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# Cover page of the integrated protocol

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

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

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

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 11 MAY 2015

(local amendment valid for Ireland, Germany and Belgium only)

* **Amendment 03**, dated 25 AUG 2015 (local amendment valid for France only)
* **Amendment 04**, dated 01 SEP 2015 (local amendment valid for Denmark only)
* **Amendment 05**, dated 13 OCT 2015 (local amendment valid for Turkey only)
* **Amendment 08**, dated 18 APR 2017 (local amendment valid for Japan only)

# Title page

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

Copanlisib and rituximab in relapsed iNHL

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| Test drug: | BAY 80-6946 / copanlisib |  | |
| Clinical study phase: | III | Date: | 22 MAY 2020 |
| EudraCT no.: | 2013-003893-29 | Version no.: | 7.0 |
| Study no.: | BAY 80-6946 / 17067 |  |  |

Sponsor: Non-US: Bayer AG, D-51368 Leverkusen, Germany

US territory: Bayer HealthCare Pharmaceuticals Inc., 100 Bayer Boulevard, P.O. Box 915, Whippany NJ 07981-0915, USA

Sponsor’s medical expert:

PPD

100 Bayer Boulevard, P.O.box 915 Whippany, NJ, USA

PPD

Telephone no.:

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

This is an electronically generated document that does not bear any sponsor signatures. The signature of the Sponsor’s medically responsible person is filed in the TMF and available on request.

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# 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

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| **Title** | **A Phase III, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of copanlisib in combination with rituximab in patients with relapsed indolent B-cell non-Hodgkin’s lymphoma (iNHL) – CHRONOS-3** |
| **Short title** | Copanlisib and rituximab in relapsed iNHL |
| **Clinical study phase** | III |
| **Study objective(s)** | The primary objective of this study is:  To evaluate whether copanlisib in combination with rituximab is superior to placebo in combination with rituximab in prolonging progression-free survival (PFS) in patients with relapsed iNHL who have received one or more lines of treatment, including rituximab, and who either had a treatment-free interval of ≥ 12 months after completion of the last rituximab-containing treatment, or who are unwilling to receive chemotherapy/for whom chemotherapy is contraindicated on reason of age, comorbidities, and/or residual toxicity  The secondary objectives of this study are to evaluate:   * The following characteristics of disease-related symptoms: “time to deterioration” and “time to improvement” * Other radiological and clinical indicators of treatment efficacy * Safety and tolerability of copanlisib   The other objectives of this study are to evaluate:   * Pharmacokinetics * Biomarkers * Quality of life |
| **Test drug(s)**  **Name of active ingredient**  **Treatment**  **administered**  **Dose(s)**  **Route of administration Duration of treatment** | Copanlisib  Copanlisib / BAY 80-6946 / phosphatidylinositol-3 kinase (PI3K) inhibitor Copanlisib in combination with rituximab  Copanlisib starting dose: 60 mg. Dose reductions to 45 mg and further to 30 mg are possible, should toxicities occur. Dosing will be administered on Days 1, 8 and 15 of each 28-day cycle. Copanlisib will be administered before rituximab.  Rituximab: 375 mg/m2 body surface weekly during Cycle 1 on Days 1, 8, 15 and 22,  and then on Day 1 of Cycles 3, 5, 7 and 9. Intravenous (IV) infusions  Copanlisib 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 (Owen Criteria for patients with Waldenström macroglobulinemia [WM]), unacceptable toxicity, or until another criterion is met for withdrawal from the study treatment.  Rituximab treatment will be continued until the same criteria as defined for copanlisib are met, for a maximum of 8 infusions (until Cycle 9). |
| **Reference drug(s)** | Placebo |

