Amsterdam, 14 October 2021
EMA/948113/2022
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Aliqopa

International non-proprietary name: copanlisib

Procedure No. EMEA/H/C/004334/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADR(s)	Adverse drug reaction(s)
AE(s)	Adverse event(s)
AKT	Protein kinase B
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aNHL	Aggressive non-Hodgkin's lymphoma
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC_u	Unbound AUC
BCR	B-cell receptor
BCRP	Breast cancer resistance protein
BMI	Body mass index
BP	Blood pressure
B/R	Benefit/risk ratio
BSEP	Bile salt exporter pump
BTD	Breakthrough therapy designation
BTK	Bruton's tyrosine kinase
C_{avg}	Average plasma concentration
C_{Blood}/C_{Plasma}	Blood-to-plasma concentration ratio
CD20	B-lymphocyte antigen CD20
CD4	Cluster of differentiation 4
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CHOP	Cyclophosphamide, doxorubicin, vincristine, and prednisone
CI	Confidence interval
CK1-ε	Casein kinase 1 isoform epsilon
CL	Clearance
CLcr	Creatinine clearance
CLL	Chronic lymphocytic leukaemia
C_{max}	Maximum drug concentration in plasma
CNS	Central nervous system
CO	Clinical overview
Copa	Copanlisib
COVID-19	Coronavirus disease 2019
CR	Complete response
CRR	Complete response rate
Cru	Unconfirmed complete response
CRS	Cytokine-release syndrome
CTCAE	Common terminology criteria for adverse events
CV	Coefficient of variation
CVP	Cyclophosphamide, vincristine, and prednisone
CYP	Cytochrome P450
CYP1A1	CYP Family 1 Subfamily A Member 1
CYP2C8	CYP Family 2 Subfamily C Member 8
CYP3A4	CYP Family 3 Subfamily A Member 4
DCR	Disease control rate
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DLBCL	Diffuse large B-cell lymphoma
DMC	Data monitoring committee
DOR	Duration of response
DPD	Dihydropyrimidine dehydrogenase
DRS-P	Disease-related symptoms – physical
ECG	Electrocardiogram
ECOG	Eastern cooperative oncology group
EMA	European Medicines Agency
EoT	End of treatment
ERK	Extracellular signal-regulated kinase
ESMO	European Society for Medical Oncology
EU	European Union

FACT-Lym	Functional assessment of cancer therapy – lymphoma
FACT-Lym LymS	Fact-Lym lymphoma subscale
FAS	Full analysis set
FDA	Food and Drug Administration
FiH	First-in-human
FL	Follicular lymphoma
FLymSI-18	Functional assessment of cancer therapy lymphoma symptom index-18
GI	Gastrointestinal
Hb	Haemoglobin
HbA1c	Haemoglobin A1c (glycosylated haemoglobin)
HLGT	High-level group term
HLT	High-level term
HR	Hazard ratio
HRQoL	Health-related quality of life
IA	Integrated analysis
IC_{50}	Half maximal inhibitory concentration
ICH	International Council for Harmonization
ICR	Independent central review
iNHL	Indolent non-Hodgkin's lymphoma
INV	Investigator
IRC	Independent review committee
ITT	Intent to treat
IV	Intravenous(ly)
LPL	Lymphoplasmacytoid lymphoma
LPLV	Last patient last visit
LVEF	Left ventricular ejection fraction
MAA	Marketing authorisation application
mAb	Monoclonal antibody
MALT	Mucosa-associated lymphoid tissue
MATE	Multidrug and toxin extrusion protein family
MATE1	Multidrug and toxin extrusion protein 1
MATE2-K	Multidrug and toxin extrusion protein 2
MCL	Mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent to treat
MLG	MedDRA labeling grouping
MM	Multiple myeloma
MR	Minimal response
MRP2	Multidrug resistance-associated protein 2
MT	Mutant
MTD	Maximum tolerated dose
MUGA	Multi-gated acquisition
MZL(s)	Marginal zone lymphoma(s)
NA	Not available
NCA	Non-compartmental analysis
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NDA	New drug application
NE	Not evaluable/estimable
NHL	Non-Hodgkin's lymphoma
NIP	Non-infectious pneumonitis
OAT1	Organic anion transporter 1
OAT3	Organic anion transporter 3
OATPs	Organic anion transporting polypeptides
OATP1B1	Organic anion transporting polypeptide 1B1
OATP1B3	Organic anion transporting polypeptide 1B3
OCTs	Organic cation transporters
OCT1	Organic cation transporter 1
OCT2	Organic cation transporter 2
OCT3	Organic cation transporter 3
ODD	Orphan drug designation
ORR	Objective/overall response rate
OS	Overall survival

pAKT	Phosphorylated AKT
Pbo	Placebo
PD	Progressive disease
PFS	Progression-free survival
P-gp	Permeability glycoprotein
PI3K(s)	Phosphatidylinositol 3-kinase(s)
PI3Ki(s)	Phosphatidylinositol 3-kinase inhibitor(s)
PID	Patient identification number
PJP	*Pneumocystis jirovecii* pneumonia
PK	Pharmacokinetic(s)
PML	Progressive multifocal leukoencephalopathy
PopPK	Population pharmacokinetic(s)
PR(s)	Partial response(s)
PRO	Patient-reported outcome
PRP	Platelet-rich plasma
PS	Performance status
PT	Preferred term
PTEN	Phosphatase and tensin homolog
PTTE	Parametric time-to-event
QoL	Quality of life
QT	QT interval in electrocardiogram
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected by Fridericia's formula
R	Rituximab
R-CHOP	Cyclophosphamide, doxorubicin, vincristine, and prednisone + rituximab
R-CVP	Rituximab, cyclophosphamide, vincristine, and prednisolone
SAE(s)	Serious adverse event(s)
SAF	Safety analysis set
SAP	Statistical analysis plan
SAWP	Scientific advice working party
SCE	Summary of clinical efficacy
SCS	Summary of clinical safety
SD	Stable disease
SLL	Small lymphocytic lymphoma
SMQ	Standardized MedDRA Query
sNDA	Supplemental New Drug Application
SOC	System organ class
ST	Solid tumour(s)
StD	Standard deviation
SUV_{max}	Maximum standardised uptake value
TEAE(s)	Treatment-emergent adverse event(s)
$t_{1/2}$	Elimination half-life
TESAE(s)	Treatment-emergent serious adverse event(s)
TL	Target lesion
TLS	Tumour lysis syndrome
TSE	Treatment side effects
TTE	Time to event
TTP	Time to progression
TTR	Time to response
UGT	Uridine diphosphate glucuronosyltransferase
ULN	Upper limit of normal
US(A)	United States (of America)
uSD	Unconfirmed early stable disease
USPI	United States prescribing information
VGPR	Very good partial response
V_z	Apparent volume of distribution
WHO	World Health Organization
WM	Waldenström macroglobulinaemia
WNT	Wingless-related integration site
WT	Wild-type

1. Recommendations

Based on the review of the data on quality, safety, efficacy, the application for Aliqopa, an orphan medicinal product, in combination with rituximab for the treatment of adult patients with previously treated marginal zone lymphoma could be approvable provided that satisfactory answers are given to the "other concerns" as detailed in the List of Questions (redacted from published report). Failure to resolve other concerns may render the application not approvable.

Based on the review of the data on quality, safety, efficacy, the application for Aliqopa, an orphan medicinal product, as monotherapy for the treatment of adult patients with marginal zone lymphoma who have received at least two prior therapies is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the List of Questions (redacted from published report).

In addition, satisfactory answers must be given to the "other concerns" as detailed in the List of Questions.

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

- The use of Aliqopa as monotherapy.

Questions to be posed to additional experts

Not applicable

Inspection issues

GMP inspection(s)

No need has been identified for an inspection.

The application form includes EudraGDMP document reference number 51034. According to the EudraGDMP data, a GMP certificate was issued by State Office of Health and Social Affairs Berlin to the finished product manufacturer Bayer AG, Müllerstrasse 178, Berlin, Berlin, 13353, Germany and dated 2018-10-12. The GMP certificate lists manufacturing of sterile products – lyophilisates

GCP inspection(s)

No need has been identified for an inspection.

New active substance status

Based on the review of the data the active substance copanlisib contained in the medicinal product Aliqopa is considered to be qualified as a new active substance in itself.

Additional data exclusivity /Marketing protection

Not applicable

Similarity with authorised orphan medicinal products

Not applicable

Derogation(s) from market exclusivity

Not applicable

2. Executive summary

2.1. Problem statement

2.1.1. Disease or condition

The claimed indications:

- Aliqopa in combination with rituximab (anti-CD20 antibody) is indicated for the treatment of adult patients with previously treated marginal zone lymphoma. *(Combination therapy)*
- Aliqopa is indicated as monotherapy for the treatment of adult patients with marginal zone lymphoma who have received at least two prior therapies. (*Monotherapy)*

2.1.2. Epidemiology

MZL represents approximately 5–15% of all NHLs in the Western world (Zucca et al. 2020). In 2018, over 11500 individuals were diagnosed with MZL in Europe (geographic area) and there were approximately 4800 deaths due to the disease (Ferlay et al. 2020).

2.1.3. Biologic features

Based on the 2016 World Health Organization (WHO) classification of lymphoid neoplasms (Swerdlow et al. 2016), histological entities of B-cell iNHL include: follicular lymphoma (FL), marginal zone lymphoma (MZL), small lymphocytic lymphoma (SLL), and lymphoplasmacytoid lymphoma (LPL).

The MZL classification is based on a common origin in the marginal-B-cell-compartment of the lymph nodes and spleen. The three distinct clinical entities, extranodal, splenic, and nodal MZL, have specific diagnostic criteria, different genetic features, clinical behaviour, and therapeutic implications.

MZL is characterised by the need for multiple lines of therapy due to the incurable nature of the disease (Broccoli and Zinzani 2020). Relapses are common even after successful therapy and can occur decades after treatment. More than 50% of MZL patients experience relapse within 10 years (Bertoni et al. 2020, Oh et al. 2009).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

The clinical presentation is dependent on subtype of MZL and stage, and may include a slow growing mass or lymph node at various locations, symptoms of bone marrow insufficiency, and/or B-symptoms. Many patients are asymptomatic at the time of diagnosis.

Several studies reported 5-year OS rates for MZL with a wide range depending on different factors such as age, gender, geographic location, disease stage at diagnosis and treatment received (Smith et al. 2015). In the UK, a 5-year survival rate of 61.2% was reported (Smith et al. 2015). In Germany, a 5-year survival rate of 83.8% was reported in patients, the majority of whom had received first line of therapy (Meyer et al. 2014). A 5-year OS rate of 62% was reported for treatment-naive patients older than 60-years of age with nodal MZL (Kuper-Hommel et al. 2013). Reports for a 10-year OS rate have varied between 42% to 58% (Olszewski and Castillo 2013).

