total study population will be 91.3%. In case the tests on primary and all secondary efficacy variables are significant in the FL subgroup, the total study population can be re-tested with the full study alpha of 1.0% in accordance with the test strategy. Under this assumption a power of 96.8% in the primary efficacy test for PFS in the total study population is achieved.~~

~~As an efficacious result in the FL subgroup could dominate the result for the total population, a pre-defined consistency assessment across iNHL subtypes will be pre-specified in the SAP.~~

New text:

All patients assigned to treatment in this study will be included in the analyses.

13.4.2.53 Section 9.3 Data processing

Old text:

[…] This is applicable for data recorded on CRF as well as for data from other sources (e.g. IVRS, laboratory~~, ePRO~~).

[…]

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

New text:

[…]

Clinical data will be entered into Rave by clinical site staff and will be transferred from Rave into SAS datasets. Data review will be performed by sponsor on an ongoing basis to ensure data is accurate, consistent and complete. Data for, external supplier sources will be checked by sponsor. Data corrections will be made under the supervision of clinical site staff.

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

[…]

13.4.2.54 Section 10. Premature termination of the study

Old text: no text was removed.

New text:

[…]

The sponsor's decision was to stop enrollment due to lack of feasibility to complete this study in reasonable time frame. Therefore, the study design is modified to reflect an open label study. All patients on study treatment will be offered the possibility to continue treatment with copanlisib after unblinding procedures are completed.

Details for individual patient's withdrawal can be found in Section 5.2.1.

13.4.2.55 Section 11.2 Patient information and consent

Old text:

[…]

~~Only if the patient voluntarily agrees to sign the ICF 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. Documentation of the informed consent process should be recorded in the patient's medical record.

[…]

New text:

[…]

As of amendment 5, all patients will be reconsented and need to voluntarily agree to sign the ICF and have to do so, to continue in 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. Documentation of the informed consent process should be recorded in the patient's medical record.

[…]

13.4.2.56 Section 12. Reference list

Old text:

~~26. Hlubocky FJ, Webster K, Beaumont J, Cashy J, Paul D, Abernethy A, et al. A preliminary study of a health related quality of life assessment of priority symptoms in advanced lymphoma: the National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy - Lymphoma Symptom Index. Leuk Lymphoma. 2013;54:1942-6.~~

~~27. Cella D, Rosenbloom SK, Beaumont JL, Yount SE, Paul D, Hampton D, et al. Development and validation of 11 symptom indexes to evaluate response to chemotherapy for advanced cancer. J Natl Compr Canc Netw. 2011;9:268-78.~~

~~28. Collett D. Modelling Survival Data in Medical Research: Chapman and Hall; 2003.~~

~~29. 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 (*added by amendment 1*).~~

~~30. Bretz F, Maurer W, Brannath W, Posch M. A graphical approach to sequentially rejective multiple test procedures. Stat Med. 2009;28:586-604 (*added by amendment 1*).~~

~~31. Bretz F, Posch M, Glimm E, Klinglmueller F, Maurer W, Rohmeyer K. Graphical approaches for multiple comparison procedures using weighted Bonferroni, Simes or parametric tests. Biometrical Journal. 2011;53:894-913 (*added by amendment 1*).~~

~~32. Rohmeyer K, Klinglmueller F, Bomkamp B. gMCP: Graph Based Multiple Test Procedures, R package version 0.8-5.2013. Available from: http://CRAN.R-project.org/package=gMCP (*added by amendment 1*).~~

New text: no reference was added.

13.4.2.57 Appendix 14.6 Quality of life questionnaire: NCCN-FACT FLymSI-18

Old text (appendix removed):

CCI

[redacted]

13.5 Amendment 6

Amendment 6 is a global amendment dated 01 DEC 2017.

13.5.1 Overview of changes

13.5.1.1 Modification 1 – Study design revised

Following sponsor's decision to stop enrollment due to lack of feasibility to complete this study in reasonable time frame, the study design was modified. Since only limited number of patients will be included in the analyses, the study design was changed to only assess the safety of copanlisib. As a consequence, Active and Survival follow-up periods were removed.

Sections affected by this modification: Synopsis, Section 2. Study objectives, Section 4. Study design, Section 5.2.1.1 Withdrawal from study treatment, Section 5.2.1.2 Withdrawal from follow-up period, Section 7.1.1 Tabulated overview, Section 7.1.2.3 Tumor assessments, Section 7.1.2.5 Follow-up periods, Section 7.1.2.5.2 Active follow-up, Section 7.1.2.5.3 Survival follow-up, Section 7.3.1 Primary efficacy variable, Section 7.3.2 Radiological tumor assessments, Section 7.5.1.3 Assessments and documentation of adverse events, Section 7.7 Appropriateness of procedures / measurements, Section 8.1 General considerations, Section 8.2 Analysis sets, Section 8.3.1 Efficacy variables, Section 8.3.1.1 Primary efficacy variable, Section 8.3.1.2 Secondary efficacy variables, Section 8.4.2 Efficacy, Section 8.4.3 Safety

13.5.1.2 Modification 2 – Change in primary endpoint

Following sponsor's decision to stop enrollment due to lack of feasibility to complete this study in reasonable time frame, the study design was modified. Since only limited number of patients will be included in the analyses, the study design was changed to only assess the safety of copanlisib. As a consequence, the study primary endpoint was changed to safety and other study objectives were removed.

Sections affected by this modification: Synopsis, Section 2. Study objectives, Section 4. Study design, Section 7.3.1 Primary efficacy variable, Section 8.2 Analysis sets, Section 8.3.1 Efficacy variables, Section 8.3.1.1 Primary efficacy variable, Section 8.3.1.2 Secondary efficacy variables, Section 8.4.2 Efficacy, Section 8.4.3 Safety

13.5.1.3 Modification 3 – Change in statistical analysis

Since the study design was changed to only assess the safety of copanlisib, the timing of the statistical analysis was changed to perform a final analysis of safety data available until all patients have completed the copanlisib study treatment and Safety follow-up period.

In addition, it was clarified that for TEAE summaries based on placebo randomized patients switching to copanlisib, the baseline reference period will be defined in the SAP.

Sections affected by this modification: Synopsis, Section 8.1 General considerations, Section 8.3.2 Safety variables

13.5.1.4 Modification 4 – Clarification in determination of sample size

The section of determination of sample size has been revised to clarify that determination of sample size has not been applicable since amendment 5 became effective.

Sections affected by this modification: Section 8.6 Determination of sample size

13.5.1.5 Modification 5 – PK and biomarker analyses removed

Following the study design modification to only assess the safety of copanlisib, the study objectives related to PK and biomarker analysis were removed. The sponsor reserves the right to perform biomarker and PK analysis on the blood/tissue samples already collected.

Sections affected by this modification: Synopsis, Section 2. Study objectives, Section 4. Study design, Section 7.1.1 Tabulated overview, Section 7.1.2.1 Screening period, Section 7.1.2.2.1 Treatment – Cycle 1, Section 7.1.2.2.2 Treatment – Cycle 2 and higher, Section 7.1.2.4 End-of-treatment visit, Section 7.4 Pharmacokinetics / pharmacodynamics, Section 7.6.1 Biomarker investigations, Section 8.2 Analysis sets, Section 8.4.4 Pharmacokinetic data

13.5.1.6 Modification 6 – Bone marrow biopsy revised

Following the removal of all efficacy variables from the study, language on bone marrow biopsy was modified. Bone marrow biopsy after first CR is no longer required.

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

13.5.1.7 Modification 7 – Meal timing on infusion days revised

Based on available safety data on copanlisib, 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.

Sections affected by this modification: Section 6.4 Dosage and administration, Section 7.1.1 Tabulated overview, Section 7.1.2.2.1 Treatment – Cycle 1, Section 7.1.2.2.2 Treatment – Cycle 2 and higher, Section 7.5.3.6 Glucose measurement on infusion days, Section 12. Reference list, Section 14.7 The average glycemic index of common foods derived from multiple studies by different laboratories

13.5.1.8 Modification 8 – Home glucose monitoring

Based on available data, post-infusion blood glucose increase related to copanlisib treatment is transient and manageable. Home glucose monitoring language was modified to allow investigator to determine based on post-infusion glucose profile and clinical status of the patient if home glucose monitoring is needed.

Sections affected by this modification: Section 6.4.2.1 Management of transient post-infusion glucose increases that can occur with study treatment, Section 7.1.1 Tabulated overview, Section 7.1.2.1 Screening period, Section 7.1.2.2.1 Treatment – Cycle 1, Section 7.1.2.2.2 Treatment – Cycle 2 and higher, Section 7.1.2.4 End-of-treatment visit

13.5.1.9 Modification 9 – Clarification and change in withdrawal criteria

It was clarified that patients who experienced clinical PD may be withdrawn from study treatment at investigator's discretion.

Based on available safety data on copanlisib and to align with Aliqopa prescribing information, withdrawal criteria for persistent occurrence of post infusion blood glucose was modified from 400 to > 500 mg/dL.

Sections affected by this modification: Section 5.2.1.1 Withdrawal from study treatment

13.5.1.10 Modification 10 – Change in glucose increase dose modification rules

Based on available safety data on copanlisib and to align with withdrawal criteria and Aliqopa prescribing information, dose reduction and drug permanent discontinuation protocol requirements for blood glucose increases were modified from 400 to 500 mg/dL.

Sections affected by this modification: Section 6.4.1.2 Non-hematological toxicity

13.5.1.11 Modification 11 – Change in tumor assessments

Following the revised study design and removal of all efficacy endpoints and variables, text was modified to allow sites to perform tumor assessments and to determine the frequency of radiological tumor assessments and serum tests (for LPL/WM patients only) based on local standards of care. For all patients who discontinue due to radiological PD or clinical PD, only date of PD will be collected and recorded in eCRF.

Sections affected by this modification: Synopsis, Section 4. Study design, Section 5.2.1.1 Withdrawal from study treatment, Section 7.1.1 Tabulated overview, Section 7.1.2.1 Screening period, Section 7.1.2.2.2 Treatment – Cycle 2 and higher, Section 7.1.2.3 Tumor assessments, Section 7.1.2.4 End-of-treatment visit, Section 7.3.2 Radiological tumor assessments, Section 7.3.3 Tumor assessments in patients with WM, Section 11.2 Patient information and consent

13.5.1.12 Modification 12 – Addition of a clarification note related to hemoglobin test results on infusion Days 8 and 15

A clarification note related to hemoglobin test results was added to clarify the protocol requirement for the laboratory test results of hemoglobin < 8 g/dL on infusion Day 8 and Day 15.

Sections affected by this modification: Section 6.4 Dosage and administration

13.5.1.13 Modification 13 – Administrative information updated and other clarification

In addition to the modifications specified above, there have been updates to administrative information as well as minor corrections for better clarity and consistency.

- The study PPD changed. Therefore the contact details were updated.

- A note was added that the screening procedures are no longer applicable by the time the protocol amendment 6 becomes effective, as screening for the study ended on 03 MAR 2017.
- On infusion days the allowed time window for post-infusion glucose measurements was modified to ± 10 min for easier site compliance.
- References to the open label study were removed for consistency.
- Introductory information on the number of patients treated with copanlisib was updated based on most recent data.
- Refererences to Imaging Manual were removed since Imaging Manual will not be applicable after amendment 6 becomes effective.
- Definition of end of study was modified by including the sites last contact with the patient along with the last study visit in the definition.
- Relevant references to placebo were removed for consistency.
- Since only year of birth is collected for screening failure patients, the language on data recording was corrected accordingly.

Sections affected by this modification: Title page, Synopsis, Section 1.1.2 Clinical experience, Section 1.2 Rationale of the study, Section 3. Investigator and other study personnel, Section 4. Study design, Section 6.4.1 Dose modification, Section 7.1.1 Tabulated overview, Section 7.1.2.1 Screening period, Section 7.1.2.2.1 Treatment – Cycle 1, Section 7.1.2.2.2 Treatment – Cycle 2 and higher, Section 7.1.2.3 Tumor assessments, Section 7.1.2.4 End-of-treatment visit, Section 7.3.2 Radiological tumor assessments, Section 7.5.3.6 Glucose measurement on infusion days, Section 8.1 General considerations, Section 9.1 Data recording, Section 10. Premature termination of the study, Section 11.2 Patient information and consent

13.5.2 Changes to the protocol text

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. 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 typing errors or omissions are not highlighted in this amendment.