**Name of active ingredient**

**Treatment administered Dose(s)**

**Route of administration**

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| **Duration of treatment** | Placebo treatment will be continued until 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 (Owen Criteria for patients with WM), unacceptable toxicity, or until another criterion is met for withdrawal from the study treatment*.*  Rituximab treatment will be continued until the same criteria as defined for placebo are met, for a maximum of 8 infusions (until Cycle 9). |
| **Indication** | Relapsed indolent B-cell non-Hodgkin’s lymphoma |
| **Diagnosis and main criteria for inclusion** | Histologically confirmed diagnosis of iNHL in CD20 positive patients with histological subtype limited to:   * Follicular lymphoma (FL) G1-2-3a * Small lymphocytic lymphoma (SLL) with absolute monoclonal lymphocyte count <5x109/L at study entry * Lymphoplasmacytoid lymphoma/Waldenström macroglobulinemia (LPL/WM) * Marginal zone lymphoma (MZL) (splenic, nodal, or extra-nodal)   Patients must have relapsed (recurrence after complete response or presented progression after partial response) after the last rituximab-, rituximab biosimilars-, or anti-CD20 monoclonal antibody (e.g. obinutuzumab)-containing therapy (other previous treatment lines after rituximab are allowed). A previous regimen is defined as one of the following: at least 2 months of single-agent therapy (less than 2 months of therapy is allowed for patients who responded to single-agent rituximab, rituximab biosimilars, or anti-CD20 monoclonal antibody); at least 2 consecutive cycles of polychemotherapy; autologous transplant; radioimmunotherapy. Previous exposure to PI3K is acceptable (except to copanlisib) provided there is no resistance. Patients with prior intolerance to PI3K inhibitors other than copanlisib are eligible.  Non-WM patients must have at least one bi-dimensionally measurable lesion (that has not been previously irradiated) according to the Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. For patients with splenic MZL this requirement may be restricted to splenomegaly alone since that is usually the only manifestation of measurable disease.  Patients affected by WM who do not have at least one bi-dimensionally measurable lesion in the baseline radiologic assessment must have measurable disease, defined as presence of immunoglobulin M (IgM) paraprotein with a minimum IgM level  ≥ 2x upper limit of normal and positive immunofixation test*.* Male or female patients ≥ 18 years of age.  Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2. Life expectancy of at least 3 months.  Availability of fresh tumor tissue and/or archival tumor tissue for central pathology |

Not applicable

Placebo in combination with rituximab

Placebo starting dose: 60 mg. Dummy dose reductions to 45 mg and further to 30 mg are possible should toxicities occur. Dosing will be administered on Days 1, 8 and 15 of each 28-day cycle. Placebo will be administered before rituximab.

Rituximab: 375 mg/m2 body surface weekly during Cycle 1 on Days 1, 8, 15 and 22,

and then on Day 1 of Cycles 3, 5, 7 and 9. IV infusions

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|  | (obtained within 5 years of the consent date) at Screening.  Adequate baseline laboratory values as assessed within 7 days before starting study treatment.  Left ventricular ejection fraction ≥ 45%. Patients must either   * have had a progression-free and treatment-free interval of ≥ 12 months after completion of the last rituximab-containing treatment   OR   * be considered unfit to receive chemotherapy on reason of age, concomitant morbidities, and/or residual toxicity from previous treatments, or unwillingness to receive chemotherapy. These patients must also have had a progression-free and treatment free interval of ≥ 6 months after completion of the last rituximab-containing treatment. Patients in whom chemotherapy is contraindicated are defined by one of the following features:   + Age ≥ 80 years   + Age < 80 years and at least 1 of the following conditions:     - at least 3 grade 3 CIRS-G comorbidities OR     - at least 1 grade 4 CIRS-G comorbidity (if considered compatible with participation in the study)*.* |
| **Main criteria for exclusion** | Follicular lymphoma grade 3b or transformed disease, or chronic lymphocytic leukemia.  Progression-free interval or treatment-free interval of less than 12 months since the last rituximab-, rituximab biosimilars-, or anti-CD20 monoclonal antibody (e.g. obinutuzumab)-containing treatment (including maintenance with these drugs). For patients considered unwilling/unfit to receive chemotherapy: progression-free interval or treatment-free interval of less than 6 months since the last rituximab-, rituximab biosimilars-, or anti-CD20 monoclonal antibody-containing treatment (including maintenance with these drugs), as assessed by the investigator*.*  History or concurrent condition of interstitial lung disease and/or severely impaired lung function.  Known lymphomatous involvement of the central nervous system. Patients with HbA1c > 8.5% at Screening.  Known history of human immunodeficiency virus (HIV) infection.  Hepatitis B (HBV) or hepatitis C (HCV). Patients positive for HBsAg or HBcAb will be eligible if they are negative for HBV-DNA, these patients should receive prophylactic antiviral therapy. Patients positive for anti-HCV antibody will be eligible if they are negative for HCV-RNA*.*  Cytomegalovirus (CMV) infection. Patients who are CMV PCR positive at baseline will not be eligible.  Prior treatment with copanlisib*.* |
| **Study design** | A randomized, double-blind, placebo-controlled, 2-arm phase III study to evaluate the efficacy and safety of copanlisib in combination with rituximab, in comparison to placebo in combination with rituximab in patients with relapsed iNHL.  Approximately 450 FL and other iNHL patients who meet the eligibility criteria will be randomly assigned in a 2:1 ratio to the double blinded treatment arms: copanlisib plus rituximab or placebo plus rituximab, respectively.  Patients will be stratified by a combination of NHL histology (FL vs. other iNHL), |