2.1.5. Management

Currently, there is no treatment specifically approved for MZL patients in the European Union (EU). The therapeutic regimens used for MZL are summarised in the European Society for Medical Oncology (ESMO) clinical practice guidelines for MZL (Zucca et al. 2020). In the absence of approved specific treatments for MZL, rituximab, ibrutinib, and lenalidomide are being used in the EU for the treatment of MZL patients. Although not specifically indicated for MZL, the IV-administered treatment option of rituximab is widely used for the treatment of patients with MZL. In FL, rituximab is indicated for the treatment of previously untreated adult patients with Stage III or IV disease in combination with chemotherapy. In addition, rituximab maintenance therapy is indicated for the treatment of refractory/relapsed FL patients.

2.2. About the product

Copanlisib (BAY 80-6946) is a potent pan-class I phosphatidylinositol 3-kinase (PI3K) inhibitor active against all of the four PI3K isoforms (α, β, γ, and δ) and has been developed for the treatment of B-cell indolent non-Hodgkin's lymphoma (iNHL) and its major histological subtypes. These indications are mainly characterised by activation of PI3K isoforms α and δ, which are inhibited by copanlisib at sub-nanomolar concentrations in kinase assays as well as cellular mode-of-action studies (Paul et al. 2017).

The PI3K/AKT/mTOR pathway is one of the prominent pathways that promote cellular survival and is constitutively active in many types of cancers (Ihle and Powis 2009, Yuan and Cantley 2008). Class I PI3K is downstream of most cancer-associated tyrosine kinase growth factor receptors such as B-cell receptor (BCR), EGFR/HER, IGF-1R, PDGFR, VEGF, c-KIT, or MET and is therefore a key mediator of oncogenic signalling. In addition, the PI3K/AKT pathway is also one of the major mechanisms tumours use to escape from, and become resistant to, the effects of cytotoxic chemotherapy, targeted agents, and radiation (Prevo et al. 2008, Yuan and Cantley 2008).

In B-cells, a part of the BCR/PI3K signalling that controls cell proliferation and cell survival is mediated by BTK and nuclear factor kappaB (NFκB). Activating NFκB mutations have been found in iNHL including MZL. They are likely to contribute to cell survival and to resistance mechanism, e.g., against targeted BTK inhibitors (like ibrutinib) that have shown efficacy in B-cell lymphomas (Efremov et al. 2020).

In a profiling analysis of a panel of 17 B-cell lymphoma cell lines derived from marginal zone lymphoma (MZL), mantle cell lymphoma (MCL), and chronic lymphocytic leukaemia (CLL), copanlisib has shown high efficacy in inhibition of cell proliferation and potent induction of apoptosis in monotherapy as well as in combination with targeted treatments (Tarantelli et al. 2020).

Due to the central and multiple roles of PI3K signalling in cell proliferation and cell survival, the use of a pan-class I PI3K inhibitor provides potential for improved efficacy in monotherapy and specifically in combination settings in initially non-PI3K-driven as well as PI3K pathway-driven tumours including iNHL.

PI3K inhibitors including idelalisib, duvelisib, umbralisib, and copanlisib have already proven to be effective in the treatment of iNHL. Copanlisib is the only PI3K inhibitor administered intravenously (IV) and dosed intermittently. This leads to a differentiated and manageable safety profile in contrast to the oral inhibitors (Brem 2020). The broad PI3K inhibitory activity against all four isoforms may enhance efficacy by preventing signalling through escape mechanisms (Liu et al. 2016, Thye et al. 2015). Based

on the results of study 17067 (CHRONOS-3), copanlisib is the only PI3K inhibitor that has demonstrated safe and effective combinability with rituximab, a standard of care in iNHL.

2.3. The development programme/compliance with CHMP guidance/scientific advice

Based on promising preclinical efficacy data, Phase 1 clinical development of copanlisib was initiated in NOV 2009 in cancer patients with advanced solid tumours and relapsed or refractory NHL. As of 13 SEP 2020, more than 1600 patients have been treated with copanlisib as a single agent or in combination with other agents in Phase 1–3 studies worldwide. The comprehensive clinical development programme comprises 11 Phase 1 studies, three Phase 1/2 studies, and three Phase 3 studies in NHL, CLL, and solid tumour patients.

Overviews of relevant clinical studies are presented in the pharmacology, efficacy, and safety sections.

Scientific Advice:

PDCO has granted a waiver of the requirement for paediatric studies with copanlisib in the paediatric population for the treatment of mature B-cell neoplasms and a deferral for the treatment of all conditions included in the category of malignant neoplasms (except haematopoietic and lymphoid tissue) from 6 month to 18 years of age. This is reflected in the SmPC with the statement "The safety and efficacy of Aliqopa in children aged under 18 years have not been established. No data are available".

2.4. General comments on compliance with GMP, GLP, GCP

GMP

No need has been identified for an inspection.

The application form includes EudraGDMP document reference number 51034. According to the EudraGDMP data, a GMP certificate was issued by State Office of Health and Social Affairs Berlin to the finished product manufacturer Bayer AG, Müllerstrasse 178, Berlin, Berlin, 13353, Germany and dated 2018-10-12. The GMP certificate lists manufacturing of sterile products – lyophilisates, however, the applicant is requested to clarify if the GMP certificate covers sterilization of packaging materials.

A QP declaration on the GMP compliance at the manufacturing site of the drug substance has been submitted. The declaration is signed by the QP of the site responsible for the drug product manufacture and is based on an on-site audit conducted on 16-17 June, 2020

Co-Rapporteur's comment:

The GMP for the Drug substance (QP declaration) should also be commented. The following is proposed:

"A QP declaration on the GMP compliance at the manufacturing site of the drug substance has been submitted. The declaration is signed by the QP of the site responsible for the drug product manufacture and is based on an on-site audit conducted on 16-17 June, 2020"

GLP

All pivotal toxicity studies (single- and repeat-dose studies) were considered to be GLP-compliant.

Several other concerns on GLP were raised with regard to the pivotal toxicity studies (See List of questions).

GCP

The clinical trials, study 17067 and study 16349 Part B, were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.5. Type of application and other comments on the submitted dossier

Legal basis

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

PRIME

Not applicable

Accelerated assessment

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on the following:

An unmet need has not been clearly justified. Furthermore, this product is not considered a major therapeutic innovation nor is it considered to impact medical practice in a substantial way. Also, considering the indolent nature of the disease, the concerning safety profile of PI3K inhibitors, the lack of mature OS data, the overall strength of evidence is not considered convincing.

Conditional marketing authorisation

Not applicable

Marketing authorisation under exceptional circumstances

Not applicable

Biosimilarity

Not applicable

Additional data exclusivity/ marketing protection

Not applicable

New active substance status

The applicant requested the active substance copanlisib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Orphan designation

Aliqopa was designated as an orphan medicinal product EU/3/18/2064 on 24 Aug 2018 in the following condition: Treatment of marginal zone lymphoma.

Similarity with orphan medicinal products

The application did not contain a critical report pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, addressing the possible similarity with authorised orphan medicinal products.

Derogation(s) from orphan market exclusivity

Not applicable

Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0133/2020 on the agreement of a paediatric investigation plan (PIP).

The PDCO issued an opinion on compliance for the PIP (P/0133/2020) on the acceptance of a modification of an agreed paediatric investigation plan for copanlisib (EMEA- 001757-PIP02-15-M02).

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The finished product is presented as a powder for concentrate for solution for infusion containing 60 mg of copanlisib dihydrochloride as active substance.

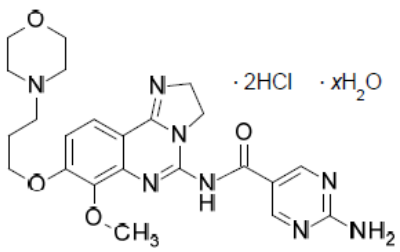
Other ingredients are: citric acid anhydrous, mannitol and sodium hydroxide.

The product is available in a 6 ml glass colourless vial (type I glass) closed with a grey bromobutyl stopper (type I) fixed with a flanged closure.

3.1.2. Active substance

General Information

INN name	Copanlisib
Chemical name	2-amino-N-{7-methoxy-8-[3-(morpholin-4-yl) propoxy]-2,3-dihydroimidazo[1,2-c] quinazolin-5-yl} pyrimidine-5-carboxamide dihydrochloride
Molecular structure	Copanlisib dihydrochloride hydrate

	
Molecular formula	$C_{23}H_{28}N_8O_4 \cdot 2HCl$
Molecular mass	553.45 (anhydrous form)
General information and chemical features	The active substance is to be considered a new active substance. It is a white to yellow powder. It is freely soluble in water. It is not optically active.

The documentation on the active substance is presented as full file.

The issue raised by the Rapporteur in this section regarding the hydrate form of the drug substance is endorsed. In addition, the Co-Rapporteur considers that the drug substance name used throughout the Module 3 should reflect the form (hydrate) and proposes Q3.

Manufacture, process controls and characterisation

Synthetic scheme, detailed description and in-process controls for every stage of the manufacturing process have been provided including raw material quantities, process conditions and yields. Process parameters and quantities of materials, reagents and solvents are laid down in the process description with both set points and ranges (PARs). However, it is not clear how the PARs are intended to be used and this should be clarified. Several issues have to be resolved before the synthesis of the drug substance is considered adequately described. A reprocessing step is questioned.

Justification for defined starting materials is supported by the impurity profile provided, which is acceptable.

Potential impurities in the starting materials have been evaluated with carry over analysis including potentially genotoxic impurities. Spiking experiments have been performed to support impurity profile although data has not been provided. Impurities are controlled in SM specifications where relevant. High purity of starting materials is demonstrated by batch analyses. Proposed raw material specifications are acceptable.

Critical process parameters have been specified to control impurities formed and hydrate form. Control of impurities in intermediate is justified.

Potential impurities in the drug substance have been evaluated. The presented control strategy for impurities is acceptable.

The chemical structure of copanlisib dihydrochloride and potential impurities have been confirmed by spectral data ^{1}H-, ^{13}C-NMR and mass spectroscopy.

Specification, analytical procedures, reference standards, batch analysis, and container closure

The control tests for active substance product are adequately drawn up. Method references are requested in the presented specification.

The specification has been justified with references to general requirements in Ph. Eur. and ICH guidelines. Proposed specification parameters are acceptable for the drug substance, but specification limits are to be tightened based on batch and stability data.

The validation of the analytical procedures is found sufficient and in accordance with the EU/ICH validation guidelines.

Batch analyses of batched The results comply with the proposed specification and confirm consistency of the product.

The primary packaging is in compliance with Commission Regulation (EU) 10/2011 Plastic materials and articles intended to come into contact with food and amendments.