13.5.2.1 Title page

Old text:

Sponsor's PPD : PPD ~~MD~~
PPD ~~Bayer Center,~~
~~No.27 Dong San Huan North Road,~~
~~Chaoyang District, Beijing, China, 100020~~
Telephone ~~no.:~~ PPD

New text:

Sponsor's PPD : PPD MD, PhD
Rua Domingos Jorge, 1100 – Bloco 301 - 2º andar
04779-900, São Paulo, SP Brasil
Telephone: PPD

13.5.2.2 Synopsis

Old text:

[…]	
Study objectives	The primary objective of this study is: • ~~To investigate objective tumor response rate (ORR) assessed in all patients with rituximab-refractory iNHL who have received two or more prior lines of treatment, have been exposed to rituximab and alkylating agent(s), and have progressed within six month of the end of the last previous rituximab-containing regimen.~~ ~~The secondary objectives of this study are to evaluate:~~ • ~~Efficacy including complete response rate and overall survival.~~ • ~~Safety.~~ ~~The other objectives of this study are to evaluate:~~ • ~~Pharmacokinetics.~~ • ~~Biomarkers.~~
[…]	
Duration of treatment	Treatment will be continued until disease progression (PD) ~~(~~per investigator's assessment~~) as defined in the Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification,~~ unacceptable toxicity, or until another criterion is met for withdrawal from the study treatment. ~~For patients with Waldenström macroglobulinemia (WM), response assessment will be done according to the Response Assessment in Waldenström macroglobulinemia: update from the VIth International Workshop.~~
[…]	
Study design	~~A~~ randomized, double-blind, two-arm Phase III study to evaluate the efficacy and safety of copanlisib as monotherapy in comparison to placebo in patients with rituximab-refractory iNHL. Following sponsor's decision to stop enrollment due to lack of feasibility to complete this study in reasonable time frame, the study design is modified ~~to reflect an open label study. After unblinding all~~ patients will be given an opportunity to continue treatment with copanlisib. Patients who are on copanlisib treatment at the time of unblinding will continue copanlisib treatment. Patients who are on placebo at the time of unblinding will be offered to switch to copanlisib treatment after unblinding procedures are completed. […]
Methodology	The study is composed of the following periods: Screening, Treatment, Safety-follow-up~~, Active follow-up (if applicable) and Survival follow-up.~~ Patients will receive 60 mg copanlisib IV infusion on Days 1, 8 and 15 of

each 28-day treatment cycle.

Treatment will be continued until PD, unacceptable toxicity, or until another criterion is met for withdrawal from the study treatment.

An End-of-treatment (EOT) visit will be performed within 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 (SFU) visit will take place 30 days (window of +5 days allowed) after the last administration of study drug.

~~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 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 radiological assessments as outlined in this protocol from the day of start of study treatment 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 least at 6-month intervals during the Survival follow-up period (up to 3 years after the last patient started study treatment), except for patients who object to follow-up data collection.~~

[…]

~~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 (less than 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 the baseline must be the same throughout the study. During the treatment period as well as during the Active follow-up period tumor assessments with the same modality will be performed per local SOC but not less than every 16 weeks. 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 evaluation of treatment response (best response: ORR and CRR) will be done by the investigator.~~

~~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. However, in cases when WM patients will develop disease progression confirmed radiologically by presenting with measurable lesion(s) without simultaneous increase in IgM. 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. Bone marrow tissue~~

	~~biopsy will be done within 28 days before first study drug infusion and must be provided at screening. Bone marrow biopsy must be performed again to confirm the first complete response (CR) on patients with previous bone marrow infiltration at baseline, and may also~~ be performed at the investigator discretion if there is clinical suspicion of bone marrow infiltration. Bone marrow biopsy will be performed per local standard of care.
[…]	
Primary variable	~~The primary efficacy analysis is ORR, which is defined as the proportion of patients who have a best response rating over the whole duration of the study of complete response (CR) or partial response (PR) according to the Lugano Classification (21), 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 (22).~~
Plan for statistical analysis	Due to the decision of stopping enrollment as protocol amendment 5 becomes effective, limited number of patients will be included in the analyses. Therefore, the statistical analyses included in this study will be focused on descriptive statistics ~~without any hypothesis testing~~. Two sets of analyses will be performed at the timing when all ~~treated~~ patients completed ~~at least 6 cycles of~~ study treatment~~:~~ 1) unblinding cutoff: analyze all data available before the unblinding (details in section 6.5); 2) final analysis: analyze all data available until all ~~treated~~ patients ~~complete at least 6 cycles of~~ study treatment.

New text:

[…]	
Study objectives	The primary objective of this study is: • <u>To assess the safety of copanlisib.</u>
[…]	
Duration of treatment	Treatment will be continued until disease progression (PD) <u>by radiological assessments or clinical progression (tumor evaluations will be made at intervals that comply with the institution's standard of care [per investigator's assessment]),</u> unacceptable toxicity, or until another criterion is met for withdrawal from the study treatment.
[…]	
Study design	<u>Initially this was a</u> randomized, double-blind, two-arm Phase III study to evaluate the efficacy and safety of copanlisib as monotherapy in comparison to placebo in patients with rituximab-refractory iNHL. Following sponsor's decision to stop enrollment due to lack of feasibility to complete this study in reasonable time frame, the study design is

	modified. All patients will be given an opportunity to continue treatment with copanlisib. Patients who are on copanlisib treatment at the time of unblinding will continue copanlisib treatment. Patients who are on placebo at the time of unblinding will be offered to switch to copanlisib treatment after unblinding procedures are completed. […]
Methodology	The study is composed of the following periods: Screening, Treatment, and Safety-follow-up. By the time the protocol amendment 6 becomes effective, screening procedures are no longer applicable as screening for the study ended on 03 MAR 2017. All screened eligible patients have started treatment. Patients will receive 60 mg copanlisib IV infusion on Days 1, 8 and 15 of each 28-day treatment cycle. Treatment will be continued until PD, unacceptable toxicity, or until another criterion is met for withdrawal from the study treatment. An End-of-treatment (EOT) visit will be performed within 7 days after the decision is made to discontinue study treatment. Following completion of the EOT visit, patients will enter the Safety follow-up. The Safety follow-up (SFU) visit will take place 30 days (window of +5 days allowed) after the last administration of study drug. […] Tumor assessments (and laboratory/clinical tests for WM patients) will be made according to the institution's standard of care. Bone marrow biopsy may be performed at the investigator discretion if there is clinical suspicion of bone marrow infiltration. Bone marrow biopsy will be performed per local standard of care.
[…]	
Primary variable	The primary analysis is safety, which includes treatment-emergent AEs (TEAEs) and serious adverse events (SAEs), laboratory parameters, and vital signs.
Plan for statistical analysis	Due to the decision of stopping enrollment as protocol amendment 5 becomes effective, limited number of patients will be included in the analyses. Therefore, the statistical analyses included in this study will be focused on descriptive statistics on safety variables only. Two sets of analyses will be performed at the timing when all patients have completed the study treatment and Safety follow-up period (if applicable): 1) unblinding cutoff: analyze all data available before the unblinding (details in section 6.5); 2) final analysis: analyze all data available until all patients have completed the copanlisib study treatment and Safety follow-up period.

13.5.2.3 Section 1.1.2 Clinical experience

Old text:

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 1, Phase 2, and Phase 3 clinical trials (please refer to IB) as a single agent or in combination with other agents.

[…]

New text:

Copanlisib is currently under investigation in various trials enrolling cancer patients. As of 21 JUN 2017, approximately 772 patients with advanced cancer have been treated with copanlisib in Phase 1, Phase 2, and Phase 3 clinical trials (please refer to IB) as a single agent or in combination with other agents.

[…]

13.5.2.4 Section 1.2 Rationale of the study

Old text:

[…]

Following sponsor's decision to stop enrollment due to lack of feasibility to complete this study in reasonable time frame, the study design is modified ~~to reflect an open label study.~~ All patients on study treatment will be offered to continue treatment with copanlisib after unblinding procedures are completed.

New text:

[…]

Following sponsor's decision to stop enrollment due to lack of feasibility to complete this study in reasonable time frame, the study design is modified. All patients on study treatment will be offered to continue treatment with copanlisib after unblinding procedures are completed.

13.5.2.5 Section 2. Study objectives

Old text:

The primary objective of this study is:

- ~~To investigate objective tumor response rate (ORR) assessed in all patients with rituximab-refractory iNHL who have received two or more prior lines of treatment, have been exposed to rituximab and alkylating agent(s), and have progressed within six month of the end of the last previous rituximab-containing regimen.~~

~~The secondary objectives of this study are to evaluate:~~

- ~~Efficacy including complete response rate and overall survival.~~
- ~~Safety.~~

~~The other objectives of this study are to evaluate:~~

- ~~Pharmacokinetics.~~
- ~~Biomarkers.~~

New text:

The primary objective of this study is:

- To assess the safety of copanlisib.

13.5.2.6 Section 3. Investigator and other study personnel

Old text:

Sponsor's PPD

Name: PPD ~~MD~~
PPD ~~Bayer Center,~~
~~No.27 Dong San Huan North Road,~~
~~Chaoyang District, Beijing, China, 100020~~
Telephone ~~no.:~~ PPD

New text:

Sponsor's PPD

Name:
PPD MD, PhD
Rua Domingos Jorge, 1100 – Bloco 301 - 2º andar
04779-900, São Paulo, SP Brasil
Telephone: PPD

13.5.2.7 Section 4. Study design

Old text:

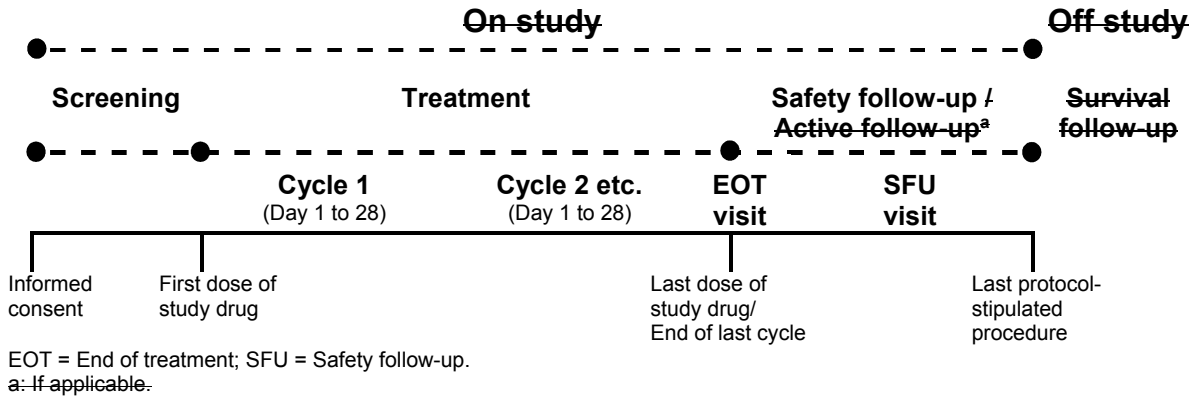
Design overview

~~This is~~ a randomized, double-blind, two-arm Phase III study to evaluate the efficacy and safety of copanlisib as monotherapy in comparison to placebo in patients with rituximab-refractory iNHL.