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|  | inclusion criteria (progression-free and treatment-free interval of ≥ 12 months after the last rituximab-containing treatment vs. unwilling/unfit to receive chemotherapy), presence of bulky disease (yes vs. no) and previous treatment with PI3K inhibitors (yes vs. no). If the patient fulfills both entry criteria, the criterion “unwilling/unfit to receive chemotherapy” should be selected.  After the 30th randomized patient has completed the first cycle of treatment, the Data Monitoring Committee will review the unblinded safety data accumulated up to that time and provide recommendation on whether it is safe to continue in the combination arm at the initial dose of copanlisib. The investigators, patients and the sponsor will remain blinded. |
| **Methodology** | The primary efficacy variable is PFS, defined as the time (in days) from randomization to PD as assessed by central review or death from any cause (if no progression is documented).  Secondary efficacy variables are objective tumor response rate (ORR), duration of response (DOR), complete response rate (CRR), time to progression (TTP), overall survival (OS), time to improvement and the time to deterioration in disease-related symptoms - physical (DRS-P) of at least 3 points as measured by the FLymSI-18 questionnaire (FLymSI = NCCN-FACT Lymphoma Symptom Index).  Other efficacy variables are FLymSI-18 subscale, total score analyses and time to onset of physical symptoms of lymphoma based on DRS-P, and ECOG performance status.  The study is composed of the following periods: Screening, Treatment, Safety follow-up, Active follow-up (if applicable) and Survival follow-up.  Patients randomized to copanlisib + rituximab arm will receive 60 mg copanlisib IV infusion on Days 1, 8 and 15 of each 28-day treatment cycle, and 375 mg/m2 rituximab during Cycle 1 on Days 1, 8, 15 and 22, and then on Day 1 of Cycles 3, 5,  7 and 9.  Patients randomized to placebo + rituximab arm will receive placebo IV infusion on Days 1, 8 and 15 of each 28-day treatment cycle, and 375 mg/m2 rituximab during Cycle 1 on Days 1, 8, 15 and 22, and then on Day 1 of Cycles 3, 5, 7 and 9.  An end-of-treatment (EOT) visit will be performed no later than 7 days after the decision is made to discontinue study treatment. Following completion of the EOT visit, patients will enter either the Safety follow-up or the Active follow-up period, if applicable. In both cases, the Safety follow-up visit will take place 30 days (window of +5 days allowed) after the last administration of study treatment.  Patients who discontinue study treatment because of PD will enter Safety follow-up period and patients who discontinue study treatment for reasons other than PD will enter the Active follow-up period (which also serves as a Safety follow-up), except for patients who object to follow-up data collection. The patients in the Active follow-up will have follow-up tumor assessments 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.  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.  Study participants may be offered the option to transition into a roll-over study (ROS).  Safety evaluations will be done at Screening, on the first day of study treatment administration (Cycle 1 Day 1), at each clinic visit during treatment, and at the safety follow-up visit.  The first radiological tumor assessments with IV (and oral, if indicated, per Imaging |