Stability

Stability indicating parameters have been investigated in both packaging intended for marketing. The stability-indicating nature of the HPLC has been questioned as results from stress studies indicate that mass balance is not 100%.

Stability studies have been performed with the active substance according to ICH guidelines. No significant changes in any parameters were observed. The proposed retest period of appears justified, the retest period could be accepted if satisfactory answer is given to the question related to the mass balance and stability-indicating nature of the HPLC methods for Assay and Impurities. Photostable by testing according to ICH Q1B Photostability.

3.1.3. Finished medicinal pProduct

Description of the product and pharmaceutical development

The finished product is a powder for concentrate for solution for infusion to be marketed in glass vials. Each vial contains 69.1 mg of copanlisib dihydrochloride (equivalent to 60 mg copanlisib free base) plus an additional overfill of 14.0 %. Another concern has been raised concerning the overfill.

To ensure stability, copanlisib is provided as a freeze-dried product (lyophilizate). Prior to administration, the lyophilizate has to be reconstituted with sodium chloride solution 0.9%, resulting in a solution with a concentration of 15 mg/ml copanlisib, free base. A 4 ml aliquot of the reconstituted solution is further diluted with sodium chloride solution 0.9% and administered intravenously.

All excipients, common for parenteral formulations, are compendial.

Another concern has been raised in regard to the chemical instability of the product compared to the active substance. No excipient compatibility study has been performed, and no discussion is included to explain this substantial change in chemical stability when API is included in the product.

The manufacturing process consists of manufacture of the bulk solution, a conventional aseptic filtration and filling process followed by lyophilization. Batches of copanlisib lyophilisate 60 mg for injection for phase II and III clinical trials were manufactured in pilot scale.

The manufacturing process for copanlisib lyophilisate 60 mg for injection uses standard unit operations that can be separated into the following general process steps:

- Manufacture of bulk solution
- Filtration
- Filling, freeze-drying, closure

The formulation of copanlisib lyophilisate 60 mg for injection and the general process for commercial manufacture of the drug product are the same compared to the formulation and manufacture of the 60 mg copanlisib formulation used for supplying the clinical studies.

The freeze-drying process was developed based on the critical formulation temperature and on the physicochemical characteristics of the product.

A design of experiment (DoE) was conducted in laboratory scale to evaluate the impact of various processing parameters (on end product variables like residual moisture, appearance, drug content, sum of impurities and solid state. All variables were robust against the process parameters tested, except the interval between targeted and actual end of primary drying.

The compatibility of the lyophilizate with the container system is primarily confirmed by testing the relevant quality parameters in the course of batch release testing and by testing batches which have undergone long-term storage or have been tested under accelerated conditions. Therefore, no additional compatibility tests with the primary container material are required.

To demonstrate the compatibility of the reconstituted lyophilizate and the further diluted solution for administration with the primary container (glass vial) and the standard application device aliquots of such solutions were kept in the glass vials respective containers for a defined period under usual ambient temperature conditions or with cold storage. However, infusion bags made of different material than PE should also be evaluated.

Another concern was raised for the use of foil covered rubber stopper in the extractables study when the rubber stopper in the marketed product

Various volatile, semi-volatile and non-volatile identified and unidentified compounds were detected from different extracts above the AET of the study. In addition, six anions and three elements were found in the aqueous extracts above the AET. The detected aqueous extractables were used as the basis for the selection of the target substances in the subsequent migration study. Clarification is required.

No volatile, semi volatile or non-volatile target compounds were detected above the AET of 4.5 µg/mL in neither of the vial samples or blank solutions. No unexpected leachables were detected by HS-GC/MS, GC/MS, HPLC/DAD/MS, IC and ICP/MS screening.

The finished product is intended for single-use. The formulation does not contain preservatives.

Microbiological attributes of the dosage form including sterility and bacterial endotoxins test have been set in accordance with Ph. Eur. 2.6.1 and 2.6.14, respectively, and limits have been included in the drug product specification.

The study design for control of container closure integrity, i.e. immersing vials into a microbial suspension and subsequent test for microbial growth is acceptable. No growth was observed; hence container closure integrity has been shown.

Manufacture of the product and process controls

The batch formula is presented for the largest batch size proposed, i.e. the batch formula is missing for the smallest batch size proposed.

The manufacturing steps comprise the manufacturing of an aqueous bulk solution, pH-adjustment, sterile filtration, aseptic filling of vials and freeze drying of the solution in the vials, closing and crimping of the vials, and visual inspection.

The description of the manufacturing process should be more detailed and information about the non-sterilizing and sterilizing filters should be provided.

The vials are sterilised using dry heat and the stoppers are sterilised using steam sterilization.

The acceptance criteria of the parameters and process controls are based on the experience made during the development of the manufacturing process in lab scale, during scale-up to pilot scale (manufacture of clinical supplies for Phase II/III).

It was clearly demonstrated during development that the manufacturing process performed within the limits of the respective parameters leads to lyophilizates which meet the requirements of the in-process controls and the release specification. However, acceptance criteria for integrity testing of filters and bioburden should be stated.

The process validation, including manufacture of bulk solution, filling, freeze-drying, crimping and visual inspection) of copanlisib 60 mg for injection was performed at commercial scale.

The sterilising filter has been validated regarding bacterial retention capacity, solution compatibility, adsorption, filter integrity test, and single use system extractables in line with the current sterilisation guideline. Sterilisation of stopper is performed using steam sterilisation The dry heat sterilization conditions used to sterilise the vials should be further justified.

A more extensive discussion is requested to ensure that the process has been developed to ensure that all vials have the appropriate dose.

In the description of the manufacturing process, it is stated that "the holding time of the solution until completed pre-filtration must not exceed a certain time" and "the holding time must not exceed a certain time from preparation of the bulk solution until end of loading of freeze-dryer". It is noted that these two holding times differs from the prolonged holding times proposed

In line with Guideline on sterilisation of the medicinal product, active substance, excipient and primary container, holding and filling times should be stated, supported by appropriate data, but also be minimised. Justification for the proposed holding and filling times should be provided, including an overview of the data supporting the individual holding and filling times.

The routine process time should be included in the description of the manufacturing process, excluding holding times. Note that routine process time should be differentiated from holding time(s) and that each individual holding time should be defined.

Product specification, analytical procedures, batch analysis

The finished product specification (release and shelf-life) should be updated to include a specific reference for each analytical procedure used. For the Ph. Eur. methods, reference should be made to the relevant monographs.

In general, the analytical methods are adequately described, although a specific reference to the Ph. Eur. method for determination of water content is missing. Also, the validation of the method should be justified, as the results for accuracy appear to be wider than acceptable.

The validation of the HPLC method for identification, assay and related substance, the UV method for identification, the LAL-kinetic turbidimetric method and test for sterility has been sufficiently performed.

The batches data confirm consistency and uniformity of the product. All results comply with the finished product specification.

The elemental impurity risk assessment conducted, concluded that no risk was present, however, the applicant performed confirmatory testing on 4 batches supported the conclusion. It is acceptable not to perform routine control testing on elemental impurities.

The applicant has presented a thorough impurity discussion in relation to all possible risks associated with the finished product. As there is no actual risk identified, no confirmatory testing is required.

The specification limits for appearance of the lyophilisate and appearance of the reconstituted solution, particulate matter, pH, identification of copanlisib, uniformity of dosage units, and sterility are acceptably set, however, the specification limits for water content, reconstitution time, degradation products, assay and endotoxins should be revised, unless otherwise justified.

Stability of the product

The stability studies have been carried out in accordance with current ICH guidance with regard to storage conditions, test frequency and batch size, however, a different glass bottle than the glass bottle proposed for commercial use was used. The applicant is required to explain the different between the two glass bottles.

Using the "former" glass vial, it is shown that the finished product is stable and well within the specification after 36 months of storage at 2-8°C. Considering the rapid increase in the content of impurities at 25°C/60% RH, it is acceptable to consider this accelerated storage condition. Therefore, the following shelf-life/storage conditions is acceptable: 36 months at a temperature between 2-8°C.

The photostability study show that the ready-to-use solution for infusion of copanlisib should be not be exposed to direct sunlight.

The in-use stability studies show that the reconstituted lyophilisate and the diluted copanlisib solution can be stored for up to 48 hours in refrigerator or at room temperature from a physico-chemical perspective, however, it is unknown if one the batches used was chosen towards the end of its shelf-life. Clarification is required.

Additional other concerns were added on recently started stability studies and colour changes observed in stability studies.

Post approval change management protocol(s)

Not applicable.

Adventitious agents

No materials of animal or human origin are used during the synthesis of the drug substance nor during the manufacturing process of the drug product. Consequently, there is no risk of transmission of spongiform encephalopathy from pharmaceutical use of the drug product.

GMP

Not applicable.

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

The chemical-pharmaceutical documentation and quality overall summary in relation to Aliqopa is currently not of sufficient quality in view of the present European regulatory requirements, and there is a need for additional information to complete quality documentation. Several other concerns have been identified.

3.2. Non-clinical aspects

The sought indication for Aliqopa is in combination with rituximab (anti-CD20 antibody) for the treatment of adult patients with previously treated marginal zone lymphoma, and as monotherapy for the treatment of adult patients with marginal zone lymphoma who have received at least two prior therapies. The indications fall within the scope of ICH S9, hence a nonclinical study programme in line with ICH S9 has been performed. This is considered acceptable.

3.2.1. Pharmacology

It was shown that copanlisib (BAY 80-6946) is a nonspecific PI3K inhibitor which inhibit PI3Kα and PI3Kδ, with IC50 values of 0.5 and 0.7 nM, respectively, and inhibition of the PI3Kβ and PI3Kγ were slightly higher with IC50 values of 3.7 and 6.4nM.