[…]

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.~~

[…]

~~Approximately 189 patients (of approx. 237 screened) will meet the eligibility criteria (see Section 5.1) and will be randomly assigned in a 2:1 ratio to one of the double-blinded treatment arms: copanlisib monotherapy (approx. 126 patients) or placebo (approx. 63 patients). Patients will be stratified at randomization based on NHL histology (FL histology: approx. 144 patients; iNHL histology: approx. 45 patients) , the time between last course of systemic anticancer therapy and most recent progression and prior treatment with PI3K inhibitors (see Section 6.3).~~

~~Following sponsor's decision to stop enrollment due to lack of feasibility to complete this study in reasonable time frame, the study design is modified to reflect an open label study. All patients on study treatment will be offered to continue treatment with copanlisib after unblinding procedures are completed (see Section 6.5).~~

[…]

The start of the treatment period is defined by first administration of study drug (copanlisib). Copanlisib will be administered IV over approximately 1 h at starting dose of 60 mg on Days 1, 8 and 15 of each 28-day treatment cycle. Treatment will be continued until PD ~~(~~per investigator's assessment~~) as defined in the Lugano Classification (21),~~ unacceptable toxicity,

or until another criterion is met for withdrawal from the study treatment (see Section 5.2). ~~For patients with WM, response assessment will be done according to the Owen criteria (22).~~

[…]

An End-of-treatment (EOT) visit will be performed within 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 (SFU) visit will take place 30 days (window of +5 days allowed) after the last administration of study drug.

~~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 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 radiological assessments by investigator as outlined in this protocol from the day of start of study treatment 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 sponsor's GPV department.~~

~~All patients will be followed off-study for overall survival at least at 6-month intervals during the Survival follow-up period (up to 3 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".~~

[…]

~~The first radiological tumor assessment 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) (see Table 7–1 and Section 7.3.2). Corticosteroids must be stopped or reduced to the allowed dose (less than 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 the baseline must be the same throughout the study. During the treatment period as well as during the Active follow-up period tumor assessments with the same modality will be performed, and the schedule of tumor assessment will be performed per local standard of care of the institution but not less than every 16 weeks. 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 (21), and for patients with WM, according to the Owen criteria (22). Detailed instructions on tumor assessment are provided in Appendix 14.1. ~~All the efficacy analyses will be done based on investigator's assessment of tumor response.~~

~~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. However, in cases when WM patients who develop extramedullary disease without simultaneous increase in IgM will have radiological assessment to confirm disease progression (per investigator's assessment). 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. Bone marrow tissue biopsy will be performed within 28 days before first study drug infusion and must be provided at screening. Bone marrow biopsy must be performed again to confirm the first complete response (CR) on patients with bone marrow infiltration at baseline, and may also~~ be performed at the investigator discretion if there is clinical suspicion of bone marrow infiltration. Bone marrow biopsy will be performed as per local standard of care.

All collected tumor tissue samples ~~will~~ be utilized ~~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).

~~Sparse blood samples for PK analysis will be collected from all patients to characterize the PK of copanlisib (see Section 7.4).~~

~~Plasma samples for biomarker analyses will be collected from all patients, according to the schedule specified in Section 7.6.1. Blood samples for exploratory genetic biomarker analysis will be collected on Cycle 1 Day 1 from patients who provide "genetic research" consent (voluntary).~~

Primary variable

Due to the decision of stopping enrollment, limited number of patients will be included in the analyses. Therefore, the statistical analyses included in this study will be focused on descriptive statistics.

~~The primary efficacy variable of this study will be objective tumor response rate (ORR), which is defined as the proportion of patients who have a best response rating up to the dates of data cutoffs (for dates of data cutoffs, see details in section 8.1) of complete response (CR) or partial response (PR) according to the Lugano Classification (21), 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 (22).~~

Justification of the design

The pre-clinical profile of copanlisib and preliminary efficacy data from Phase I study 12871 and Phase II study 16349 suggest that copanlisib may improve PFS in patients with rituximab-refractory iNHL who have received two or more prior lines of treatment and have been exposed to rituximab and alkylating agent(s). The purpose of this study is to ~~demonstrate efficacy and~~ safety of ~~treatment with~~ copanlisib ~~in patients where treatment is indicated, with ORR as the primary endpoint~~.

End of study

For each participating 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.

[…]

New text:

Design overview

Following sponsor's decision to stop enrollment due to lack of feasibility to complete this study in reasonable time frame, the study design is modified. All patients on study treatment will be offered to continue treatment with copanlisib after unblinding procedures are completed (see Section 6.5).

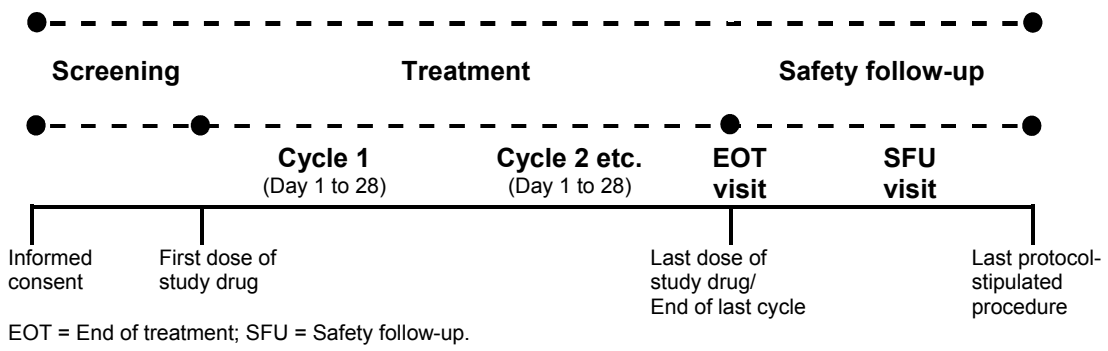
By the time the protocol amendment 6 becomes effective, screening procedures are no longer applicable as screening for the study ended on 03 MAR 2017. All screened eligible patients have started treatment.

Initially this was a randomized, double-blind, two-arm Phase III study to evaluate the efficacy and safety of copanlisib as monotherapy in comparison to placebo in patients with rituximab-refractory iNHL.

[…]

The overview of study periods updated by amendment 6 is presented in Figure 4–1.

Figure 4-1 Study periods as of amendment 6



EOT = End of treatment; SFU = Safety follow-up.

[…]

The start of the treatment period is defined by first administration of study drug (copanlisib). Copanlisib will be administered IV over approximately 1 h at starting dose of 60 mg on Days 1, 8 and 15 of each 28-day treatment cycle. Treatment will be continued until PD by radiological assessments or clinical progression (tumor evaluations will be made at intervals that comply with the institution's standard of care [per investigator's assessment]),

unacceptable toxicity, or until another criterion is met for withdrawal from the study treatment (see Section 5.2).

[…]

An End-of-treatment (EOT) visit will be performed within 7 days after the decision is made to discontinue study treatment. Following completion of the EOT visit, patients will enter the Safety follow-up. The Safety follow-up (SFU) visit will take place 30 days (window of +5 days allowed) after the last administration of study drug.

[…]

Tumor assessments (and laboratory/clinical tests for WM patients) will be made according to the institution's standard of care.

The response assessment will be done according to the Lugano Classification (21), and for patients with WM, according to the Owen criteria (22). Detailed instructions on tumor assessment are provided in Appendix 14.1.

Bone marrow biopsy may be performed at the investigator discretion if there is clinical suspicion of bone marrow infiltration. Bone marrow biopsy will be performed as per local standard of care.

All collected blood, plasma and tumor tissue samples may be utilized for biomarker analysis to contribute to better understanding the mechanism of action and the disease (see Section 7.6.1).

Primary variable

Due to the decision of stopping enrollment, limited number of patients will be included in the analyses. Therefore, the statistical analyses included in this study will be focused on descriptive statistics for safety only.

Justification of the design

The pre-clinical profile of copanlisib and preliminary efficacy data from Phase I study 12871 and Phase II study 16349 suggest that copanlisib may improve PFS in patients with rituximab-refractory iNHL who have received two or more prior lines of treatment and have been exposed to rituximab and alkylating agent(s). The purpose of this study is to evaluate the safety of copanlisib treatment.

End of study

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

[…]

13.5.2.8 Section 5.2.1.1 Withdrawal from study treatment

Old text:

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 Active or Survival follow-up unless they object to follow-up data collection~~ (see Section 11.2).
- […]
- Persistent occurrence of post-infusion blood glucose > ~~400~~ mg/dL based on laboratory analysis which occurred at the lowest study drug dose level despite optimal glucose lowering therapy (after at least one cycle of treatment) ~~with consultation of a diabetes specialist (e.g. diabetologist or endocrinologist)~~.
  Definition of persistent occurrence is based on repeated post-infusion blood glucose laboratory analysis taken at different time during the whole cycle of treatment.
- […]

Patients *may* 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).

[…]

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.

[…]

New text:

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. (<u>S</u>ee Section 11.2).
- […]
- Persistent occurrence of post-infusion blood glucose > <u>500</u> mg/dL based on laboratory analysis which occurred at the lowest study drug 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.

- […]

Patients *may* 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).
- Clinical progression per investigator assessment.

[…]

For all patients who discontinue due to radiological PD or clinical PD, only date of PD will be collected and recorded in eCRF.

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

[…]

13.5.2.9 Section 5.2.1.2 Withdrawal from follow-up period

Old text:

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 the Active follow-up period (which also serves as a Safety follow-up)~~.

~~All patients will be contacted at least every 6 months to determine survival status during the Survival follow-up period (up to 3 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

New text:

Following completion of the EOT visit, patients will enter the Safety-follow up period.

Reasons for not performing the Safety follow-up include the following:

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

13.5.2.10 Section 6.4 Dosage and administration

Old text:

[…]

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)	~~Fasting required before study drug infusion~~
Day 1 of cycle 1	Yes	≤125 mg/dL (non-diabetic patients) <160 mg/dL (diabetic patients)	~~Yes~~ [a]
~~**Day 1 of subsequent cycles**~~	~~Yes~~	~~<160 mg/dL (fasting)~~ ~~< 200 mg/dL (non-fasting)~~ [c]	~~Conditional~~ [a, b, d]
~~**Days 8 and 15 of each cycle**~~	No	<160 mg/dL (fasting) <200 mg/dL (non-fasting)	~~Conditional~~ [a, b, d]

a: Diabetic patients who take insulin treatment at any cycle visit: Timing and content of ~~caloric~~ intake ~~on infusion days~~ will be managed ~~and monitored~~ by the investigator. Consultation with treating physician or ~~diabetes specialist~~ 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 ~~(see text below "Recommendations on meal timing on infusion days" for further details)~~.

~~c: In case of non-compliance with the fasting requirement.~~

~~d: A low glycemic index meal may be taken at least 4 h before the start of the study drug infusion for patients who have their infusions scheduled at a later hour, or due to their age or medical condition when fasting prior to infusion is not viable.~~

~~The investigator will accurately document fasting/non-fasting for each glucose measurement done at the site.~~

[…]

~~Any capillary or plasma glucose levels > 250 mg/dL should be confirmed by repeated laboratory analysis.~~

Recommendations on meal timing on infusion days

[…]

It is recommended that timing ~~and content of caloric~~ intake ~~on infusion days is~~ managed and monitored by the investigators. Consultation with treating physician or diabetes specialist (e.g. diabetologist or endocrinologist) is advised.

~~The investigator will review the glucose profile during and post the study drug infusions.~~

~~The investigator may manage the timing of post-infusion meals based on the glucose profile during prior infusion(s) to minimize glucose increases. This is in addition to glucose lowering medication. Low glycemic index meals (see Appendix 14.7) should be provided for patients who are kept in clinic for continued observation.~~

~~A low glycemic index diet is recommended for the first 48 h after study drug infusion. However, caloric restriction is not intended for the population under study.~~

All glucose measurements, oral glucose lowering medication and/or insulin administration, if applicable, and meal timing will be collected as part of the clinical source documentation.

~~Note: Caloric intake and timing recommendations for diabetic patients who require insulin treatment prior to the infusion at any cycle visit should be managed and monitored by the investigator based on consultation with treating physician or diabetes specialist.~~

- **On infusion days at any cycle:**

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

  ~~Note: If patient needs to take a low glycemic meal, then glucose test should be taken prior to meal intake and at 1 h and 2 h after the meal (see Section 7.5.3.6).~~

- **Cycle 1 Day 1:**

  Fasting is required before start of infusion.