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|  | Manual) contrast-enhanced computed tomography / magnetic resonance imaging (CT/MRI) scans of neck, chest, abdomen and pelvis will be performed at Screening (including WM patients). Corticosteroids must be stopped or reduced to the allowed dose (≤ 15 mg of prednisone or equivalent) at least 7 days before performing the screening CT/MRI (if a patient is on chronic corticosteroid therapy, corticosteroids should be de-escalated to the maximum allowed dose before the screening). The method chosen at baseline must be the same throughout the study. MRI shall be performed instead of CT when local regulations do not permit the use of CT as requested per protocol schedule.  During the treatment period as well as during the Active follow-up period, tumor assessments with the same modality will be performed every 8 weeks ( 7 days) during Year 1, every 12 weeks ( 7 days) during Year 2, and every 24 weeks  ( 7 days) during Year 3 and onwards, starting from Cycle 1 Day 1*.* CT/MRI scans are not required at the EOT visit if the patient discontinues because of PD which has been radiologically confirmed within the 4 weeks preceding the EOT.  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. Radiological real-time confirmation will only be conducted until the database cut-off for the primary analysis. 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 and will be sent to central pathology review after local bone marrow assessment. Biopsies taken up to 28 days prior to first dose are acceptable. If the baseline biopsy is positive for lymphoma infiltration at Screening, it will be mandatory to perform it again to confirm the first complete response (CR) by sending the sample to central review after local bone marrow assessment, and also at the investigator discretion if clinical evaluation leads to suspicion of bone marrow infiltration without further radiological findings. |
| **Type of control** | Inactive control: placebo |
| **Number of patients** | Assuming 30% screening failure rate, 643 patients (including FL and other iNHL) need to be enrolled to have 450 randomized patients. Patients will not be replaced. |
| **Primary variable** | The primary variable is PFS, defined as the time (in days) from randomization to PD as assessed by central review or death from any cause (if no progression is documented). |
| **Plan for statistical analysis** | **Efficacy analysis**: The primary efficacy variable is PFS, as assessed by central review in the full analysis set (FAS), which is defined as all patients who were randomized. Patients alive without documented progression at the time of analysis will be censored at the date of their last tumor evaluation. Copanlisib in combination with rituximab vs. placebo in combination with rituximab will be compared in the FAS, using a one-sided log-rank test stratified by the same factors as used for randomization: FL vs. other iNHL histologies and progression-free and treatment- free interval of ≥ 12 months after completion of the last rituximab-containing treatment vs. unwilling/unfit to receive chemotherapy. |

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

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# List of abbreviations

AE Adverse event

Ab Antibody

Ag Antigen

AKT Protein kinase B

ALT Alanine aminotransferase

ANC Absolute neutrophil count

AST Aspartate aminotransferase

AUC Area under the curve

BfS Federal Office for Radiation Protection

BP Blood pressure

BTK Bruton’s tyrosine kinase

BUN Blood urea nitrogen

1. Cycle

CBC Complete blood count

CD Cluster of differentiation

c-KIT Proto-oncogen c-KIT (CD117)

CHGRAO China Human Genetic Resources Administration Office

CHOP Cyclophosphamide, hydroxydaunorubicin, vincristine, prednisolone CI Confidence interval

CIRS-G Cumulative Illness Rating Scale for Geriatrics CLL Chronic lymphocytic leukemia

Cmax Maximum drug concentration

CMV Cytomegalovirus

CR Complete response

CRF Case report form

CRO Contract research organization

CRP C-reactive protein

CRR Complete response rate

CT Computed tomography

CTCAE Common Terminology Criteria for Adverse Events CVP Cyclophosphamide, vincristine, prednisolone CYP3A4 Cytochrome P450 isoenzyme 3A4

1. Day

dL Deciliter

DLBCL Diffuse large B-cell lymphoma DMC Data monitoring committee

DNA Deoxyribonucleic acid

DOR Duration of response

DPP4 Dipeptidyl peptidase-4

DRS-E Disease-related symptoms – emotional (subscale) DRS-P Disease-related symptoms – physical (subscale) EC Ethics committee

ECG Electrocardiogram

ECOG Eastern Cooperative Oncology Group eCRF Electronic case report form

e.g. For example (*exempli gratia*)

EGFR Epidermal growth factor receptor

EOT End of treatment

ePRO Electronic patient-reported outcome

EU European Union

FAS Full analysis set

FDA Food and Drug Administration

FDG Fluorodeoxyglucose

FFPE Formalin-fixed paraffin-embedded

FL Follicular lymphoma

FLIPI Follicular lymphoma International Prognostic Index FLymSI-18 NCCN-FACT Lymphoma Symptom Index-18

FND Fludarabine, mitoxantrone, dexamethasone

FSH Follicle stimulating hormone

FU Follow-up

FWB Functional and well-being (subscale)