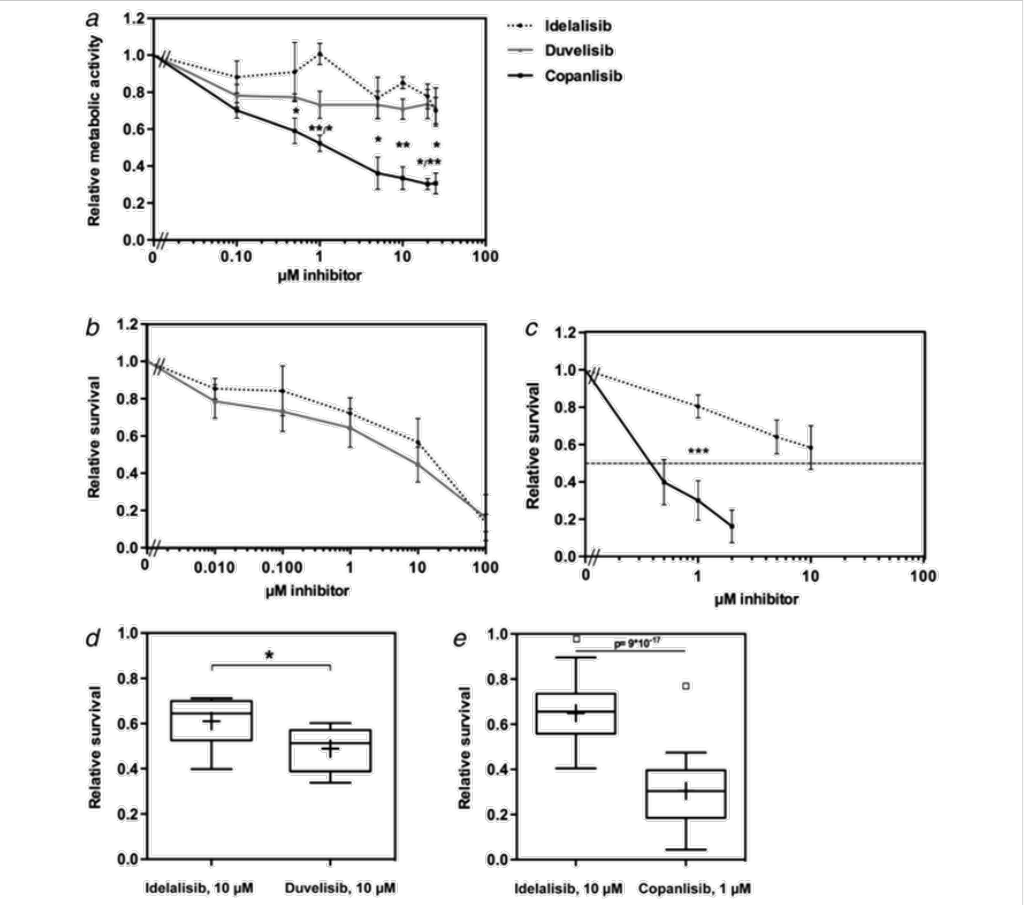
The primary pharmacological profile of copanlisib was assessed *in vitro* using panels of kinases, other molecular receptors and in human tumour cells exposed to copanlisib dihydrochloride alone or in combination with other anti-cancer drugs. The inhibition of the PI3K target kinase function as well as downstream targets in the PI3K/AKT/mTOR pathway by copanlisib and the active and minor metabolite M-1 (BAY 84-5795) was addressed in a large panel of cancer cell lines including analysis of inhibition of cell proliferation, inhibition of downstream signalling e.g. inhibition of protein kinase B pAKT-S473 formation and induction of cell death by apoptosis. The athymic rat and mouse models were used to evaluate the effects of copanlisib on xenografts of human cancers, because these are commonly used model systems for this purpose.

A study comparing PI3K and mTOR inhibition, suggest that copanlisib has a 100- to 1000-fold cellular selectivity of PI3K vs. mTOR signalling and therefore it is not a dual PI3K/mTOR inhibitor in cells.

It was reported that copanlisib reduced the survival of CLL cells approximately 20-fold more potently than idelalisib (at doses of 10 µM idelalisib compared to doses of 1 µM copanlisib). Idelalisib and copanlisib was found to have similar IC50 values against PI3Kδ (7.4 nM vs 7.9 nM, respectively). It was suggested that the efficacy of PI3K-δ inhibitors for reducing the survival of CLL cells was enhanced by additionally targeting PI3Kα, but not PI3Kγ (see figure below). Furthermore, inhibition of PI3Kδ or PI3Kα alone is not sufficient to reach substantial growth inhibition and simultaneous inhibition of PI3Kα

and PI3Kδ by copanlisib enhanced anti-tumour profile in ABC-DLBCL models compared to selective inhibition of either PI3Kδ, PI3Kα or BTK.

Sensitivity of CLL cells for PI3K inhibitors



Sensitivity of CLL cells for PI3K inhibitors. (a) The sensitivity of JVM-3 cells for PI3K inhibitors was determined in three independent XTT assays after 48 hr of incubation. Asterisks indicate significantly higher efficacy of copanlisib versus idelalisib and duvelisib at common inhibitor concentrations according to paired Student's t test. (b, c) Two different sets of six CLL samples were treated with duvelisib (b) or copanlisib (c) for 48 hr with idelalisib as a common reference and examined for phosphatidylserine exposure. (d,e) Survival inhibition by duvelisib (d) or copanlisib (e) was compared to idelalisib at fixed inhibitor concentrations reflecting pharmacologically achievable levels in 6 or 32 CLL samples, respectively. Means are indicated by plus signs, outliers by empty squares.

In CLL samples, the combination of idelalisib and copanlisib with CD20+ Mab (either Rituximab or obinutuzumab) was more direct cytotoxic compared to PI3K inhibitor alone, with obinuztuzumab appearing more potent than rituximab.

The metabolite M-1 (BAY-84-5975) was characterised with regards to biochemical activity, inhibition of phosphorylation PRAS40 and inhibition of cell proliferation. In general, M-1 showed similar activity compared to parent compound with respect to IC50 of PI3Kα or PI3Kδ enzyme inhibition. With respect to inhibition of PRAS40 approximately 10-fold lower activity of M-1 was observed compared to parent compound. However, when tested in an *in vitro* cell proliferation assay, with tumour cell lines, comparable activity was observed between the parent compound and M-1. Furthermore, M-1 is not a major human metabolite, but was found to be to less than 10% of parent compound.

In vivo pharmacology

Report MRC-01363 (2006) entitled "Identification of BAY 80-6946, a Novel Inhibitor of Class phosphatidyl-inositol 3-Kinases for the Treatment of Cancer", presents both *in vitro* and *in vivo* pharmacology studies as summaries in a form suitable for publication. Hence, raw data are missing and the responsibilities of individual investigators are not clear. Nevertheless, the presentation and discussion of data was supported by *in vivo* PK data and appears reliable. Therefore, an overall non-clinical *in vivo* proof of concept in the treatment of cancers using four different tumour xenografts including lung (H460), colon (HCT-116), glioblastoma (U87), and breast (KPL-4) in nude athymic rats, is considered acceptable. Vinblastine was used as positive control. It should be noted that vinblastine was more efficacious than copanlisib in three out of four tumour studies, but body weight loss in the vinblastine groups was not shown. For copanlisib, there appear to be a separation between beneficial effect of tumour weight reduction and body weight loss using these four cancer animal models with the breast cancer KPL4 tumour xenograft being the most sensitive to copanlisib (BAY 80-6946).

The *in vivo* mechanism of action of copanlisib as a selective PI3K inhibitor was demonstrated in the BT-474 (ductal carcinoma, breast) xenograft model in immunocompromised mice. Intravenous administration of copanlisib caused rapid (within 10 minutes) inhibition of PI3K activity, as measured by decreased phosphorylation of AKT S473 and T308, and of ERK phosphorylation. Interestingly, the effects of pulsatile copanlisib treatment (14 mg/kg copanlisib dihydrochloride, three times/wk) and continuous administration of copanlisib via a mini-pump (42 mg/kg/wk copanlisib dihydrochloride) was compared. Pulsatile administration of copanlisib suppressed tumour growth to a much greater extent than continuous dosing. The applicant proposed that it is likely that transient inhibition of PI3K was more effective because of more complete inhibition of the target for a short time and limited relief of feedback and reactivation of upstream signalling. The pulsatile dosing regime is in principle in line with the intermittent dosing schedule as described in section 4.2. of SmPC.

Study demonstrated statistically significant tumour reducing effect of copanlisib in four ABC-DLBCL (Activated B cell-like Diffuse Large B-Cell Lymphoma) patient derived xenograft models in mice including a xenograft (LY257) resistant to ibrutinib (a Bruton's kinase inhibitor). In these studies, the intermittent intravenous dosing regime shown to be the most efficacious in rats were confirmed in mice. Copanlisib was typically administered to mice xenografts as split doses of 10 or 14 mg/kg copanlisib dihydrochloride according to the Q2D or 2 on/5off dosing schedule. The studies were supported by a PK study confirming exposure. Whereas the patient derived xenografts used in the previously discussed *in vivo* pharmacology studies were targeting other types of cancer, the xenografts used in this study appear to be more relevant to the actual indication sought for, namely marginal zone lymphoma in combination with rituximab, which is designed to target CD20+ B-cells.

PK/PD relationship

A discussion of the PK/PD relationship was presented. The lowest active dose in the *in vivo* pharmacology studies in rats and mice supported by separate PK studies and determined fraction unbound was used and compared to mean human exposure at the dose of 60 mg. To be able to compare across species and dosing regimens, AUC(0-168h) during the first week was used. It is acknowledged that unbound AUCs appear in a similar range, see Table 2.1.3. Hence, from a non-clinical point of view the 60 mg dose can be considered relevant.

Secondary Pharmacology

An MDS Pharma secondary pharmacology screen of a range of receptors, enzymes and ion channels was presented (32 targets in total)). No targets were affected in any meaningful way. The selection of targets appears somewhat limited. In light of the vast range of adverse effects as presented in SmPC

section 4.8, e.g. hypertension, a justification of the limited selection of targets for the secondary pharmacology screen should be justified.

A much more thorough and targeted screening in the form of a kinase profiling was performed at Millipore testing 220 kinase targets. Only mTOR was inhibited. It appears that the intended targets of copanlisib, namely PI3K were not included in the screening, which could have been informative for comparison. An IC50 of 45 nM for mTOR is mentioned in 2.1.1.1 in Pharmacology written summary, however any reporting reference for this result could not be located. This should be clarified.

Safety Pharmacology

The safety pharmacology studies addressed the effects of copanlisib dihydrochloride salt (BAY 841236) on vital organ functions (central nervous system (CNS), cardiovascular system [including electrocardiogram (ECG)], respiratory system) as well as on supplemental organ systems (haematology and blood coagulation, gastrointestinal function, renal function, metabolism [glucose, lipids], platelet aggregation). The studies were designed according to the ICH S7A and ICH S7B guidelines *in vitro* and *in vivo* (rat, dog) using a single dose (for an overview of the studies, see the table below). With the exception of a few studies (of supportive nature that evaluated glucose homeostasis and platelet aggregation), all studies were conducted under the principles of good laboratory practice (GLP). Only the two *in vitro* studies (respectively showing no effect on hERG K+ current and decreased platelet aggregation) documented a large margin to the expected maximum exposures in human patients. In the key rat studies, the highest dose (in mg/kg) was approximately 10 times higher than the planned human dose – but in one of the studies where exposures were measured, it was found that this dose level only resulted in a maximum exposure in the same range as that found in human patients in the phase I trial (or lower if testing is done later than at the end of infusion). Similarly, in the dog study, the highest dose only resulted in a maximum exposure in the same range as that found in human patients in the phase I trial. If the free fraction in blood is approximately two times higher in rats and dogs than in healthy human volunteers (as has been found by the applicant in studies), the safety margin will be similarly improved. Uncertainties about the protein binding in cancer patients and whether the 14C-marked compound behaves as the unmarked compound (see section 3.2), however, weakens comparisons regarding protein binding. Two pivotal studies in rats and anaesthetised dogs documented lack of safety signals regarding the key parameters pulmonary function and QT interval (and other ECG findings). As mentioned above, the maximum exposures in those two studies were at a similar rather than clearly higher exposure than expected in human cancer patients. Also, in case of the dog study, current guidelines strongly recommend using un-anaesthetised, unrestrained animals instrumented for telemetry to properly study cardiovascular effects. However, in the case of copanlisib there is now a considerable knowledge about the side effect profile of the compound in human patients, as summarised in several recent reviews (Chauhan and Cheson, 2021; Le et al., 2021; Munoz et al., 2021) – all showing no safety signals relating to pulmonary function. As PI3kinase inhibitors can contribute to drug-induced QT prolongation and arrhythmias by increasing cardiac late sodium current, this effect may need a chronic exposure and thus, the QT prolongation might not be addressed appropriately during the pre-clinical testing. The applicant is asked to comment on this aspect.