  ~~A low glycemic index meal (see Appendix 14.7) may be taken 3 h after start of infusion.~~

- ~~**Day 1 of each subsequent cycle after Cycle 1 Day 1:**~~

  ~~Fasting is required before the first glucose measurement.~~

  ~~After Cycle 1, a low glycemic index meal may be taken at least 4 h before the start of the study drug infusion for patients who have their infusions scheduled at a later hour, or due to their age or medical condition when fasting prior to infusion is not viable.~~

- ~~**Day 8 and Day 15 of each cycle:**~~

  Fasting is not required before start of infusion.

  ~~A low glycemic index meal may be taken at least 4 h before the start of the study drug infusion for patients who have their infusions scheduled at a later hour, or due to their age or medical condition when fasting prior to infusion is not viable.~~

[…]

Dosing criteria

[…]

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

- CTCAE Grade ≥ 3 neutrophil count decreased (ANC < 1,000/mm^3)
- CTCAE Grade ≥ 3 platelet count decreased (platelets < 50,000/mm^3)
- CTCAE Grade ≥ 3 anemia (hemoglobin < 8 g/dL)

Doses scheduled for Days 1 (after Cycle 1 Day 1), 8 and 15 may be delayed by up to 2 days. A delay of more than 2 days will be considered a missed dose. Missed doses will not be replaced. The minimum interval needed between two infusions of study drugs is 5 days.

New text:

[…]

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)
Day 1 of cycle 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 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.

[…]

Recommendations on meal timing on infusion days

[…]

It is recommended on infusion days that timing of meal intake and additional glucose testing (if applicable) are managed and monitored by the investigators. Consultation with treating physician or diabetes specialist (e.g. 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.

- **On infusion days at any cycle:**

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

- **Cycle 1 Day 1:**

  Fasting is required before start of infusion.

- **Subsequent visits after C1D1 visit:**

  Fasting is not required before start of infusion.

[…]

Dosing criteria

[…]

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

- CTCAE Grade ≥ 3 neutrophil count decreased (ANC < 1,000/mm^3)
- CTCAE Grade ≥ 3 platelet count decreased (platelets < 50,000/mm^3)
- CTCAE Grade ≥ 3 anemia (hemoglobin < 8 g/dL)

  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 on schedule 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 the source documentation and in the eCRF.

Doses scheduled for Days 1 (after Cycle 1 Day 1), 8 and 15 may be delayed by up to 2 days. A delay of more than 2 days will be considered a missed dose. Missed doses will not be replaced. The minimum interval needed between two infusions of study drugs is 5 days.

13.5.2.11 Section 6.4.1 Dose modification

Old text:

[…]

The dose modification levels of study treatment (copanlisib ~~or placebo~~) will follow the pre-defined dose levels shown in Table 6-3. ~~Dummy dose modifications are used for placebo.~~

[…]

New text:

[…]

The dose modification levels of study treatment (copanlisib) will follow the pre-defined dose levels shown in Table 6–3.

[…]

13.5.2.12 Section 6.4.1.2 Non-hematological toxicity

Old text:

[…]

a) Glucose increases

[…]

- Continuing occurrence of post-infusion blood glucose > ~~400~~ mg/dL based on repeated laboratory analysis despite optimal glucose lowering therapy after 2 infusions of study drug will require dose reduction by one dose level.
- Further dose reduction is allowed as long as discontinuation criteria ~~was~~ not met.
- […]
- Persistent occurrence of post-infusion blood glucose > ~~400~~ mg/dL based on laboratory analysis which occurred at the lowest study drug dose level despite optimal glucose lowering therapy (after at least one cycle of treatment) with consultation of a diabetes specialist requires permanent discontinuation of the study treatment (see Section 5.2.1.1).

New text:

[…]

a) Glucose increases

[…]

- Continuing occurrence of post-infusion blood glucose > <u>500</u> mg/dL based on repeated laboratory analysis despite optimal glucose lowering therapy after 2 infusions of study drug will require dose reduction by one dose level.
- Further dose reduction is allowed as long as discontinuation criteria <u>were</u> not met.
- […]
- Persistent occurrence of post-infusion blood glucose > <u>500</u> mg/dL based on laboratory analysis which occurred at the lowest study drug dose level despite optimal glucose

lowering therapy (after at least one cycle of treatment) with consultation of a diabetes specialist requires permanent discontinuation of the study treatment (see Section 5.2.1.1).

13.5.2.13 Section 6.4.2.1 Management of transient post-infusion glucose increases that can occur with study treatment

Old text:

[…]

Table 6-9 Management of transient post-infusion glucose increases

Criteria	Recommendation	Suggested Treatment
[…]		
[…]		

~~**Glucose monitoring at home**~~

~~At least 3 times per full day including fasting glucose (morning before breakfast) and 2 further measurements approximately 2 h after intake of food for at least 72 h after the start of infusion is required for:~~

- ~~All diabetic patients regardless of glucose level on infusion day~~
- ~~Non-diabetic patients who experience persisting glucose > 250 mg/dL or who require insulin administration post-infusion. Consultation with diabetes specialist is recommended.~~

~~Patients will be trained how to measure their capillary blood glucose levels at home. If applicable, patients will be provided with glucose meter and supplies (lancets, test strips and diary) to register measured values and record meal timing, oral glucose lowering medication and/or insulin administration. The appropriate calibration of glucose meters will be documented.~~

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. ~~In this situation, patients should add the study specific measurements to their routine, if applicable. After the required 72 h, if blood glucose values are at goal (random non-fasting glucose < 200 mg/dL) after each infusion, patients can then stop only the study specific measurements until the next day of infusion, but should keep their routine measurements unchanged and ongoing as usual.~~

~~Sites recruiting patients with diabetes should have the option to extend glucose monitoring overnight.~~

New text:

[…]

Table 6-9 Management of transient post-infusion glucose increases

Criteria	Recommendation	Suggested Treatment
[…]		
[…]		

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.

13.5.2.14 Section 7.1.1 Tabulated overview

Old text:

Table 7-1 Study flow chart

	Screening maximum days before C1D1			**Treatment ***						**EOT**	**SFU**	~~**Active follow-up** [aa]~~	~~**Survival follow-up** [bb]~~
				Cycle 1			**Cycle 2 and higher**			Within (days) after			
Days	**-28**	**-14**	**-7**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**7**	**30 + 5** days window[z]		~~**every 6 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) [jj]	X[cc,dd]												
Check in- and exclusion criteria		X	X	X									
Medical history [a]		X											
IVRS/IWRS transaction [b, dd]	X			X[b]			X			X			
HBsAg, HBcAb, HCV IgG	X												
CMV PCR test [ff,ii]	X			X[ff]			X[ff]						
Serum pregnancy test (if applicable) [c]			X				X[c]			X[c, ee]			
UPCR / 24 h total urine protein quantification [ee]			X										
GFR [dd]			X				X						
Safety													
Toxicity / AE assessment [d]		X		X	X	X	X	X	X	X	X	~~(X)~~[d]	
Concomitant medication [d]		X		X	X	X	X	X	X	X	X		
Complete physical examination [e]		X		X			X			X			
Brief physical examination [f, dd]					X	X		X	X		(X)		
12-lead ECG [g, dd]	X									X[g]			
MUGA scan or echocardiogram [h, dd]	X[h]									X[h]			
HbA1c [i]			X							X			
Complete blood count [j]			X		X[x]	X[x]	X[x]	C2 only[x]	C2 only[x]	X	(X)		

Table 7-1 Study flow chart

Days	Screening maximum days before C1D1			Treatment *						EOT	SFU	~~Active follow-up~~ [aa]	~~Survival follow-up~~ [bb]
				Cycle 1			Cycle 2 and higher			Within (days) after			
	-28	-14	-7	D1	D8	D15	D1	D8	D15	7	30 + 5 days window[z]		~~every 6 months~~
Acceptable deviation (in days)				-1 to +2 days			-1 to +2 days			Decision to stop	Last dose		~~±14 days~~
Hemoglobin, ANC and platelet counts (C3->)								X[x]	X[x]				
Chemistry panel [k]			X[k]		X[x]	X[x]	X[k,x]	C2 only[x]	C2 only[x]	X[k]	(X)		
Coagulation panel: PT, INR and PTT			X			X[x]	X[x]			X	(X)		
CD4 (for patients with signs of infection) and blood cultures when low ANC of CTCAE Grade 4 [gg, hh,ii]													
Urinalysis (dipstick)			X				X			X			
Glucose [l]				X	X	X	X	X	X				
~~Home glucose monitoring~~ [m, dd]			~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~			
Blood pressure [n]				X	X	X	X	X	X				
~~Efficacy~~													
Bone marrow biopsy [o]	X												
CT/MRI and tumor evaluations [p]	X[p]									X[p]		~~X~~[p]	
~~Pharmacokinetic sampling~~ [r, dd]					~~X~~								
~~Biomarkers~~													
~~Tumor tissue for central pathology and biomarkers~~ [s, dd]	~~X~~									~~(X)~~			
~~Plasma for tumor genetics~~ [t, dd]				~~X~~						~~X~~			
~~Plasma for non-genetic biomarker analysis~~ [u dd]				~~X~~	~~X~~	~~X~~	~~C2 only~~	~~C2 only~~	~~C2 only~~	~~X~~			
Study drug administration													
Copanlisib IV infusion				X	X	X	X	X	X				
~~Survival status, new anticancer therapy~~													~~X~~

Table 7-1 Study flow chart

	Screening maximum days before C1D1			Treatment *						EOT	SFU	~~Active follow-up~~ [aa]	~~Survival follow-up~~ [bb]
				Cycle 1			Cycle 2 and higher			Within (days) after			
Days	**-28**	**-14**	**-7**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**7**	**30 + 5** days window[z]		~~**every 6 months**~~
Acceptable deviation (in days)				-1 to +2 days			-1 to +2 days			Decision to stop	Last dose		~~±14 days~~
~~**For LPL/WM patients only**~~													
~~Serum protein electrophoresis~~ [w]		~~X~~[w]								~~(X)~~[w]			
~~Immunofixation~~ [w]		~~X~~[w]								~~(X)~~[w]			
~~Serum quantitative IgM test~~ [w]		~~X~~[w]								~~(X)~~[w]			
~~Serum beta-2-microglobulin~~ [dd]		~~X~~[w]											
~~Serum or plasma viscosity~~ [w]		~~X~~[w]					~~(X)~~[w]			~~(X)~~[w]			

[…] ~~IgM = Immunoglobulin M;~~

[…] ~~PD = Disease progression; PK = Pharmacokinetic(s);~~

[…] ~~SAE = Serious adverse event;~~

[…]

d After Screening: AE assessment and concomitant medication review must be updated before each dose and all AEs starting within 30 days after the last dose of study drug should be collected and recorded in eCRF. 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. 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.~~

[…]

l On Cycle 1 Day 1, glucose will be measured at pre-dose and post-dose after the end of study drug infusion (0), 1 h and 2 h. Additional measurements to be performed at the clinic as clinically indicated. On subsequent infusions, glucose will be measured prior to and 1 h after the end of infusion. Deviation of ± ~~5~~ min is allowed for glucose measurements, except for the pre-dose measurement. ~~The pre-dose glucose sample on Day 1 of each cycle should be after an 8 h fasting.~~ For details on fasting requirements and pre-dose glucose levels, see Section 6.4. Glucose is also measured as part of the chemistry panel.

~~m Home glucose monitoring is required for all diabetic patients after each infusion. For non-diabetic patients home glucose measurement is~~

~~required if patients experience persisting glucose > 250 mg/dL or require insulin administration post-infusion. Measurements should be performed according to guidance provided in Section 6.4.2.1. Patients will be trained to measure their capillary blood glucose levels at home starting at Screening. On Cycle 1 Day 1, patients will be provided with glucose meter and supplies, (lancets, test strips and diary) to record glucose values, meal timing, oral glucose lowering medication and/or insulin administration, if applicable.~~

[…]

o Bone marrow biopsy ~~must~~ be performed ~~within 28 days before first study drug infusion, and to confirm the first complete response if there is bone marrow infiltration at baseline, and also~~ at the investigator discretion if there is clinical suspicion of bone marrow infiltration Bone marrow biopsy will be performed as per local standard of care.