1. Gram

GCP Good Clinical Practice

G-CSF Granulocyte colony-stimulating factor GFR Glomerular filtration rate

GMP Good Manufacturing Practice

GPV Global Pharmacovigilance

1. Hour(s)

Hb Hemoglobin

HbA1c Glycated hemoglobin

HBcAb Hepatitis B core antibody

HBeAg Hepatitis B e antigen

HBsAg Hepatitis B surface antigen

HBV Hepatitis B Virus

HCG β-human chorionic gonadotropin

HCV Hepatitis C Virus

HCVAb Anti-HCV antibody

HDL High-density lipoprotein

HER Human epidermal growth factor receptor

HIV Human immunodeficiency virus

HR Hazard ratio

IB Investigator’s Brochure

ICF Informed Consent Form

IC50 Half maximal inhibitory concentration

ICH International Conference on Harmonization

IDMS Isotope dilution mass spectroscopy

i.e. That is (*id est*)

IEC Independent Ethics Committee

IGF-1R Insulin-like growth factor 1 receptor IgM Immunoglobulin M

IHC ImmunoHistoChemistry

iNHL Indolent non-Hodgkin’s lymphoma

INR International normalized ratio

IRB Institutional review board

ISO International Organization for Standardization

IUD Intrauterine device

IUS Intrauterine hormone-releasing system

IV Intravenous

IVRS Interactive Voice Response System

IWRS Interactive Web Response System

kg Kilogram

LDH Lactate dehydrogenase

LDi Longest diameter

LDL Low-density lipoprotein

LPL Lymphoplasmacytoid lymphoma

LVEF Left ventricular ejection fraction

M-1 Metabolite 1

MALT Marginal-zone lymphoma of mucosa-associated lymphoid tissue MD Medical Doctor

MDRD Modification of diet in renal disease MedDRA Medical Dictionary for Regulatory Activities mg Milligram

min Minutes

mmHg Millimeter of mercury

mL Milliliter

MR Minor response

MRI Magnetic resonance imaging

MTD Maximum tolerated dose

mTOR Mammalian target of rapamycin

MUGA Multiple gated acquisition

MZL Marginal-zone lymphoma

NaOH Sodium hydroxide

NCCN National Comprehensive Cancer Network

NCCN-FACT National Comprehensive Cancer Network – Functional Assessment of Cancer Therapy

NCI National Cancer Institute

NHL Non-Hodgkin’s Lymphoma

NIP Non-infectious pneumonitis

nM Nanometer

NMZL Nodal marginal-zone lymphoma

NYHA New York Heart Association

OI Opportunistic infection

ORR Objective tumor response rate

OS Overall survival

PCR Polymerase chain reaction

PD Disease progression

PDGFR Platelet-derived growth factor receptor PDK1 Phosphoinositide-dependent kinase 1

PET Positron emission tomography

PFS Progression-free survival

pH Negative log of hydrogen ion concentration PI-4,5-P2 Phosphatidylinositol-4,5-bisphosphate

PID Patient identification number

PI3K Phosphatidylinositol-3-kinase

PIP3 Phosphatidylinositol-3,4,5-trisphosphate

PK Pharmacokinetic(s)

PPD Product of perpendicular diameters

PR Partial response

PRO Patient-reported outcomes

PT Prothrombin time

PTEN Phosphatase and tensin homolog

PTT Partial thromboplastin time

QoL Quality of life

RBC Red blood cell count

RNA Ribonucleic acid

ROS Roll-over study

RR Response rate

SAE Serious adverse event

SAF Safety analysis set

SAP Statistical analysis plan

SAS Statistical analysis system

SCR Serum creatinine

SDi Shortest diameter

SFU Safety follow-up

SGLT-2 Sodium/glucose co-transporter 2 SLL Small lymphocytic lymphoma

SmPC Summary of Product Characteristics

SPD Sum of the product of the diameters

SMZL Splenic marginal-zone lymphoma

SOC Standard of care

SUSAR Suspected, unexpected, serious adverse reaction TEAE Treatment-emergent adverse event

TSE Treatment side effects (subscale)

TTP Time to progression

ULN Upper limit normal

UPCR Urine protein to creatinine ratio

vs. Versus

VEGF Vascular endothelial growth factor

VGPR Very good partial response

WBC White blood cell count

WHO World Health Organization WHO-DD WHO Drug Dictionary

WM Waldenström macroglobulinemia WOCBP Woman of childbearing potential

# Definitions of terms

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

Lugano Classification – criteria for tumor response assessment as defined in the Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma ([27](#_bookmark195)).