Several findings were made at exposures within the range expected in human patients: vasoconstriction and hypertension, enhanced insulin and glucose levels, impaired glucose tolerance, reduced gastrointestinal motility, increased renal volume and electrolyte excretion, and CNS depressant effects. Some of these effects (hypertension, hyperinsulinaemia, hyperglycaemia) showed signs of a ceiling effect; can be explained by inhibition of PI3K dependent signalling pathways; and are well-known from the clinical setting. The CNS depressant (and most other) effects seen likely reflect severe hyperglycaemia, and has typically not been seen in humans where great focus has been paid on

avoiding severe hyperglycaemia. Such effects seen in rats at high doses included piloerection, ptosis, salivation, splayed limbs, backward walking, stereotypic chewing, hypoactivity, hypothermia, decreased nocifensive responsiveness, reduced muscle tone, and signs of mild haemoconcentration.

Study (GLP-status)	Brief description	Key findings	Exposure vs human Cmax* (dose/conc.)
PH-35657 (GLP)	In vitro, hERG K^+ current in HEK cells	None	Higher (10 µM)
PH-39082 (Non-GLP)	In vitro, platelet aggregation	Impaired platelet aggregation	Higher (IC_{50} = 1 µM)
A44104 (GLP)	Rat, pulmonary function (whole body plethysmography)	None	Similar§ (9 mg/kg)
A44114 (GLP)	Rat, motor coordination (rotarod)	Impaired coordination	Lower§ (1 mg/kg)
PH-35529 (Non-GLP)	Rat, oral glucose tolerance	Impaired glucose tolerance	Lower§ (0.345 mg/kg)
PH-35533 (Non-GLP)	Rat, metabolic parameters	Increased insulin, glucose and glucagon	Lower§ (0.35 mg/kg)
PH-35621 (GLP)	Rat, intestinal motility	Delayed intestinal transit	Lower§ (1.15 mg/kg)
PH-35752 (GLP)	Rat, renal function, hematology, metabolism	Polyuria, glucosuria, hemoconcentration	Lower§ (1.15 mg/kg)
PH-35753 (GLP)	Rat, convulsion threshold, hexobarbital anesthesia, nociception	Impaired nociception	Lower/similar§ (10.35 mg/kg)
PH-35754 (GLP)	Rat, blood glucose	Increased glucose concentration	Lower§ (1.15 mg/kg)
PH-35763 (GLP)	Rat, behavior, locomotion, body temperature	Affected behavior, locomotion and hypothermia	Lower (3.45 mg/kg)
PH-35749 (GLP)	Anesthetized dogs, cardiovascular and respiratory effects	Increased peripheral vascular resistance and blood pressure	Lower (0.159 mg/kg cumulative dose)
		No effects on QT-interval or pulmonary function	Similar (4.95 mg/kg cumulative dose)

* The expected human Cmax is based on cancer patients treated with 0.8 mg/kg in the phase I study. The animal exposures are either the highest exposure at which no findings were made or – if safety findings were made – the lowest exposure at which those findings were observed. Similar indicates that the maximum exposures (animals versus humans) are approximately the same; Lower indicates that the findings in the animals were made at exposures clearly lower than the expected human Cmax (i.e. within the range that will be seen with typical use); Higher indicates a markedly higher exposure than the expected maximum exposure in human patients. § Exposures estimated based on findings in study.

3.2.2. Pharmacokinetics

Pharmacokinetics of copanlisib was studied in five non-GLP *in vivo* studies in CD-1 mice, Wistar rats, Beagle dogs and Cynomolgus monkeys after a single i.v. administration of copanlisib or [14C]copanlisib.

The toxicokinetics of copanlisib in rat and Beagle dog after repeated administration were assessed from four pivotal toxicology studies carried out in accordance with Good Laboratory Practice (GLP) consistent with the ICH guideline S3A. The rat and Beagle dog were selected as the relevant test species in the pivotal toxicology studies.

Methods of analysis

Copanlisib and metabolite M-1 was labelled with 14C in the quinazoline moiety of the molecule and 3H in the central aromatic moiety of the molecule, respectively.

The HPLC-MS/MS method for quantitation of copanlisib in CD1 mouse, Wistar rat, Beagle dog and Cynomolgus monkey plasma was validated with regard to accuracy, precision, selectivity, recovery, matrix effect, dilution integrity, robustness/reproducibility (incurred sample reanalysis), lower limit of quantitation (LLOQ) and stability in a non-GLP study. The range for the determination of plasma concentrations was from 1.00 to 500 µg/L in all animal species. The LLOQ of the method was 1.00 µg/L, precision was ≤ 15% and accuracy ranged between 85 and 115%. It is unclear whether the validation method to support bioanalysis and toxicokinetics in the pivotal repeat-dose study was carried out according to the principles of GLP. It is stated in the report that the study was conducted to GLP however no GLP certificate, QA statement or GLP compliance statement was provided. The GLP status of the validation method should be clarified.

The validation of the liquid scintillation counting method to assess the radioactivity in body fluids, organs, tissues and in excreta should be provided.

Absorption

The study was a non-GLP pharmacokinetic study performed using company standard procedures. This is acceptable as no GLP compliance is required. The study design was generally acceptable, using an appropriate dose and sampling schedule (0, 2, 5, 15, 30 minutes and 1, 2, 3, 5, and 8 hours after dosing) – and a sufficiently validated method for analysis. Using a sample volume of 0.1 mL plasma, the lower limit of quantitation (LLOQ) of the assay was 1.0 µg/L, with a linear range between 1.0 and 500 µg/L and with an acceptable precision (1.7 - 2.9 %) and accuracy (95.2 - 99.4 %). Five hours post dosing, the plasma concentrations had already decreased to 0.5 % of the concentrations found 2 minutes post dosing, and at eight hours, the plasma concentrations were below LLOQ. The coefficients of variation were between 6 and 27 at all timepoints except the 5-hour one (where it was 53). The half-life estimate was based on five time points (30 minutes to 5 hours after dosing), and as the initial distribution phase - based on the PK curve – appeared to last approximately 1 to 2 hours, this was not optimal and likely resulted in a slightly underestimated half-life. No reporting was made of clinical observations in the mice.

The study was a non-GLP pharmacokinetic study performed using company standard procedures. This is acceptable as no GLP compliance is required. The study design was acceptable, although the low dose was too low to allow a clear separation between the distribution phase and the elimination phase. The infusion time and sampling schedule (0, 5, 15, 30 minutes and 1, 2, 4, 8, and 23 hours after ended infusion) were suitable – and a sufficiently validated method for analysis was used. Using a sample volume of 0.1 mL plasma, the lower limit of quantitation (LLOQ) of the assay was 1.0 µg/L, with a linear range between 1.0 and 500 µg/L and with an acceptable precision (2.5 - 4.6%) and accuracy (100.6 - 102.7%). With one exception, the coefficients of variation were between 2 and 26 at all timepoints in all 4 groups. In short, the study showed dose proportionality (except for a tendency to over-proportionality at the high dose), no influence of feeding status, a half-life of approximately 3.3 to 6 h, distribution of the compound into blood cells (with blood concentrations slightly more than double that of plasma concentrations), and increased blood glucose concentrations (at the 1 and 3 mg/kg doses). In two groups, the half-lives were calculated from only two (0.3 mg/kg) or three (1 mg/kg fed) points, which is not optimal. It appeared that the elimination of the 14C-marked compound (the two 1 mg/kg groups; half-lives 3.3 and 3.7 hours) was faster than that of the unmarked compound (the two other groups; half-lives 5.2 and 6 hours). In addition to a falsely low half-life estimate in those two groups, such a difference in elimination will result in an overestimation of the formation of metabolites.

However, as each group only contained 3 animals and as the estimates were based on few time points, firm conclusions on this cannot be made.

The study was a non-GLP pharmacokinetic study performed using company standard procedures. This is acceptable as no GLP compliance is required. In general, the study design was acceptable, although the low dose was too low to allow a clear separation between the initial distribution phase and the elimination phase prior to the concentrations dropping below the LLOQ. This likely resulted in an underestimation of the half-life in the two 0.2 mg/kg groups. The method used for analysis was sufficiently validated and had acceptable performance: Using a sample volume of 0.1 mL plasma, the lower limit of quantitation (LLOQ) of the assay was 1.0 µg/L, with a linear range between 1.0 and 500 µg/L and with an acceptable precision (1.7 - 5.2%) and accuracy (100.0 – 107.2%). With one exception (the 24-hour timepoint for the 0.2 mg/kg infusion group where one of the three concentrations was < LLOQ), the coefficients of variation were low at all timepoints in all 4 groups.

The study was a non-GLP pharmacokinetic study performed using company standard procedures. This is acceptable as no GLP compliance is required. In general, the study design was acceptable, although the dose was slightly too low to allow a clear separation between the initial distribution phase and the elimination phase prior to the concentrations dropping below the LLOQ. This likely resulted in a slight underestimation of the half-life. The method used for analysis was sufficiently validated and had acceptable performance: Using a sample volume of 0.1 mL plasma, the lower limit of quantitation (LLOQ) of the assay was 1.0 µg/L, with a linear range between 1.0 and 500 µg/L and with an acceptable precision (1.2 – 6.5%) and accuracy (96.0 – 105.2%). The coefficients of variation were generally quite high, ranging from 17 to 66 at the timepoints from end of infusion to 23 hours later (with values > 50 at 3 timepoints).