~~p 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 be stopped or reduced to the allowed dose (less than 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 the baseline must be the same throughout the study. During treatment, tumor scans will be done with the same modality, and the schedule of tumor assessment will be done per local standard of care of the institution but no less than 16 weeks). Time points for assessments are calculated from Cycle 1 Day 1. Tumor assessments must be performed within 14 days after the last dose (Day 15) and before the next dose (Day 1 of the subsequent cycle) starting from Cycle 3. 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. During Active follow-up period patients will have radiological assessments at same intervals as during treatment until PD is documented or new anti-tumor treatment is administered (see Section 7.1.2.3 and Section 7.3.2). For tumor assessments in patients with WM, see Section 7.3.3.~~

[…]

~~r PK sampling will be performed for copanlisib, its metabolite M-1 and other metabolites, if needed, in all patients on Cycle 1 Day 8: pre-infusion, 5 to 15 min, 55 min (or within 5 min prior to end of infusion) and 1.5 to 5 h after start of infusion. If sampling is not feasible at Cycle 1, samples may be collected at Cycle 2. A separate IV line should be used for PK draws.~~

~~s 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. 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) (see Section 7.6.1).~~

~~t Plasma for tumor genetics: blood samples will be collected on Cycle 1 Day 1 and at the EOT visit. 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. Samples are to be collected on Cycle 1 (Days 1, 8 and 15), Cycle 2 (Days 1, 8 and 15), and at the EOT visit.~~

[…]

w Only for patients affected by LPL/WM: Serum protein electrophoresis, immunofixation, serum quantitative IgM test and serum beta-2-microglobulin measurement will be performed at Screening. Serum or plasma viscosity will 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 will be performed on the days of tumor evaluation and at the EOT visit only if the last assessment is older than 4 weeks. If serum or plasma viscosity is abnormal at baseline, the measurement will be repeated every 3rd cycle starting from Day 1 of Cycle 3, and at the EOT visit.

[…]

aa 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 radiological 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.

bb 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 at least every 6 months (± 14 days), until death or until the end of the trial (up to 3 years after the last patient started study treatment), whichever comes first. Information to be recorded: date of contact, survival status, the first new anticancer regimen including response (if applicable), and date and cause of death (if applicable).

cc Written informed consent must be obtained prior to any study-specific procedures. Certain results from diagnostic testing performed as part of the standard of practice prior to the informed consent date and time may be used to fulfill screening criteria. This includes fresh tissue as noted in the protocol as well as results from CT/MRI scans, bone marrow sample, MUGA/echocardiogram and hepatitis testing which may also be used provided that they fall into the protocol-specified time window. Archival tissue obtained from the patients at any time during the course of their iNHL may also be used prior to the informed consent date and time if performed as part of the standard of practice. 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).

[…]

New text:

Table 7-1 Study flow chart

	Screening			Treatment *						EOT	SFU
	maximum days before C1D1			Cycle 1			Cycle 2 and higher			Within (days) after	
Days	**-28**	**-14**	**-7**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**7**	**30 + 5** days window[z]
Acceptable deviation (in days)				-1 to +2 days			-1 to +2 days			Decision to stop	Last dose
Screening and enrollment											
Patient informed consent (including genetic) [jj]	X[cc,dd]										
Check in- and exclusion criteria		X	X	X							
Medical history [a]		X									
IVRS/IWRS transaction [b, dd]	X			X[b]			X			X	
HBsAg, HBcAb, HCV IgG	X										
CMV PCR test [ff,ii]	X			X[ff]			X[ff]				
Serum pregnancy test (if applicable) [c]			X				X[c]			X[c, ee]	
UPCR / 24 h total urine protein quantification [ee]			X								
GFR [dd]			X				X				
Safety											
Toxicity / AE assessment [d]		X		X	X	X	X	X	X	X	X
Concomitant medication [d]		X		X	X	X	X	X	X	X	X
Complete physical examination [e]		X		X			X			X	
Brief physical examination [f, dd]					X	X		X	X		(X)
12-lead ECG [g, dd]	X									X[g]	
MUGA scan or echocardiogram [h, dd]	X[h]									X[h]	
HbA1c [i]			X							X	
Complete blood count [j]			X		X[x]	X[x]	X[x]	C2 only[x]	C2 only[x]	X	(X)
Hemoglobin, ANC and platelet counts (C3→)								X[x]	X[x]		
Chemistry panel [k]			X[k]		X[x]	X[x]	X[k,x]	C2 only[x]	C2 only[x]	X[k]	(X)
Coagulation panel: PT, INR and PTT			X			X[x]	X[x]			X	(X)

Table 7-1 Study flow chart

	Screening			Treatment *						EOT	SFU
	maximum days before C1D1			Cycle 1			Cycle 2 and higher			Within (days) after	
Days	**-28**	**-14**	**-7**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**7**	**30 + 5** days window[z]
Acceptable deviation (in days)				-1 to +2 days			-1 to +2 days			Decision to stop	Last dose
CD4 (for patients with signs of infection) and blood cultures when low ANC of CTCAE Grade 4 [gg, hh,ii]											
Urinalysis (dipstick)			X				X			X	
Glucose [l]				X	X	X	X	X	X		
Blood pressure [n]				X	X	X	X	X	X		
Bone marrow biopsy [o]	X										
CT/MRI and tumor evaluations and laboratory/clinical tests for LPL/WM patients[p]	X[p]									X[p]	
Study drug administration											
Copanlisib IV infusion				X	X	X	X	X	X		

[…]

d After Screening: AE assessment and concomitant medication review must be updated before each dose and all AEs starting within 30 days after the last dose of study drug should be collected and recorded in eCRF. 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. Contrast media does not need to be recorded as concomitant medication unless there is an AE related to its administration (e.g. allergic reaction).

[…]

l On Cycle 1 Day 1, glucose will be measured at pre-dose and post-dose after the end of study drug infusion (0), 1 h and 2 h. Additional measurements to be performed at the clinic as clinically indicated. On subsequent infusions, glucose will be measured prior to and 1 h after the end of infusion. Deviation of ± 10 min is allowed for glucose measurements, except for the pre-dose measurement. For details on fasting requirements and pre-dose glucose levels, see Section 6.4. Glucose is also measured as part of the chemistry panel.

m *Footnote removed by amendment 6.*

[…]

o Bone marrow biopsy may be performed at the investigator discretion if there is clinical suspicion of bone marrow infiltration. Bone marrow biopsy will be performed as per local standard of care.

p Tumor assessments and their frequency as well as laboratory/clinical tests for WM patients will follow the institution's standard of care.

[…]

r *Footnote removed by amendment 6.*

s *Footnote removed by amendment 6.*

t *Footnote removed by amendment 6.*

u *Footnote removed by amendment 6.*

[…]

w *Footnote removed by amendment 6.*

[…]

aa *Footnote removed by amendment 6.*

bb *Footnote removed by amendment 6.*

cc Written informed consent must be obtained prior to any study-specific procedures. Certain results from diagnostic testing performed as part of the standard of practice prior to the informed consent date and time may be used to fulfill screening criteria. This includes fresh tissue as noted in the protocol as well as results from CT/MRI scans, bone marrow sample, MUGA/echocardiogram and hepatitis testing which may also be used provided that they fall into the protocol-specified time window. Archival tissue obtained from the patients at any time during the course of their iNHL may also be used prior to the informed consent date and time if performed as part of the standard of practice. 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).

13.5.2.15 Section 7.1.2.1 Screening period

Old text:

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 as noted in the protocol as well as results from CT/MRI scans, bone marrow sample, MUGA/echocardiogram and hepatitis testing which may also be used provided that they fall into the protocol-specified time window. Archival tissue obtained from the patients at any time during the course of their iNHL may also be used prior to the informed consent date and time if performed as part of the standard of practice. ~~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 administration of study drug:

- […]
- Bone marrow biopsy: mandatory at Screening ~~and to confirm the first complete response in patients with previous bone marrow infiltration at baseline~~. A bone marrow biopsy may ~~also~~ be performed at the investigator discretion if there is clinical suspicion of bone marrow infiltration. Bone marrow biopsy will be performed as per local standard of care.
- IV (and oral, if indicated~~, per Imaging Manual~~) contrast-enhanced CT/MRI of neck, chest, abdomen and pelvis (including WM patients). Corticosteroids must be stopped or reduced to the allowed dose (less than 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 the baseline must be the same throughout the study (see Section 7.3.2).
- ~~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).~~

Within 14 days before the first administration of study drug:

- […]
- ~~Only in patients affected by Lymphoplasmacytoid lymphoma/Waldenström macroglobulinemia (LPL/WM):~~
    - ~~Serum protein electrophoresis.~~

- ~~Immunofixation.~~
- ~~Serum quantitative IgM test.~~

- ~~Serum beta-2-microglobulin.~~
  - ~~Serum or plasma viscosity (if hyperviscosity syndrome is suspected).~~

Within 7 days before the first administration of study drug:

- […]
- ~~Training on glucose self-monitoring with a glucose meter~~.

New text:

By the time the protocol amendment 6 becomes effective, screening procedures are no longer applicable as screening for the study ended on 03 MAR 2017. All screened eligible patients have started treatment.

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 as noted in the protocol as well as results from CT/MRI scans, bone marrow sample, MUGA/echocardiogram and hepatitis testing which may also be used provided that they fall into the protocol-specified time window. Archival tissue obtained from the patients at any time during the course of their iNHL may also be used prior to the informed consent date and time if performed as part of the standard of practice. 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 administration of study drug:

- […]
- Bone marrow biopsy: mandatory at Screening. A bone marrow biopsy may be performed at the investigator discretion if there is clinical suspicion of bone marrow infiltration. Bone marrow biopsy will be performed as per local standard of care.
- IV (and oral, if indicated) contrast-enhanced CT/MRI of neck, chest, abdomen and pelvis (including WM patients). Corticosteroids must be stopped or reduced to the allowed dose (less than 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 the baseline must be the same throughout the study (see Section 7.3.2).

- *Tumor tissue collection removed by amendment 6.*

Within 14 days before the first administration of study drug:

- […]
- *Laboratory/clinical tests for LPL/WM patients removed by amendment 6.*

Within 7 days before the first administration of study drug:

- […]
- *Training on glucose self-monitoring removed by amendment 6.*

13.5.2.16 Section 7.1.2.2.1 Treatment – Cycle 1

Old text:

Cycle 1 Day 1

[…]

- Glucose will be measured at pre-dose and post-dose after the end of study drug infusion (0), 1 h and 2 h (deviation of ± ~~5~~ min is allowed, except for the pre-dose measurement). Additional measurements to be performed at the clinic as clinically indicated~~.~~
  ~~Note: If patient needs to take a low glycemic meal, then glucose test should be taken prior to meal intake and at 1 h and 2 h after the meal~~ (see Section 6.4 and Section 7.5.3.6).
- ~~Home blood glucose monitoring:~~
  - ~~All diabetic patients regardless of glucose level on infusion day.~~
  - ~~Non-diabetic patients who experience persisting glucose > 250 mg/dL or who require insulin administration post-infusion.~~
- ~~Training on glucose self-monitoring with a glucose meter, if needed. Patients will be provided with glucose meter and supplies (lancets, test strips and diary) to record glucose values, meal timing, oral glucose lowering medication and/or insulin administration, if applicable (see Section 6.4.2.1).~~
- […]
- ~~Collection of blood for biomarker analyses prior to infusion (see Section 7.6.1):~~
  - ~~Plasma for tumor genetics.~~
  - ~~Plasma for non-genetic biomarker analysis~~.
  - […]

Cycle 1 Day 8

- […]
- Glucose test prior to study drug infusion and 1 h after the end of study drug infusion (deviation of ± ~~5~~ min is allowed, except for the pre-dose measurement)~~. Patients are not required to be fasting prior to pre-dose glucose measurement.~~
  ~~Note: If patient needs to take a low glycemic meal, then glucose test should be taken prior to meal intake and at 1 h and 2 h after the meal~~ (see Section 6.4 and Section 7.5.3.6).
- Review of the ~~home~~ blood glucose measurements/meal timing/oral glucose lowering medication/insulin administration, if applicable~~. Provide glucose monitoring supplies if necessary~~ (see Section 6.4.2.1).
- ~~Home blood glucose monitoring:~~
  - ~~All diabetic patients regardless of glucose level on infusion day.~~
  - ~~Non-diabetic patients who experience persisting glucose > 250 mg/dL or who require insulin administration post-infusion.~~
- […]
- ~~PK sampling for copanlisib, its metabolite M-1 and other metabolites, if needed: pre-infusion, 5 to 15 min, 55 min (or within 5 min prior to end of infusion) and 1.5 to 5 h after start of infusion. If sampling is not feasible at Cycle 1, samples may be collected at Cycle 2. A separate IV line should be used for PK draws (see Section 7.4).~~
- ~~Collection of plasma for non-genetic biomarker analyses prior to infusion (see Section 7.6.1).~~
- […]

Cycle 1 Day 15

- […]
- Glucose test prior to study drug infusion and 1 h after the end of study drug infusion (deviation of ± ~~5~~ min is allowed, except for the pre-dose measurement)~~. Patients are not required to be fasting prior to pre-dose glucose measurement~~
  ~~Note: If patient needs to take a low glycemic meal, then glucose test should be taken prior to meal intake and at 1 h and 2 h after the meal~~ (see Section 6.4 and Section 7.5.3.6).
- Review of the ~~home~~ blood glucose measurements/meal timing/oral glucose lowering medication/insulin administration, if applicable~~. Provide glucose monitoring supplies if necessary~~ (see Section 6.4.2.1).