Owen Criteria – criteria for tumor response assessment applicable for patients with Waldenström macroglobulinemia (WM), as defined in the Response Assessment in Waldenström macroglobulinemia: update from the VIth International Workshop ([35](#_bookmark203)).

# Introduction

## 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](#_bookmark172)).

It is estimated that worldwide there were around 356,000 new cases of NHLs in 2008 ([2](#_bookmark173)). 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](#_bookmark172)).

NHLs can be divided according to their clinical behavior in two main prognostic groups: indolent NHL and aggressive NHL. Aggressive lymphomas are characterized by an aggressive clinical course and may evolve into a lethal presentation if not immediately treated. However, with modern chemo-immunotherapy regimens and stem cell transplant consolidation a definitive cure can be reached in 50-60% of patients. Indolent NHLs have a relatively good prognosis with a median survival longer than 10 years, but they are incurable with current available therapeutic options, especially in advanced stages. While they are highly responsive to standard chemotherapy regimens and to radiotherapy, their natural history is characterized by a continuous pattern of relapses, which can be generally treated with success, but the time to next relapse progressively decreases each time, finally evolving into a refractory disease or 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 WHO classification of lymphoid neoplasm: follicular lymphoma (FL), small lymphocytic lymphoma (SLL), lymphoplasmacytic lymphoma (LPL), which is defined as Waldenström’s macroglobulinemia (WM) when associated with a monoclonal IgM component and bone marrow involvement, splenic marginal-zone lymphoma (SMZL), nodal marginal-zone lymphoma (NMZL) and marginal-zone lymphoma of mucosa-associated lymphoid tissue (MALT) ([3](#_bookmark174)). FL is the second most common subtype of NHL (22% of newly diagnosed cases) ([4](#_bookmark175)), followed by MALT lymphoma (7% of all NHL), while other subtypes are rather rare, with SLL, LPL, SMZL and NMZL accounting for 3%, 2%, 2% and 1% of NHL patients, respectively.

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

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

While the good tolerability of rituximab makes repeated administration possible, alkylating agents and purine nucleoside analogs can progressively reduce the bone marrow reserve ([5](#_bookmark176))

and cause secondary malignancies ([6](#_bookmark177), [7](#_bookmark178)). Doxorubicin is associated with dose-dependent cardiac toxicity. Cardiac abnormalities can occur in patients treated with doxorubicin for lymphoma in the absence of congestive heart failure, even in patients who received moderate anthracycline doses ([8](#_bookmark179), [9](#_bookmark180)). More than half of all lymphomas occur in patients older than

65 years ([10](#_bookmark181)). Acute and residual toxicities of chemotherapy are particularly important in an elderly patient population because they interfere with the ability of the patient to tolerate treatment at optimum dose and schedule, and reduce the number of options for subsequent treatments. In addition, these elderly patients will frequently have various comorbidities, which further limit their ability to cope with toxicity.

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

## Copanlisib (BAY 80-6946)

The phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway is one of the prominent pathways that promote cellular survival and constitutively is activated in many types of cancers ([11](#_bookmark182), [12](#_bookmark183)). Class I PI3K is downstream of most cancer- associated tyrosine kinase growth factor receptors (such as epidermal growth factor receptor [EGFR]/ human epidermal growth factor receptor [HER], insulin-like growth factor 1 receptor [IGF-1R], platelet-derived growth factor receptor [PDGFR], vascular endothelial growth factor [VEGF], c-KIT or mesenchymal epithelial transition factor [Met]). Once PI3K is activated, it activates Pleckstrin Homology Domain (PH-domain) proteins including 3- phosphoinositide-dependent protein kinase-1 (PDK-1) and AKT as well as guanine nucleotide exchange factor by generation of phosphoinositol-3-phosphate (PIP3). The tumor suppressor phosphatase and tensin homolog (PTEN) antagonizes PI3K by dephosphorylating PIP3, and its activity is frequently lost in cancer cells ([13](#_bookmark184)). In addition to mediating cancer associated signals, activation of the PI3K/AKT pathway is also one of the major mechanisms by which tumors escape from, and become resistant to, the effects of cytotoxic chemotherapy, targeted agents such as trastuzumab ([12](#_bookmark183)), and radiation ([12](#_bookmark183), [14](#_bookmark185)).