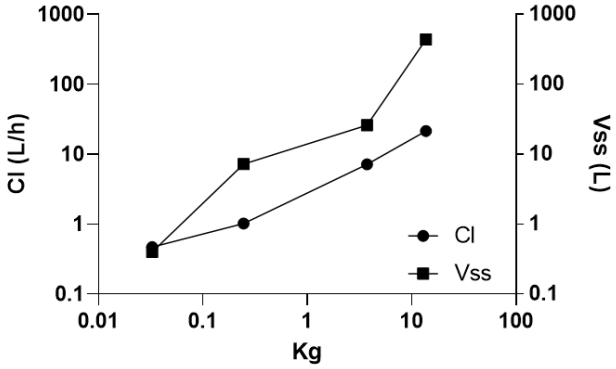
The study was a non-GLP pharmacokinetic study performed using company standard procedures. This is acceptable as no GLP compliance is required. The study design was acceptable, with a suitable dose level, suitable sampling points, and a sufficiently validated and well-performing method used for analysis: Using a sample volume of 0.1 mL plasma, the lower limit of quantitation (LLOQ) of the assay was 1.0 µg/L, with a linear range between 1.0 and 500 µg/L and with an acceptable precision (1.9 - 5.3%) and accuracy (92.9 – 102.5%). The coefficients of variation were low at all timepoints, with a maximum of 17 at the 24-hour timepoint. The half-life was slightly lower than that seen in dogs where the dogs were infused with unmarked copanlisib. This trend towards a higher elimination of 14C-marked copanlisib was also seen in the rat study.

Conclusions drawn by the applicant: *The pharmacokinetics of copanlisib were dose-proportional in rats and dogs at lower dose levels (0.3 and 1 mg/kg in rats and 0.2 and 1 mg/kg in dogs). There was a slight tendency to an over-proportional increase in the AUC (area under the plasma concentration vs. time curve from zero to infinity) after administration of 3 mg/kg to rats and 2 mg/kg to dogs. In rats and dogs, the Cmax (maximum drug concentration in plasma) increased proportionally with dose. In mice the plasma clearance was higher compared to rat, dog and monkey. In rats and dogs, the whole blood clearance was 2.8 L/(h·kg) and 0.74 L/(h·kg) and thus, 66 and 35% in relation to hepatic blood flow (blood clearance in the range of 30 - 70% in relation to hepatic blood flow considered as moderate. The volume of distribution was very high in all investigated species (Vss: 7 - 32 L/kg). Except in mice (t1/2: 1 hour), elimination of copanlsib occurred with moderate to long half-lives (t1/2: between 4 and 17 hours). There was obviously no influence of the feeding status on the pharmacokinetics of copanlisib or [14C]copanlisib radioactivity in rats. The elimination of total radioactivity (parent compound and radiolabeled metabolites) occurred in rat plasma with very similar half-lives as calculated for unchanged compound in comparable time intervals. The terminal elimination half-life of total radioactivity was 58 h in dog plasma and was determined in the time interval up to 120 h. This terminal elimination occurred at low plasma concentration levels of 3.5% or less related to*

maximum radioactivity concentrations. The half-life for the corresponding elimination phase for parent compound could not be calculated, because the plasma concentrations were below the LLOQ of 2.02 µg/L at time points later than 24 h after administration.

In the single dose pharmacokinetic studies conducted, an initial distribution phase lasting approximately 2 hours in mice, 3-5 hours in rats, and 5-9 hours in dogs and Cynomolgus monkeys was seen after dosing. Due to this, and the fact that the LLOQ was reached relatively fast after low doses, it was only the high doses in rats and dogs that showed an elimination phase with sufficient data points to allow a solid estimate of the elimination half-life. In the remaining cases, the calculations were either based on (too) few data points or partly on data from the final part of the distribution phase. This could explain some of the apparent non-linearity that was seen, and it could have resulted in a slight underestimation of the half-life in some cases, e.g. in the mouse. In the phase I study in humans, dose-proportionality was found in the range 0.1 to 1.2 mg/kg (Patnaik et al 2016).

The volume of distribution was high in all four species, and the clearance was also high – especially in the mouse. In the graph below, the mean Cl and Vss values from the four species are depicted relative to the mean body weight of the respective groups (using values from the high doses in rats and dogs to get the best estimates). From this, it appears that copanlisib scales with allometry – with an exponent around 1 for Vss and lower for Cl (around 0.65 in the graph). This implies that the half-life, which is a function of both, will be longer and longer with increasing bodyweight. In accordance with this, the half-life was found to be around 1 h in mice, 5-6 hours in rats and NHPs and 12-17 hours in dogs. In the phase I study in humans, the half-life was found to be 38.2 hours in 41 patients dosed with 0.8 mg/kg (Patnaik et al 2016).



It appeared that the 14C-marked compound was eliminated faster than the unmarked compound (especially in rats, but a tendency was also seen in dogs). In addition to a falsely low half-life estimate in those study groups, such a difference in elimination could result in an overestimation of the formation of metabolites. However, as each group only contained 3-4 animals and as the estimates were based on few time points, firm conclusions on this cannot be made. Total radioactivity was distributed into blood cells to a considerable extent in rats, with maximum concentrations in whole blood being 2.14-fold higher in whole blood than in plasma.

In conclusion, the plasma profiles showed an initial distribution phase lasting from 2 hours in mice to 5-9 hours in dogs. Overall, dose-proportionality was seen; and the minor deviations observed in that regard could be due to insufficient PK profiles being obtained at the lower doses. The volume of distribution was high in all species (7-32 L/kg) and the clearance was also generally high. Copanlisib appeared to scale with allometry (with an allometric scaling exponent around 1 for Vss and lower for Cl), implying that the half-life will be longer and longer with increasing bodyweight. In agreement with this, the half-life was around 1 hour in mice, 5-6 hours in rats and NHPs and 12-17 hours in dogs. Ingestion of food was found to have no influence on the data in rats and dogs. A tendency was seen

towards 14C-marked copanlisib being eliminated faster than unmarked copanlisib, which in theory could lead to a slight overestimation of the formation of metabolites. In rats and dogs, the high doses resulted in increased plasma glucose concentrations in the period from 1 hour and up to 9 hours (rat) and 24 hours (dog) after intravenous infusion.

Distribution

By means of equilibrium dialysis the extent of plasma protein binding of copanlisib was shown to be low in the various species with free fractions between 10 and 48% (15.8% in human plasma). Copanlisib was distributed from plasma into blood cells of rat, dog and humans to a considerable extent (CBlood/CPlasma: 2.06, 3.01 and 1.74, respectively). The free fractions (fu) of the metabolite M-1 ranged between 20 and 56% (20% in human plasma). There was no saturation of plasma protein binding of copanlisib and metabolite M-1 within the investigated pharmacological and toxicological relevant concentration range (about 100 - 10000 µg/L). The investigations on plasma protein binding and plasma/blood cell distribution of copanlisib and metabolite M-1 indicate that there is no risk for saturation of plasma protein binding and plasma/blood cell distribution with unexpected increases in the unbound copanlisib plasma concentrations even after administration of high doses exceeding the therapeutic range.

Organs and tissue distribution of radioactivity was investigated by quantitative whole-body autoradiography (radioluminography) after a single intravenous infusion (T= 1 hour) of 1 mg/kg body weight of [14C]copanlisib to male and female albino rats (Wistar) as well as to male pigmented rats (Long Evans). Radioactivity was distributed rapidly to organs and tissues following intravenous administration of 1 mg/kg [14C]copanlisib. The radioactivity concentrations were higher in the majority of organs and tissues in comparison with blood. Among others, high radioactivity concentrations were determined in the kidneys as well as in the lymphatic tissues including spleen, thymus and lymph nodes. The testes and the accessory genital glands (prostate, epididymides, seminal vesicles) contained higher radioactivity concentrations than blood. [14C]copanlisib radioactivity penetrated the blood brain barrier to a moderate extent (brain/blood AUC(0-24) ratio of 24%). The distribution patterns of radioactivity were virtually identical in both sexes. Radioactivity showed high affinity for melanin-bearing tissues including pigmented skin and eye wall after intravenous administration of [14C]copanlisib to the pigmented Long Evans rats.

Total radioactivity was progressively and regularly eliminated from the organs and tissues in rats. It was eliminated from blood (t1/2: 4.16 hours) and plasma (t1/2: 5.86 hours) with half-lives very similar to the parent compound (t1/2: 3.33 to 5.99 hours) in the time interval up to 9 or 24 hours after administration. Radioactivity elimination occurred continuously and was almost complete on Day 7. At this observation time point, the radioactive residues in the animal body (excluding the gastrointestinal tract) amounted to only 0.244% of the dose. Overall there was no evidence for retention of radioactivity in any of the organs and tissues investigated, with the exception of melanin-bearing tissues in pigmented rats, such as eye wall and skin. Therefore, the phototoxic potential of copanlisib dihydrochloride was assessed.

In rats, the radioactivity of [14C]copanlisib showed remarkable distribution into most organs and tissues with the exception of brain. The high radioactivity concentrations determined in the lymphatic tissues including spleen and lymph nodes might be indicative for high affinity of the compound to the potential pharmacological target organs and tissues.

Conclusions on the distribution pattern between sexes was based on only two female Wistar rats. In addition, organ and tissue distribution in pigmented rats did not include any female animals.

[14C]Copanlisib was administered at single intravenous infusions (T = 1 hour) to pregnant Wistar rats to investigate the distribution and elimination of radioactivity (parent compound and radioactive

metabolites) in maternal and fetal organs and tissues by means of quantitative whole-body autoradiography.

The radioactivity of [14C]copanlisib penetrated the placental barrier of rats to a low to moderate extent. At the end of the 1 hour infusion of [14C]copanlisib to pregnant rats less than 1% of the administered radioactivity was detected in the fetuses.

The distribution pattern of radioactivity in the dams was very similar to that in the nonpregnant rats. Most of the investigated maternal organs and tissues showed higher radioactivity concentrations than blood, with the exception of brain and amniotic fluid which were lower (20% of blood exposure). The radioactivity AUCs for amnion, mammary glands, uterus and ovaries were 12 - 30-fold higher than the maternal blood AUCs. The radioactivity concentrations in the placenta were 4-fold higher in comparison to maternal blood. Fetal organ and tissue radioactivity concentrations were lower than the concentrations in the analogous maternal organs, and tissues with the exception of brain. The elimination of the radioactivity from the fetuses occurred with a half-life of 19 hours.

The distribution in organs and tissues and the placental transfer of copanlisib was only investigated in the rat.

The non-GLP study report appeared to be dated and signed electronically however this should be documented.

Metabolism

In vitro biotransformation of copanlisib was investigated in liver microsomes and hepatocytes of different species including rat, dog, monkey, mouse, rabbit and man. Metabolite profiles were generated and metabolite structures elucidated using HPLC-14C-MS/MS analysis. [14C]Copanlisib was metabolised *in vitro* in all species investigated. Main metabolic pathways in liver microsomes and hepatocytes of all species, were reactions at the morpholine moiety, leading to several oxidation products, as well as dealkylation products. In this *in vitro* study no major human-specific metabolic pathways and no major species differences in the *in vitro* metabolism of [14C]copanlisib were found in all species investigated.