- ~~Home blood glucose monitoring:~~
  - ~~All diabetic patients regardless of glucose level on infusion day.~~
  - ~~Non-diabetic patients who experience persisting glucose > 250 mg/dL or who require insulin administration post-infusion.~~
- […]
- ~~Collection of plasma for non-genetic biomarker analyses prior to infusion (see Section 7.6.1).~~
- […]

New text:

Cycle 1 Day 1

[…]

- Glucose will be measured at pre-dose and post-dose after the end of study drug infusion (0), 1 h and 2 h (deviation of ± 10 min is allowed, except for the pre-dose measurement). Additional measurements to be performed at the clinic as clinically indicated (see Section 6.4 and Section 7.5.3.6).
- *Home blood glucose monitoring removed by amendment 6.*
- […]
- *Biomarker sampling removed by amendment 6.*
- […]

Cycle 1 Day 8

- […]
- Glucose test prior to study drug infusion and 1 h after the end of study drug infusion (deviation of ± 10 min is allowed, except for the pre-dose measurement) (see Section 6.4 and Section 7.5.3.6).
- Review of the blood glucose measurements/meal timing/oral glucose lowering medication/insulin administration, if applicable (see Section 6.4.2.1).
- *Home blood glucose monitoring removed by amendment 6.*
- […]
- *PK sampling removed by amendment 6.*
- *Biomarker sampling removed by amendment 6.*
- […]

Cycle 1 Day 15

- […]
- Glucose test prior to study drug infusion and 1 h after the end of study drug infusion (deviation of ± 10 min is allowed, except for the pre-dose measurement) (see Section 6.4 and Section 7.5.3.6).
- Review of the blood glucose measurements/meal timing/oral glucose lowering medication/insulin administration, if applicable (see Section 6.4.2.1).
- *Home blood glucose monitoring removed by amendment 6.*
- […]
- *Biomarker sampling removed by amendment 6.*
- […]

13.5.2.17 Section 7.1.2.2.2 Treatment – Cycle 2 and higher

Old text:

Cycle 2 and higher, Day 1

~~On Day 1 of each subsequent cycle, 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.~~

- […]
- Glucose test prior to study drug infusion and 1 h after the end of study drug infusion (deviation of ± ~~5~~ min is allowed, except for the pre-dose measurement)~~. The pre-dose glucose sample on Day 1 of each cycle should be after an 8 h fasting~~
  ~~Note: If patient needs to take a low glycemic meal, then glucose test should be taken prior to meal intake and at 1 h and 2 ho after the meal~~ (see Section 6.4 and Section 7.5.3.6).
- Review of the ~~home~~ blood glucose measurements/meal timing/oral glucose lowering medication/insulin administration, if applicable~~. Provide glucose monitoring supplies if necessary~~ (see Section 6.4.2.1).
- ~~Home blood glucose monitoring:~~
  - ~~All diabetic patients regardless of glucose level on infusion day.~~
  - ~~Non-diabetic patients who experience persisting glucose > 250 mg/dL or who require insulin administration post-infusion.~~
- […]

- ~~Only in Cycle 2: collection of plasma for non-genetic biomarker analyses prior to infusion (see Section 7.6.1).~~
- […]
- ~~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

- […]
- Glucose test prior to study drug infusion and 1 h after the end of study drug infusion (deviation of ± ~~5~~ min is allowed, except for the pre-dose measurement)~~. Patients are not required to be fasting prior to pre-dose glucose measurement~~
  ~~Note: If patient needs to take a low glycemic meal, then glucose test should be taken prior to meal intake and at 1 h and 2 h after the meal~~ (see Section 6.4 and Section 7.5.3.6).
- Review of the ~~home~~ blood glucose measurements/meal timing/oral glucose lowering medication/insulin administration, if applicable~~. Provide glucose monitoring supplies if necessary~~ (see Section 6.4.2.1).
- ~~Home blood glucose monitoring :~~
  - ~~All diabetic patients regardless of glucose level on infusion day.~~
  - ~~Non-diabetic patients who experience persisting glucose > 250 mg/dL or who require insulin administration post-infusion.~~
- […]
- ~~Only in Cycle 2: collection of plasma for non-genetic biomarker analyses prior to infusion (see Section 7.6.1).~~
- […]

Cycle 2 and higher, Day 15

- […]
- Glucose test prior to study drug infusion and 1 h after the end of study drug infusion (deviation of ± ~~5~~ min is allowed, except for the pre-dose measurement)~~. Patients are not required to be fasting prior to pre-dose glucose measurement~~
  ~~Note: If patient needs to take a low glycemic meal, then glucose test should be taken prior to meal intake and at 1 h and 2 h after the meal~~ (see Section 6.4 and Section 7.5.3.6).
- Review of the ~~home~~ blood glucose measurements/meal timing/oral glucose lowering medication/insulin administration, if applicable~~. Provide glucose monitoring supplies if necessary~~ (see Section 6.4.2.1).

- ~~Home blood glucose monitoring:~~
  - ~~All diabetic patients regardless of glucose level on infusion day.~~
  - ~~Non-diabetic patients who experience persisting glucose > 250 mg/dL or who require insulin administration post-infusion.~~
- […]
- ~~Only in Cycle 2: collection of plasma for non-genetic biomarker analyses prior to infusion (see Section 7.6.1).~~
- […]

New text:

Cycle 2 and higher, Day 1

Fasting requirement removed by amendment 6.

- […]
- Glucose test prior to study drug infusion and 1 h after the end of study drug infusion (deviation of ± 10 min is allowed, except for the pre-dose measurement) (see Section 6.4 and Section 7.5.3.6).
- Review of the blood glucose measurements/meal timing/oral glucose lowering medication/insulin administration, if applicable (see Section 6.4.2.1).
- *Home blood glucose monitoring removed by amendment 6.*
- […]
- *Biomarker sampling removed by amendment 6.*
- […]
- *Laboratory/clinical tests for LPL/WM patients removed by amendment 6.*

Cycle 2 and higher, Day 8

- […]
- Glucose test prior to study drug infusion and 1 h after the end of study drug infusion (deviation of ± 10 min is allowed, except for the pre-dose measurement) (see Section 6.4 and Section 7.5.3.6).
- Review of the blood glucose measurements/meal timing/oral glucose lowering medication/insulin administration, if applicable (see Section 6.4.2.1).
- *Home blood glucose monitoring removed by amendment 6.*
- […]

- *Biomarker sampling removed by amendment 6.*
- […]

Cycle 2 and higher, Day 15

- […]
- Glucose test prior to study drug infusion and 1 h after the end of study drug infusion (deviation of ± 10 min is allowed, except for the pre-dose measurement) (see Section 6.4 and Section 7.5.3.6).
- Review of the blood glucose measurements/meal timing/oral glucose lowering medication/insulin administration, if applicable (see Section 6.4.2.1).
- *Home blood glucose monitoring removed by amendment 6.*
- […]
- *Biomarker sampling removed by amendment 6.*
- […]

13.5.2.18 Section 7.1.2.3 Tumor assessments

Old text:

~~Radiological tumor evaluations (IV [and oral, if indicated, per Imaging Manual] contrast-enhanced CT/MRI scans of neck, chest, abdomen and pelvis) will be performed during the treatment period as well as during the Active follow-up period, the frequency of tumor assessment will be determined by investigator per local standard of care of the institution but not less than every 16 weeks. Time points for assessments are calculated from Cycle 1 Day 1.The method chosen at the baseline must be the same throughout the study (see also Section 7.3.2):~~

~~During treatment, tumor assessments must be performed within 14 days after the last dose (Day 15) and before the next dose (Day 1 of the subsequent cycle).~~

~~During Active follow-up, tumor assessments will be done until PD is documented or new anti-tumor treatment is administered.~~

Bone marrow biopsy ~~is mandatory at baseline and to confirm the first CR if there is bone marrow infiltration at baseline. It~~ may ~~also~~ be performed at the investigator discretion if there is clinical suspicion of bone marrow infiltration. Biopsy will be performed as per local standard of care.

~~In addition, the following procedures will be performed on the days of tumor assessments (deviation of ± 2 days is allowed):~~

- ~~Only in patients affected by WM:~~
  - ~~Serum protein electrophoresis.~~

- ~~Immunofixation.~~
- ~~Serum quantitative IgM test.~~

~~For further details on tumor assessments in patients with WM, see Section 7.3.3.~~

New text:

After amendment 6 is effective, tumor assessments and their frequency as well as laboratory/clinical tests for WM patients will follow the institution's standard of care.

Bone marrow biopsy may be performed at the investigator discretion if there is clinical suspicion of bone marrow infiltration. Biopsy will be performed as per local standard of care.

13.5.2.19 Section 7.1.2.4 End-of-treatment visit

Old text:

[…]

- Review of the ~~home~~ blood glucose measurements/meal timing/oral glucose lowering medication/insulin administration, if applicable (see Section 6.4.2.1).
- ~~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).~~
- ~~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).~~
- ~~Collection of plasma for tumor genetics and non-genetic biomarker analyses (see Section 7.6.1).~~
- ~~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.~~

New text:

[…]

- Review of the blood glucose measurements/meal timing/oral glucose lowering medication/insulin administration, if applicable (see Section 6.4.2.1).

- *CT/MRI removed by amendment 6.*
- *Tumor biopsy removed by amendment 6.*
- *Biomarker sampling removed by amendment 6.*
- *Laboratory/clinical tests for LPL/WM patients removed by amendment 6.*

13.5.2.20 Section 7.1.2.5 Follow-up periods

Old text:

~~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. data analysis).~~

New text:

Section removed by amendment 6.

13.5.2.21 Section 7.1.2.5.2 Active follow-up

Old text:

~~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 radiological assessments as outlined in this CSP from the day of start of treatment until PD is documented or new anti-tumor treatment is administered (see Section 7.1.2.3).~~

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

~~The end of Active follow-up period is defined when either PD is documented or a new anti-tumor treatment is administered, whichever occurs first.~~

New text:

As the study design is modified, patients will be followed for safety only. All patients who have already completed the safety follow-up visit at the time the amendment 6 becomes effective will discontinue the study.