Four of these PI3K isoforms (PI3Kα, PI3Kβ, PI3Kγ, and PI3Kδ) are categorized as class I enzymes because they can use phosphatidylinositol-4,5-bisphosphate (PI-4,5-P2) as a substrate to generate phosphatidylinositol-3,4,5-trisphosphate (PIP3). Elevated PIP3 in cellular membranes drives several hallmarks of the cancer phenotype: cell proliferation, survival, metabolic reprogramming, and migration. PI3Kα and β are ubiquitous; PI3Kγ and δ are expressed mostly in the hematopoietic tissue. The clinical relevance of PI3K inhibition has been demonstrated by the activity of idelalisib (PI3Kδ-targeted compound) in patients with refractory iNHL ([15](#_bookmark186)).

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 IC50 of 0.5 nM, but also PI3Kδ with IC50 of

0.7 nM. Copanlisib also potently regulates nuclear localization of the forkhead family members resulting in the induction of transcriptional programs that lead to rapid cell death by

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

## Clinical experience

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

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

As of 10 FEB 2014, a total of 57 cancer patients were treated in the Phase I monotherapy study 12871, with 17 patients in the dose escalation cohorts and 34 patients in the maximum tolerated dose (MTD) expansion cohorts (two cohorts including 9 patients with NHL and

25 patients with solid tumors), as well as 6 patients with Type II diabetes mellitus in the diabetic expansion cohort at 0.4 mg/kg. In AUG 2013, the enrollment in study 12871 was completed. Dose-limiting toxicity was observed at 1.2 mg/kg with MTD established at

0.8 mg/kg when administered intravenously (IV) over 1 h, on Days 1, 8 and 15 of every

28 days as a single agent. The flat dose of 65 mg correlates with 0.8 mg/kg (MTD level) dose and was selected in order to control copanlisib exposure in obese patients.

In the NHL expansion cohort of Study 12871, a total of 6 non-diabetic patients with FL and 3 patients with diffuse large B-cell lymphoma (DLBCL) were treated, all initially dosed at

0.8 mg/kg. As of 01 FEB 2014, according to investigator’s assessment, 7 patients (77.8%) with NHL experienced partial response (PR) as best overall response and 2 patients (22.2%) had progressive disease. Partial responders included 6 patients with FL and 1 patient with DLBCL. A retrospective independent review performed in 8 of the 9 NHL patients (excluding the clinical assessment) concluded that a complete response (CR) was the best overall response in the 2 FL long-term responders (assessed as partial responders by the investigators).

The most common treatment-emergent adverse events (TEAEs), regardless of seriousness, severity, and causality, occurring in ≥20% of the 57 subjects were hyperglycemia (64.9%), nausea (52.6%), fatigue (40.4%), diarrhea (33.3%), hypokalemia (31.6%), hemoglobin (decreased) and hypertension (29.8% each), rash / desquamation and vomiting (28.1%, each), anorexia (26.3%), constipation (24.6%), cough and dehydration (22.8%, each), and

dyspnea (21.1%).

Pharmacokinetic (PK) results indicate nearly dose proportional increase in maximum concentration (Cmax) and area under curve (AUC(0-25)) values in the 0.1 to 1.2 mg/kg dose range and lack of significant accumulation after once weekly dosing. At the maximum tolerated dose of 0.8 mg/kg, the geometric mean half-life, (t1/2) was approximately 36-42 h (preliminary data), supporting a once weekly dosage regimen. To date, one metabolite, the morpholinone derivate M-1, showing approximately 4 to 16% of the AUC(0-25) of copanlisib has been identified and is currently being investigated in clinical studies. Results of a preliminary population PK analysis of copanlisib in studies 12871, 15205 (Phase I monotherapy study in Japanese subjects) and Phase II study 16349 (part A) showed no correlation between body weight and copanlisib clearance, indicating that body weight-based dosing does not reduce between-subject variability in copanlisib PK*.* The use of a fixed dose regimen for all patients was therefore considered suitable. Using the available data on preliminary safety and efficacy of copanlisib monotherapy, a fixed dose of 60 mg copanlisib has been defined as the recommended dose for use in all patients in future clinical studies.