From a panel of 20 recombinant CYP isoforms, CYP1A1 and CYP3A4 most effectively catalysed the oxidative biotransformation of copanlisib under formation of M-3, M-4 and M-15. Based on the performed *in vitro* investigations and the liver abundances of CYP3A4 and CYP1A1 it was suggested that biotransformation of copanlisib was primarily mediated by CYP3A4 (> 90%) and to a minor extent by CYP1A1 (< 10%).

In vitro investigations revealed that enzymatic activities of major cytochrome P 450 (CYP) and uridine-diphosphate glucuronosyltransferase (UGT) isoforms as well as dihydropyrimidine dehydrogenase (DPD) were not affected in the presence of copanlisib (concentration required for < 50% inhibition: IC50: > 50 µM) or metabolite M-1 (IC50: > 20 µM).

Copanlisib and its metabolite M-1 showed no induction of CYP1A2 and CYP3A4 in the *in vitro* test system up to concentrations of 1111 µg/L corresponding to a human plasma concentration of about 6600 µg/L (13.7 µM) taking the differences in protein binding into account. Based on the *in vitro* data and the total plasma Cmax values of about 1 µM for copanlisib and < 0.2 µM for metabolite M-1 observed at the clinical 60 mg dose in patients, clinically relevant pharmacokinetic drug interactions with major CYP and UGT substrates as well as DPD substrates are unlikely. The study report appeared to be dated and signed electronically however this should be documented.

Following i.v. administration of [14C]copanlisib to mice, rats, dogs, and humans, copanlisib was the predominating component in plasma with > 84% of AUC of total radioactivity. The morpholinone derivative M-1 was the only relevant circulating metabolite in rat and human plasma. The ratio M-1/total radioactivity was about 10% in rat plasma and about 5% in human plasma. Consequently, metabolite M-1 is considered as a minor human plasma metabolite according to ICH guideline M3(R2) (2) because it contributes to less than 10% total systemic exposure. Metabolite M-1 was only occasionally present in mouse plasma, whereas in dog plasma besides copanlisib no circulating metabolites were observed.

A balanced excretion of unchanged drug and oxidative biotransformation products was observed in rats (about 40% and 60%, respectively) and humans (about 50% and 50%, respectively). In dogs, elimination of copanlisib was dominated by oxidative biotransformation (> 80%) and less pronounced by unchanged excretion (< 20%). Excreted metabolites were almost solely formed by dealkylation and/or oxidation at the alkylmorpholine side chain. In study only male or female animals were selected. A justification for not including both sexes in these studies should be provided.

Excretion

In rats, following a single intravenous administration of [14C]copanlisib radioactivity was excreted mainly via the biliary/fecal route after intravenous administration of [14C]copanlisib. The renal route contributed to the elimination with less than 10% of the administered radioactivity. The radioactivity recovered in the gastrointestinal tract and feces after intravenous administration to bile duct cannulated rats (in sum 26.9%) can be assigned to direct secretion in gastrointestinal tract. The radioactive residues in the animals excluding gastrointestinal tract amounted to 20.1% of dose at 24 hours after administration, but decreased continuously to less than 1% on Day 7.

In dogs, following a single intravenous administration of [14C]copanlisib at 1 mg/kg bw radioactivity was excreted mainly via the biliary/fecal route (74.7% of administered radioactivity) after intravenous administration of [14C]copanlisib. The renal route contributed to the elimination with about 10% of the administered radioactivity. The lower than expected recovery of radioactivity in the excreta was the result of incomplete collection of feces and moderate residual radioactivity in the animal body. On Day 16, the radioactive residues in the organs and tissues amounted to about 4.6% in relation to the administered radioactive dose as determined in one animal and were mainly located in the liver. Excretion of radioactivity was slower in humans compared to rats and dogs and reached a mean recovery of 85.9% (range 81.8 - 91.0%) until the end of the collection period (up to 20 - 34 days).

In lactating rats, following a single intravenous administration of [14C]copanlisib at 1 mg/kg bw radioactivity was secreted into the milk of lactating rats to a low extent. The estimated amount of radioactivity excreted with milk was 1.7% of dose within 32 hours after administration. It is not known whether copanlisib is excreted into human milk however it cannot be excluded based on the animal data.

The following Quality Statement for Non-GLP Studies was issued in the report: This pharmacokinetic study was conducted according to internal quality standards established in the department of Development Pharmacokinetics for non-GLP studies. This study was formally not performed according to GLP as GLP-regulations are not applicable to studies of this nature and no formal GLP compliance is required.

All routine activities conducted during the course of this study are detailed in Standard Operating Procedures. The study was performed according to the Study Protocol by experienced staff. The involved staff is trained regularly and the training records routinely archived.

Validated procedures (and systems) were used for data acquisition and data evaluation. The raw data of the study are stored in an archive with restricted and controlled access. The report and the corresponding raw data on animal experiments and associated analytics were subject to an independent review by experienced staff of Development Pharmacokinetics. It should be noted that the study was initiated at the end of October 2007 and the report was signed six years later.

Pharmacokinetic drug interactions

A battery of *in vitro* assays evaluating the potential effect of copanlisib and its minor metabolite M-1 on transporter test systems (substrate or inhibitor), UGT inhibition and CYP induction and inhibition was undertaken to determine the potential for drug interactions. The permeability of copanlisib was also assessed. Additionally, the effect of the unmarketed investigational anticancer drug refametinib on the oxidative metabolism of copanlisib was investigated *in vitro* and *in vivo*.

The effect of refametinib on the oxidative metabolism of copanlisib was investigated *in vitro*. Refametinib was shown to be an inhibitor of CYP3A4 *in vitro*, the major metabolizing enzyme of copanlisib. Refametinib had no influence on the turnover of copanlisib up to a concentration of 20 µM which exceeded maximum refametinib concentration (4 µM). In addition, there seemed to be no influence of refamtinib on the pharmacokinetics of copanlisib in mice *in vivo*. In conclusion, the risk for clinically relevant pharmacokinetic drug interaction between refametinib and copanlisib was considered to be low.
Comparison with historic data of reference compounds revealed copanlisib to be highly permeable according to the FDA guideline for the biowaiver classification system (BCS). Copanlisib was characterised as substrate of the efflux transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) substrate *in vitro* studies. Copanlisib was not a substrate of multidrug and toxin extrusion protein 1/2K (MATE1/MATE2K). No biliary efflux was detected within the investigated timeframe (30 min) in human sandwich-cultured hepatocytes.

P-gp (IC50: 7 µM and 7.6 µM for digoxin and dipyridamol, respectively) and breast cancer resistance protein (IC50: 11.5 µM for topotecan) mediated transport was inhibited by copanlisib *in vitro*. Metabolite M-1 very slightly inhibited the efflux of the P-gp probe substrate dipyridamole and the breast cancer resistance protein substrate topotecan, however IC50 values were not reached up to the maximal concentration tested (IC50: > 40 µM). No inhibition towards the efflux of P-gp probe substrate digoxin could be detected in the investigated concentration range up to 40 µM. Clinically relevant pharmacokinetic drug interactions due to inhibition of P-gp and BCRP were unlikely with respect to maximum metabolite M-1 plasma concentration of < 0.03 µM in clinical studies.

Furthermore, copanlisib was a potent inhibitor of MATE2K (IC50: 0.09 µM for metformin, 0.59 µM for MPP+) and an inhibitor of MATE1 (IC50: 10.8 µM for metformin). Copanlisib did not reveal inhibitory potency on MRP2 (multidrug resistance-associated protein 2) (IC50 > 30 µM) or BSEP (bile salt export pump) (up to concentrations of 10 µM), thus clinically relevant pharmacokinetic drug interactions with MRP2 or BSEP substrates are unlikely.

Copanlisib was neither a substrate for uptake transporters OCT1, OCT2, OCT3, OAT1 and OAT3 nor for OATP1B1 and OATP1B3. Consequently, the observed slight inhibition of hepatic uptake of copanlisib in hepatocytes with the known uptake inhibitors was caused by other mechanisms. Therefore, clinically relevant pharmacokinetic drug interactions of copanlisib with hepatic uptake inhibitors of the investigated transporters are unlikely.

The uptake transporters OATP1B1, OATP1B3, OAT1, OAT3, OCT1, and OCT2 were not inhibited by copanlisib. Thus, clinically relevant pharmacokinetic drug interactions due to inhibition of OATP1B1, OATP1B3, OAT1, OAT3, OCT1 and OCT2 by copanlisib are unlikely.

Based on the *in vitro* data and the plasma Cmax values of about 1 µM for copanlisib and < 0.2 µM for M-1 observed in patients receiving a 60 mg dose, clinically relevant pharmacokinetic drug interactions with P-gp, BCRP, MATE1, BSEP and MRP2 substrates as well as substrate of hepatic and renal uptake transporters are unlikely. Furthermore, no clinically relevant drug interaction was observed of copanlisib with metformin, a MATE2-K substrate. Therefore, it is accepted that the potential risk of interaction between copanlisib or the metabolite M-1 of copanlisib and other drugs is considered minimal.

Some study reports appeared to be dated and signed electronically however this should be documented.

Other pharmacokinetic studies

No other pharmacokinetic studies were conducted.

3.2.3. Toxicology

The non-clinical toxicology programme included studies to investigate the systemic toxicity of copanlisib after single and repeated administration, a pilot embryo-fetal developmental toxicity study, genotoxicity studies, and studies addressing specific questions including phototoxicity, toxicity of impurities and local tolerance.

The rat and Beagle dog were selected as the main test species in the pivotal toxicology studies for the evaluation of copanlisib, because they were expected to be responsive to the pharmacological mode of action which was confirmed in the pilot studies by the pattern of toxicity. Both species showed a human-like metabolite pattern *in vitro* in hepatocytes and adequate exposure after intravenous injection. Furthermore, both species are frequently used in toxicological testing so that extensive background data exist including intravenous infusion data. They are well established for testing of anti-cancer drugs.

The toxicology programme was conducted using either copanlisib lyophilisate drug product (repeated-dose toxicity studies, pilot embryo-fetal developmental toxicity study, and clinical studies) or copanlisib drug substance (single-dose toxicity and genetic toxicology studies). To mimic the intended clinical treatment regimen, intravenous infusions (1 hour) were administered on an intermittent schedule (once per week for 3 weeks plus 1 week off = 1 cycle, i.e. dosing on days 1, 8, and 15 of a 28-day cycle).

Single-dose toxicity

In the GLP rat single-dose toxicity study i.v. administration of copanlisib dihydrochloride induced clear signs of intolerance reactions in male and female rats, which were transient (occurrence within 1 hour after administration) at the low dose of 11.5 mg/kg (corresponding to 10.0 mg/kg copanlisib) and were not all reversible within the 3-week observation period at higher doses.