13.5.2.22 Section 7.1.2.5.3 Survival follow-up

Old text:

~~All patients will be followed off study for overall survival at least at 6-month intervals during the Survival follow-up period (up to 3 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 anticancer treatment regimen including response, if given.~~
- ~~Date and cause of death, if applicable.~~

New text:

<u>As the study design is modified, patients will be followed for safety only. All patients who have already completed the safety follow-up visit at the time the amendment 6 becomes effective will discontinue the study.</u>

13.5.2.23 Section 7.3.1 Primary efficacy variable

Old text:

~~The primary efficacy variable of this study is objective tumor response rate (ORR), which is defined as the proportion of patients who have a best response rating over the whole duration of the study up to the dates of data cutoffs (for dates of data cutoffs, see details in section 8.1) of complete response (CR) or partial response (PR) according to the Lugano Classification (21), 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 (22).~~

~~For the other efficacy variables to be analyzed for this study please refer to Section 8.3.1.~~

New text:

<u>As study primary endpoint was changed to safety by amendment 6, primary efficacy variable was removed.</u>

13.5.2.24 Section 7.3.2 Radiological tumor assessments

Old text:

Radiological tumor assessments with IV (and oral, if indicated~~, per Imaging Manual~~) contrast-enhanced CT/MRI 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).

[…]

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, per local standard of care of the institution ~~but no less than every 16 weeks~~ (see Section 7.1.2.3). ~~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.~~

[…]

If the patients on placebo treatment had symptoms/signs of clinical progressive disease prior to switching to copanlisib treatment, it is recommended to have radiological tumor assessments before starting copanlisib therapy unless CT/MRI scans performed within 4 weeks prior to a scheduled date of the first copanlisib infusion. For patients who previously received placebo and will be treated with copanlisib the tumor assessments should be continued as the initial schedule. ~~For further instructions please refer to the Imaging Manual.~~

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

~~As long as the patient has not experienced PD, investigator's assessment is sufficient for case management. In case of uncertain radiological disease progression the patient may stay on treatment at the investigator's discretion until progression is definitely confirmed on the subsequent tumor assessment.~~

[…]

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 IV (and oral, if indicated~~, per Imaging Manual~~) contrast-enhanced CT is medically contraindicated, sites may acquire contrast-enhanced MRI of the neck, abdomen and pelvis, and an unenhanced CT of the chest above lung apices to the bottom of the adrenals. Chest CT is preferred. Only if a patient develops contra-indication to both CT and MRI contrast medium during the treatment phase of the study, the case examinations should be continued without contrast. In certain countries MRI should be used based on local regulations.

~~The primary efficacy variable will be analyzed based on the assessment by the investigator.~~

New text:

After amendment 6 is effective, tumor assessments and their frequency as well as laboratory/clinical tests for WM patients will follow the institution's standard of care.

Radiological tumor assessments with IV (and oral, if indicated) contrast-enhanced CT/MRI will include neck, chest, abdomen and pelvis, and will be evaluated locally at the study site.

The first radiological (IV [and oral, if indicated] contrast-enhanced CT/MRI) tumor assessment will be performed at Screening (including WM patients).

[…]

During the treatment phase, radiological (IV [and oral, if indicated] contrast-enhanced CT/MRI) tumor assessment will be performed, per local standard of care of the institution (see Section 7.1.2.3).

[…]

If the patients on placebo treatment had symptoms/signs of clinical progressive disease prior to switching to copanlisib treatment, it is recommended to have radiological tumor assessments before starting copanlisib therapy unless CT/MRI scans performed within 4 weeks prior to a scheduled date of the first copanlisib infusion. For patients who previously received placebo and will be treated with copanlisib the tumor assessments should be continued as the initial schedule.

[…]

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 IV (and oral, if indicated) contrast-enhanced CT is medically contraindicated, sites may acquire contrast-enhanced MRI of the neck, abdomen and pelvis, and an unenhanced CT of the chest above lung apices to the bottom of the adrenals. Chest CT is preferred. Only if a patient develops contra-indication to both CT and MRI contrast medium during the treatment phase of the study, the case examinations should be continued without contrast. In certain countries MRI should be used based on local regulations.

13.5.2.25 Section 7.3.3 Tumor assessments in patients with WM

Old text:

[…]

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).

[…]

New text:

[…]

WM patients who have radiologically measurable lesion at Screening will continue having radiological assessments and, in addition, will have laboratory tests performed at intervals that comply with the institution's standard of care (see Section 7.1.2.3).

[…]

13.5.2.26 Section 7.4 Pharmacokinetics / pharmacodynamics

Old text:

~~PK sampling will be performed in all patients for copanlisib, its metabolite M-1 and other metabolites, if needed, on (see flowchart in Section 7.1):~~

- ~~Cycle 1 Day 8:~~
  ~~Pre- infusion, 5 to 15 min, 55 min (or within 5 min prior to end of infusion) and 1.5 to 5 h after start of infusion (*clarified by amendment 1*).~~
  ~~If sampling is not feasible at Cycle 1, samples may be collected at Cycle 2. A separate IV line should be used for PK draws.~~
- ~~*PK sampling associated with 12-lead ECG removed by amendment 1.*~~

~~After individual patient unblinding, patients receiving placebo who switch to copanlisib will have PK assessments reset to the initial schedule as if the patient was restarting the study at Cycle 1 Day 1.~~

~~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.~~

~~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 (AUCs), 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.~~

New text:

No further PK samples will be collected. However, blood samples already collected may be used for the PK analysis.

13.5.2.27 Section 7.5.1.3 Assessments and documentation of adverse events

Old text:

[…]

AEs to be documented include all AEs that were ongoing at the end of study 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 GPV 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 study drug.

[…]

New text:

[…]

AEs to be documented include all AEs that were ongoing at the end of study 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.

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 study drug.

[…]

13.5.2.28 Section 7.5.3.6 Glucose measurement on infusion days

Old text:

- […]
- On all infusion days: time window of ± ~~5~~ min is allowed for glucose measurements, except for the pre-dose measurement. ~~If patient needs to take a low glycemic meal, then glucose test should be taken prior to meal intake and at 1 h and 2 h after the meal.~~

New text:

- […]
- On all infusion days: time window of ± 10 min is allowed for glucose measurements, except for the pre-dose measurement.

13.5.2.29 Section 7.6.1 Biomarker investigations

Old text:

~~**Overview**~~

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

1. ~~Tumor genetic research 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) (RNA: ribonucleic acid, DNA: deoxyribonucleic acid). Details on the collection, processing, storage and shipment of biomarker samples will be provided in separate documents (e.g. sample handling sheets or laboratory manual).~~

~~The biomarker results may be reported separately.~~

~~**Collection and use of biomarker specimens**~~

~~**Tumor Tissue**~~:

~~Tumor tissue collection will be mandatory at Screening for central pathology review. Patients without historical material or fresh tissue biopsy will not be eligible for randomization.~~

~~In addition, one or more of the following pre-treatment tumor tissue samples will be collected during Screening when available with the purpose of investigating or identifying biomarkers~~

~~that may be predictive of copanlisib effects/efficacy in NHL and to contribute to better understanding the disease.~~

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

~~A tumor biopsy is also encouraged at the time of progression (optional) to allow investigation of copanlisib resistance. 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 formalin-fixed paraffin-embedded (FFPE) tissue may be supplied as a block (preferred) or as precut slides. Details on the preparation of slides and number of slides to be prepared as well as detailed guidance on fresh biopsy sample preparation and storage will be described in separate documents (e.g. Sample Handling Sheets or laboratory manual).~~

~~All tumor tissues may be used as a source of RNA or protein for the study of gene and protein expression. The tumor tissue may 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 tumor genetics 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 as a source of circulating tumor DNA for the evaluation of mutations in tumor-related genes of interest.~~

~~**Plasma for non-genetic biomarker analysis**: Blood samples will be obtained and used for plasma preparation at the time points as indicated in the study flow chart (see Table 7-1). Plasma may be used to quantify the circulating levels of various proteins.~~

~~After individual patient unblinding, patients receiving placebo who switch to copanlisib upon discretion of the investigator and patient's consent will have biomarker plasma sampling analogous to the initial schedule as if the patient was restarting the study at Cycle 1 Day 1.~~

~~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.~~

New text:

No further biomarker samples will be collected. However tumor tissue, plasma and whole blood (if consented) samples collected may be used for the biomarker analysis.

13.5.2.30 Section 7.7 Appropriateness of procedures / measurements

Old text:

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 Lugano Classification (21) 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.

[…]

New text:

The tumor 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 Lugano Classification (21) 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.
[…]

13.5.2.31 Section 8.1 General considerations

Old text:

[…]

Due to the decision of stopping enrollment as protocol amendment 5 becomes effective, limited number of patients will be included in the analyses. Therefore, the statistical analyses included in this study will be focused on descriptive statistics ~~without any hypothesis testing~~.

Two sets of analyses will be performed at the timing when all ~~treated~~ patients completed ~~at least 6 cycles of~~ study treatment~~.~~

1) unblinding cutoff: analyze all data available before the unblinding (details in section ~~6.5~~);
2) final analysis: analyze all data available until all ~~treated~~ patients ~~complete at least 6 cycles of~~ study treatment.

The data cutoffs and treatment groups included for each analysis are summarized in the following table.

Table 8-1 Analysis data cutoffs and treatment group overview

	Analysis cutoff on the date of unblinding	Final analysis cutoff[4]
Patients randomized to Copanlisib[1]	✓	✓
Placebo Patients: Period 1 (before their PD) [2]	✓	Not shown
Placebo Patients: Period 2 (after PD period 2) [2]	Not shown	✓
Placebo Patients: switching to Copanlisib per protocol amend 5[3]	NA	✓

[1] All patients randomized/assgined into Copanlisib arm
~~[2] Patients randomized into Placebo arm, with at least one tumor response assessment until date of unblinding~~
~~[3] Includes patients switched from Placebo to Copanlisib before their first tumor response assessment~~
~~[4]When all treated patients complete at least 6 cycles of study treatment~~

New text:

[…]

Due to the decision of stopping enrollment as protocol amendment 5 becomes effective, limited number of patients will be included in the analyses. Therefore, the statistical analyses included in this study will be focused on descriptive statistics on safety variables only.

Two sets of analyses will be performed at the primary analysis timing when all patients have completed the study treatment and Safety follow-up period (if applicable).

1) unblinding cutoff: analyze all data available before the unblinding (details in section 6.5);
2) final analysis: analyze all data available until all patients have completed the copanlisib study treatment and Safety follow-up period.

The data cutoffs and treatment groups included for each analysis are summarized in the following table.

Table 8-1 Analysis data cutoffs and treatment group overview

	Analysis cutoff on the date of unblinding	Final analysis cutoff[2]
Patients randomized to Copanlisib[1]	✓	✓
Placebo Patients: Period 1 (before their PD)	✓	Not shown
Placebo Patients: Period 2 (after PD period 2)	Not shown	✓
Placebo Patients: switching to Copanlisib per protocol amend 5	NA	✓

[1] All patients randomized/assigned into Copanlisib arm
[2] When all patients have completed the study treatment and Safety follow-up period.

13.5.2.32 Section 8.2 Analysis sets

Old text:

The statistical analysis sets are defined as follows:

- ~~Full analysis set (FAS): all patients assigned to treatment. Following the intent to treat (ITT) principle, the treatment the patient is assigned to will be used in the analysis (as assgined rather than as treated).~~
- Safety analysis set (SAF): all patients with at least one intake of study drug. The SAF will be analyzed as treated.

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.~~

New text:

The statistical analysis sets are defined as follows:

- Safety analysis set (SAF): all patients with at least one intake of study drug. The SAF will be analyzed as treated.

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

The SAF will be used for the analyses of the safety variables.

13.5.2.33 Section 8.3.1 Efficacy variables

Old text:

~~If PD was reported after a switch to copanlisib treatment in placebo patients (see Section 6.4), this information is not used for calculation of primary or secondary efficacy variables.~~

New text:

Due to the limited number of patients enrolled in this study, the study efficacy objectives and analyses were removed and the efficacy variables, including but not limited to date of progression, time to progression, and best response will be listed descriptively.

13.5.2.34 Section 8.3.1.1 Primary efficacy variable

Old text:

~~**Objective tumor response rate (ORR)** assessed in all patients, which is defined as the proportion of patients who have a best response rating up to the dates of data cutoffs (for dates of data cutoffs, see details in section 8.1) of complete response (CR) or partial response (PR) according to the Lugano Classification (21), 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 (22). Detailed instructions on tumor assessment are provided in Appendix 14.1. In addition to the ORR by treatment group, and period, a listing will be provided for all patients with their best response, histology type along with other important demographic and disease characteristics information.~~

New text:

Section removed by amendment 6.