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

6 cycles in the indolent group. The objective response rate (ORR) was 40% in FL, 38% in CLL, 100% in SLL, and 67% in MZL.

The most frequent TEAEs, regardless of relationship to study drug, occurring in >20% of the whole study population were hyperglycemia (59.3%), hypertension (56.8%), diarrhea (40.7%), fatigue (35.8%), nausea (32.1%), neutropenia (28.4%) and anemia (27.2%). The two most common study drug-related TEAEs were hyperglycemia (56.8%) and hypertension (53.1%). A t the time of the cut-off, a total of 75 patients (92.6%), 30 with indolent, and

45 with aggressive lymphomas, had discontinued the study treatment. Altogether 20 patients (24.7%) stopped treatment because of AEs. No conspicuous cluster of AEs causing treatment discontinuation emerged. Overall 17 out of 81 patients received treatment with short-acting insulin.

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

## Rationale for the study

Rituximab is approved for the treatment of CD20+ relapsed or refractory iNHL, and is widely used as a single drug or in combination regimens ([16](#_bookmark187)-[20](#_bookmark188)). Retreatment with rituximab alone or in combination has been shown to be feasible and active ([21](#_bookmark189), [22](#_bookmark190)) also in a large comparative trial involving rituximab retreatment in relapsed patients with FL initially responsive to rituximab-containing therapy ([23](#_bookmark191)).

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

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

The prolonged rituximab treatment (4 weekly infusions + 4 bimonthly) has proved to be associated with a longer event-free survival and response duration compared to the standard 4 weekly infusions schedule, without additional clinical toxicity in both relapsed iNHL ([24](#_bookmark192),

[25](#_bookmark193)) and as front line therapy ([26](#_bookmark194)), and this is the reason why it was chosen as a reference drug in this study.

## Benefit-risk assessment

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

Copanlisib showed activity in patients with relapsed or refractory iNHL (see Section [1.1.2](#_bookmark12)). Hyperglycemia and hypertension, the most frequently observed and expected toxicities with copanlisib, proved to be manageable, without CTCAE Grade 4 events. Toxicities will be carefully monitored during the course of the study with a detailed and tailored program of management. Rituximab and copanlisib have different targets and mechanisms of action, and their safety profiles indicate that no major overlapping toxicities are expected. Furthermore, the safety and feasibility of combination will be evaluated after the first 30 patients have been treated for at least one cycle. A Data Monitoring Committee (DMC) will be instituted to ensure the safety of patients participating in the study.

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

# Study objectives

The primary objective of this study is:

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

The secondary objectives of this study are to evaluate:

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

The other objectives of this study are to evaluate:

* Pharmacokinetics
* Biomarkers
* Quality of life

# Investigator and other study personnel

### Sponsor’s Medical Expert

Name:

PPD PPD

Title:

Address: 100 Bayer Boulevard, P.O.box 915 Whippany, NJ, USA

Telephone no.:PPD

### Coordinating Co-Investigators:

Name: Title: Address:

PPD PPD PPD

Italy

Telephone no.PPD

Fax no.:

E-mail:

Name: Address:

Telephone no: Fax no:

E-mail:

PPD PPD

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

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PPD PPD

PPD

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

The principal investigator of each center must sign the protocol signature sheet before patient recruitment may start at the respective center. Likewise, all protocol amendments/integrated protocols must be signed and dated by the principal investigator before coming into effect at the respective center.

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

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

### External data evaluation bodies Data Monitoring Committee (DMC)

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

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

The DMC will conduct its reviews based on data summaries and on an individual case basis. The summaries (i.e., tables and listings) will be generated by or under supervision of the study statistician. Details will be decided based on the sponsor’s currently valid operational instruction manual. The format and content of these data summaries will be specified by the sponsor in conjunction with the DMC and may change during the study if indicated. All summaries will be based on data provided by the sponsor from the study database.

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

### Central radiological evaluation

Radiological evaluation of computed tomography/magnetic resonance imaging (CT/MRI) scans will be performed centrally.

### Central pathology review

The retrospective confirmation of histopathological diagnosis will be performed centrally.