13.5.2.35 Section 8.3.1.2 Secondary efficacy variables

Old text:

~~**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 (*modified by amendment 1*). Patients without PD or death at the time of analysis will be considered as responders till at the date of their last tumor evaluation. DOR will be summarized by descriptive statistics. Further details will be included in the SAP.~~

~~**Complete response rate (CRR)**, defined as the proportion of patients who have a best response up to the dates of data cutoffs (for dates of data cutoffs, see details in section 8.1) of complete response (CR) according to the Lugano Classification (3), and for patients with WM, a response rating of CR according to the Owen criteria (4).~~

~~**Overall survival (OS)**, defined as the time (in days) from assignment to study drug 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.~~

New text:

Section removed by amendment 6.

13.5.2.36 Section 8.3.2 Safety variables

Old text:

Safety variables will include treatment-emergent AEs (TEAEs), 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 study drug. TEAE 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).

New text:

Safety variables will include treatment-emergent AEs (TEAEs), 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 study drug. TEAE 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). For TEAE summaries based on placebo randomized patients switching to copanlisib (see Table 8–1), the baseline reference period will be defined in the SAP.

13.5.2.37 Section 8.4.2 Efficacy

Old text:

~~Evaluations by investigators will be used for the primary efficacy analyses of primary and secondary variables containing radiological tumor assessments.~~

~~For variables other than OS, the data collected after switching from placebo to copanlisib will be summarized separately using descriptive statistics and frequency tables. Further details will be included in the SAP~~.

New text:

Due to the limited number of patients enrolled in this study, the study efficacy objectives and analyses were removed and the efficacy variables, including but not limited to date of progression, time to progression, and best response will be listed descriptively.

13.5.2.38 Section 8.4.3 Safety

Old text:

[…]

In addition, results of physical examination, vital signs, and ECG will be summarized ~~with descriptive statistics and/or frequency tables.~~

New text:

[…]

In addition, results of physical examination, vital signs, and ECG will be summarized in accordance with SAP.

13.5.2.39 Section 8.4.4 Pharmacokinetic data

Old text:

Individual concentration-time data of copanlisib and M-1 ~~will~~ be provided in a clinical study report appendix. Sparse copanlisib concentration data from this study, which might be augmented with PK data from other studies, ~~will~~ be analyzed to evaluate the variability of the copanlisib PK in this Phase III population. The possible effect of relevant covariates on the PK of copanlisib might also be evaluated. A population pharmacokinetic approach will be applied for these evaluations, which will be described in detail in a separate Modeling & Simulation (M&S) Plan ~~and~~ the results will be reported separately in the M&S Report.

New text:

Individual concentration-time data of copanlisib and M-1 may be provided in a clinical study report appendix. Sparse copanlisib concentration data from this study, which might be augmented with PK data from other studies, may be analyzed to evaluate the variability of the copanlisib PK in this Phase III population. The possible effect of relevant covariates on the PK of copanlisib might also be evaluated. A population pharmacokinetic approach will be applied for these evaluations, which will be described in detail in a separate Modeling & Simulation (M&S) Plan if the results will be reported separately in the M&S Report.

13.5.2.40 Section 8.6 Determination of sample size

Old text:

~~All patients assigned to treatment in this study will be included in the analyses.~~

New text:

Determination of sample size has not been applicable since amendment 5 became effective.

13.5.2.41 Section 9.1 Data recording

Old text:

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 in the CRF are demographic information (patient number, ~~date~~ 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.

New text:

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 in 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.

13.5.2.42 Section 10. Premature termination of the study

Old text:

[…]

The sponsor's decision was to stop enrollment due to lack of feasibility to complete this study in reasonable time frame. Therefore, the study design is modified ~~to reflect an open label study~~. All patients on study treatment will be offered the possibility to continue treatment with copanlisib after unblinding procedures are completed.

[…]

New text:

[…]

The sponsor's decision was to stop enrollment due to lack of feasibility to complete this study in reasonable time frame. Therefore, the study design is modified. All patients on study

treatment will be offered the possibility to continue treatment with copanlisib after unblinding procedures are completed.

[…]

13.5.2.43 Section 11.2 Patient information and consent

Old text:

[…]

Archival tissue obtained from the patients at any time during the course of their iNHL may also be used prior to the informed consent date and time if performed as part of the standard of practice. CT/MRI must also meet the quality standards ~~of the Imaging Manual~~.

[…]

New text:

[…]

Archival tissue obtained from the patients at any time during the course of their iNHL may also be used prior to the informed consent date and time if performed as part of the standard of practice. CT/MRI must also meet the quality per local standards.

[…]

13.5.2.44 Section 12. Reference list

Old text:

~~38. Atkinson FS, Foster-Powell K, Brand-Miller JC. International Tables of Glycemic Index and Glycemic Load Values: 2008. Diabetes Care 2008;31:2281-2283.~~

New text:

38. Removed by amendment 6.

13.5.2.45 Section 14.7 The average glycemic index of common foods derived from multiple studies by different laboratories

Old text:

~~Foods are categorized as having a low glycemic index if the glucose reference index is ≤ 55. The summary table below contains glucose reference for common foods, please see reference 38 for additional information.~~

High-carbohydrate foods		Breakfast cereals		Fruit and fruit products		Vegetables	
White wheat bread*	75 ± 2	Cornflakes	81 ± 6	Apple, raw†	36 ± 2	Potato, boiled	70 ± 4
Whole wheat/whole meal bread	74 ± 2	Wheat flake biscuits	69 ± 2	Orange, raw†	43 ± 3	Potato, instant mash	87 ± 3
Specialty grain bread	53 ± 2	Porridge, rolled oats	55 ± 2	Banana, raw†	51 ± 3	Potato, french fries	63 ± 5
Unleavened wheat bread	70 ± 8	Instant oat porridge	79 ± 3	Pineapple, raw	59 ± 8	Carrots, boiled	39 ± 4
Wheat roll	62 ± 3	Rice porridge/congee	78 ± 9	Mango, raw†	51 ± 3	Sweet potato, boiled	63 ± 6
Chapati	52 ± 4	Millet porridge	67 ± 5	Watermelon, raw	76 ± 4	Pumpkin, boiled	64 ± 7
Corn tortilla	46 ± 4	Muesli	57 ± 2	Dates, raw	42 ± 4	Plantain/green banana	55 ± 6
White rice, boiled*	73 ± 4			Peaches, canned†	43 ± 5	Taro, boiled	93 ± 2
Brown rice, boiled	68 ± 4			Strawberry jam/jelly	49 ± 3	Vegetable soup	48 ± 5
Barley	28 ± 2			Apple juice	41 ± 2		
Sweet corn	52 ± 5			Orange juice	50 ± 2		
Spaghetti, white	40 ± 2						
Spaghetti, whole meal	48 ± 5						
Rice noodles†	53 ± 7						
Udon noodles	55 ± 7						
Couscous†	65 ± 9						

Dairy products and alternatives		Legumes		Snack products		Sugars	
Milk, full fat	39 ± 3	Chickpeas	28 ± 9	Chocolate	40 ± 3	Fructose	15 ± 4
Milk, skim	37 ± 4	Kidney beans	24 ± 4	Popcorn	65 ± 5	Sucrose	65 ± 4
Ice cream	51 ± 3	Lentils	32 ± 5	Potato crisps	56 ± 3	Glucose	103 ± 3
Yogurt, fruit	41 ± 2	Soya beans	16 ± 1	Soft drink/soda	59 ± 3	Honey	61 ± 3
Soy milk	34 ± 1			Rice crackers/crisps	87 ± 2		
Rice milk	86 ± 7						

Data are mean ± SEM. *Low GI varieties were also identified. †Average of all available data.

GI = glycemic index.

Source: (38)

New text:

Appendix 14.7 removed by amendment 6.

14. Appendices

14.1 Evaluation of tumor response

Section changed by amendment 1, table clarified by amendment 3 and modified by amendment 4.

Tumor response will be evaluated according to Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification (21).

	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 and/or PCR 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
SD	• 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 <u>from baseline length</u> and be > 13 cm • Recurrent splenomegaly: the splenic length must increase ≥ 2 cm from <u>nadir</u> length and be > 13 cm • Progressive splenomegaly: the splenic length must increase by > 50% of the extent beyond normal at baseline (=value over 13 cm) and must increase ≥ 1 cm in total vertical length	Yes: • New node > 1.5 cm in any axis • New extranodal site > 1.0 cm in any axis (if < 1.0 cm in any axis its presence must be unequivocal and must be attributable to lymphoma)	New or recurrent involvement

CR = complete response; IHC = Immunohistochemistry; LDi = longest diameter; PD = progressive disease; PPD = product of perpendicular diameters; PR = partial response; SD =stable disease; SDi = shortest diameter; SPD = sum of the product of the diameters

* 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.
Table modified by amendment 3 and 4.

Response criteria in patients affected by Waldenström macroglobulinemia (WM):

CR	• Absence of serum monoclonal IgM by immunofixation AND normal serum IgM level • Complete resolution of extramedullary disease • Normal bone marrow
VGPR	• IgM M protein still detectable by immunofixation BUT ≥ 90% reduction in serum IgM level from baseline • Complete resolution of extramedullary disease • No new sings/symptoms of active disease
PR	• 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
MR	• 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
SD	• 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
PD	**After PR:** • ≥ 25% increase in serum IgM level from lowest nadir (an absolute value of 5 g/L is required if IgM level is the only criterion) OR • Progression in clinical features (signs/symptoms) attributable to disease **After CR:** • Reappearance of IgM M protein OR • Recurrence of bone marrow involvement, extramedullary disease, symptoms attributable to disease

CR = complete response; IgM = immunoglobulin M; MR = minor response; PD = progressive disease; PR = partial response; SD = stable disease; VGPR = very good partial response
Source: Adapted from (22).

14.2 A list of CYP3A4 inhibitors and inducers

CYP3A4 inhibitors (strong inhibitors are underlined and not permitted during this study)

Indinavir
Nelfinavir
Ritonavir
Saquinavir
Clarithromycin
Itraconazole
Ketoconazole
Nefazodone (withdrawn in the United States)
Grapefruit juice
Erythromycin
Verapamil
Diltiazem
Cimetidine
Amiodarone
Fluvoxamine
Mibefradil (withdrawn in the United States)
Troleandomycin

CYP3A4 inducers (not permitted during this study)

Rifampin
Carbamazepine
Phenobarbital
Phenytoin
Pioglitazone
Rifabutin
St. John's wort
Troglitazone

Source: (33)

14.3 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)

14.4 New York Heart Association (NYHA) Functional Classification

NYHA Class	Symptoms
Not applicable	No cardiac disease
I	No symptoms and no limitation in ordinary physical activity, e.g., shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g., walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while **at rest**. Mostly bedbound patients.

Source: (34)

14.5 Glomerular filtration rate

In accordance with established nephrology practice and guidelines, renal function at baseline and throughout the study will be assessed by means of the estimated Glomerular filtration rate (GFR), calculated using the Modification of Diet in Renal Disease (MDRD) study abbreviated formula.

This equation of 4 variables (serum creatinine level [SCR], age, sex, and ethnicity) is recommended by the National Kidney Foundation for use in individuals 18 years or older.

The formula is as follows:

$$GFR\ (mL/min/1.73m^2) = k \times 186 \times SCR^{-1.154} \times age^{-0.203}$$

where k = 1 (men) or 0.742 (women), GFR indicates glomerular filtration rate, and serum creatinine level (SCR) 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 IDMS.
If standardized IDMS-traceable creatinine assay is used, please use the calculator provided in the following link: http://www.kidney.org/professionals/kdoqi/gfr_calculator (*added by amendment 1*).

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.

For further information on assessing renal function using GFR estimates, see 35-37.

14.6 Quality of life questionnaire: NCCN-FACT FLymSI-18

Appendix removed by amendment 5.

14.7 The average glycemic index of common foods derived from multiple studies by different laboratories

Appendix removed by amendment 6.