The LD_{50} of copanlisib dihydrochloride in male and female rats after a single i.v. administration is >23.0 mg/kg (corresponding to 20.0 mg/kg copanlisib). The minimal lethal dose tested was 34.5 mg/kg copanlisib dihydrochloride (corresponding to 30.0 mg/kg copanlisib). No toxicokinetic assessment was performed. The GLP certificate was missing in the study report and should be made available.

Repeat-dose toxicity

Repeat-dose toxicity studies were performed in rats and dogs.

Rats
In a GLP single-cycle (once weekly for 3 administrations (q1w x 3w) followed by a 4-week recovery) repeat-dose copanlisib was administered intravenously by 1-hour i.v. infusion to 11 male and 11 female Wistar [CRL:(WI) BR] rats per dose group at doses of 0, 0.6, 2, and 6 mg/kg. The highest dose level (6 mg/kg) was poorly tolerated, resulting in death of one female three days after the first treatment and early termination of two additional rats/sex in poor condition at the start of the second recovery week. Clinical observations in these animals included high stepping gait, multiple wounds attributed to grooming after harness removal, bloody muzzle, thin coat, and piloerection. Histologically, severe suppression of immune tissues (cellular depletion/atrophy) and bone marrow were observed in these animals.

Histological investigations of lymphoid tissues revealed cellular depletion, cellular necrosis, decreased mature haematopoietic cells and increased immature blood forming cells of the spleen in the rat. The bone marrow showed hypocellularity, myelofibrosis and increased myelopoiesis while the liver and adrenals showed secondarily, extra-medullary haematopoiesis and the spleen showed compensatory haematopoiesis at the end of the recovery period. Reversible effects on liver function and kidney function were demonstrated based on changes in clinical chemistry parameters and urinalysis parameters. Unspecific/secondary histopathological changes were seen in the liver that were fully reversible (hypertrophy and haematopoiesis) or still present in a few animals (reduced glycogen content and diffuse Kupffer cell activation) and in the kidneys that was fully reversible (increased basophilic tubules). Histological findings were seen in teeth (dentin alteration, pulp necrosis/degeneration etc.) and bone growth plates (thickening). Minimal to slight focal myocardial degeneration of the right ventricle was seen in some rats given 6 mg/kg/day. Morphological findings were seen in the female reproductive system (ovaries (haemorrhage, haemorrhagic cysts), uterus (atrophy), vagina (oestrus reduced) and the male reproductive system (testes (minimal giant cells/debris)/epididymides (spermatic debris), prostate (reduced secretion) and mammary gland (atrophy)) of rats.

Most histological findings were reversible or partially reversible by the end of the 4-week recovery period. Exceptions were the findings in teeth (dentin alteration, pulp necrosis/degeneration etc.) and bone (thickening femora-tibial growth plates, osteochondrosis) which worsened, heart (minimal to slight focal myocardial degeneration), testes (degeneration)/ epididymides (spermatic debris), and persisting signs of local intolerability at the infusion site. With regard to additional investigations, open field observations showed behavioural changes mainly at the dose levels that were poorly tolerated and included mortality. No NOAEL could be established.

In a GLP multi-cycle (3 cycles (females)/4 cycles (males) followed by an 8-week recovery period) repeat-dose copanlisib was administered intravenously by 1-hour i.v. infusion to 10 male and 10 female Wistar rats per dose group at doses of 0, 0.3, 1, and 3 mg/kg. Findings were generally consistent with those seen in the 1-cycle repeated-dose toxicity study in rats. Mortality was observed at the mid (1 mg/kg) and high dose (3 mg/kg), being more pronounced in females. In the animals that died, severe changes like inflammation, abscess formation, thrombi, thrombophlebitis and bacterial clusters along the course of the surgically implanted catheter were found. Thus, the cause of death in these animals was most likely ascending bacterial infection as consequence of the immunosuppressive effect of copanlisib in combination with the administration technique using permanently implanted catheter facilitating ascending infections. No supportive care, i.e. antibiotics, were used in the rat study.

Body weight development was clearly affected at all dose levels. Histological investigations of lymphoid tissues revealed cellular depletion, cellular necrosis, decreased mature haematopoietic cells and increased immature blood forming cells of the spleen. The bone marrow in the rat showed hypocellularity, myelofibrosis and increased myelopoiesis while the liver and adrenals showed secondarily, extra-medullary haematopoiesis and the spleen showed compensatory haematopoiesis in rats at the end of the recovery period. Reversible effects on liver function and kidney function were demonstrated in the rat based on changes in clinical chemistry parameters and urinalysis parameters. Unspecific/secondary histopathological changes in the rat were seen in the liver that were fully reversible (hypertrophy and haematopoiesis) or still present in a few animals (reduced glycogen content and diffuse Kupffer cell activation) and in the kidneys that was fully reversible (increased basophilic tubules). Histological findings were seen in teeth (dentin alteration, pulp necrosis/degeneration etc.) and bone growth plates (thickening) in rats but not in dogs. Minimal to slight focal myocardial degeneration of the right ventricle was seen in some rats given at 1 mg/kg/day and above. Morphological findings were seen in the male reproductive system (testes (degeneration germinal epithelium)/epididymides (spermatic debris), prostate (reduced secretion) and mammary gland (atrophy)] of rats. Unlike the 1-cycle rat study, effects on red blood cell parameters, bone and on the female genital system, with the exception of the vagina, were not seen in the longer-term multi-cycle rat study conducted over a lower dose range.

Body weight development affected at all dose levels was not reversible. Most histological findings were reversible or partially reversible in high dose rats within 8 weeks after cessation of treatment except the following findings: Reduced body weight development (not fully reversible), decreased serum potassium (females), decreased coagulation (males), blood in urine (n = 2/10 males), and increased popliteal lymph node weights (females). With regard to additional investigations, open field observations showed behavioural changes mainly at the dose levels that were poorly tolerated and included mortality. Immunotoxicity investigations in the context of the longer term, multi-cycle rat study showed decreased splenic cell and B-cell counts in males at 3.0 mg/kg and significantly reduced IgG antibody titre in both males and females at 1.0 and 3.0 mg/kg after the end of treatment that were reversible within the 8-week recovery period. Ophthalmological evaluations revealed no adverse ocular effects after repeated administration of copanlisib. No NOAEL could be established.

Effects on glucose homeostasis are an expected consequence of PI3K inhibition related to reduced tissue utilization of glucose and/or insulin resistance. Reversible effects of copanlisib on glucose homeostasis occurred in the rat after repeated dosing.

Dogs

In a GLP single-cycle (once weekly for 3 administrations (q1w x 3w) followed by a 2-week recovery) repeat-dose copanlisib was administered intravenously by 1 hour i.v. infusion to 3 male and 3 female Beagle dogs per dose group at doses of 0, 0.6, 2, and 6 mg/kg. Additional groups of male and female dogs (n = 3/sex/dose group) were similarly treated weekly for 3 weeks with 0, and 0.6 mg/kg copanlisib followed by a recovery period of 2 weeks. Copanlisib was generally well tolerated at all dose levels tested in the dog 1-cycle repeated-dose study despite comparable dose levels on a body surface area (mg/m2) basis (0, ~4, ~12 and ~40 mg/m2). The only clinical observation was blood admixture in the feces at the high dose (2 mg/kg).

Histological investigations of lymphoid tissues revealed cellular depletion in the spleen. Bone marrow myelopoiesis was activated after administration of 0.6 mg/kg and above. Atrophy of the fundic mucosa of the stomach was seen in male dogs given ≥0.6 mg/kg copanlisib. In the genital system, immaturity of the germinal epithelium of the testes was slightly higher in males at 0.70 mg/kg and above. Minimal degeneration was also observed in the dosed males (0.70 mg/kg) of the recovery group. The severity

score of prostatic immaturity was higher at 2.30 mg/kg. In females, the grade of uterine immaturity was increased at 2.30 mg/kg. The relevance of these mild changes in the male and female genital system remains debatable due to the young age of the animals being in puberty. Based on an extensive investigation of various heart localizations an effect of treatment with copanlisib dihydrochloride could not be detected.

Most histological findings in the dog 1-cycle repeated-dose toxicity studies were reversible or partially reversible by the end of the 2-week recovery period. No NOAEL could be established.

In a GLP multi-cycle (Once weekly for 16 weeks followed by a 4-week recovery period or once weekly for three weeks, followed by one week off dose) repeat-dose copanlisib was administered intravenously by 1-hour i.v. infusion to 3 male and 3 female Beagle dogs per dose group at doses of 0, 0.1, 0.3, 1/0.75 mg/kg. There were six decedents during the study, five given 1/0.75 mg/kg/hr/week with causes of morbidity and mortality related to treatment with copanlisib dihydrochloride. Findings in the lymphoid system (GALT, mandibular and mesenteric lymph nodes, spleen, thymus), testes and at the injection sites were similar to those seen at the terminal kill. Local findings which exceeded the MTD were observed at the administration site of dogs given 1.0/0.75 mg/kg once weekly or 1.0/0.75 mg/kg cyclically (once weekly for three weeks, followed by one week off dose).

On microscopic examination, there were findings in the lymphoid system (GALT, mandibular lymph node, mesenteric lymph node, spleen, thymus), testes and epididymides related to treatment with copanlisib. In the lymphoid system (GALT, mandibular and mesenteric lymph nodes), decreased germinal centre development was present in animals from all treated groups. Lymphoid atrophy was present in the mesenteric lymph node of one male given 0.1 mg/kg/hr/week and in the spleen of males given 0.1 or 0.3 and females given 0.3 or 1/0.75 mg/kg/hr/week. In the thymus, increased cellularity was present in males given 1/0.75 mg/kg/hr/week and females from both groups given 1/0.75 mg/kg/hr/week. In the testes, tubular atrophy was present in animals given copanlisib. In the epididymides, oligospermia was present in one male given 1/0.75 mg/kg/hr/week. Minimal or slight cellular debris was present in two males given 1/0.75 mg/kg/hr/week.

At the end of the 4-week treatment-free period findings were either completely or partially reversible following withdrawal of copanlisib. No NOAEL could be established and The Highest Non-Severely Toxic Dose of copanlisib was assessed to 0.3 mg/kg/hr/week.

Effects on glucose homeostasis are an expected consequence of PI3K inhibition related to reduced tissue utilization of glucose and/or insulin resistance. Reversible effects of copanlisib on glucose homeostasis occurred in dog after repeated dosing.

All pivotal repeat-dose studies were conducted to GLP according to the ICH guideline M3(R2) on Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals and the duration of the repeat-dose (multi-cycle/weekly) systemic toxicity studies (3 months) was in line with the expectation for an anti-cancer pharmaceutical for patients with advanced disease refractory to treatment as outlined in the ICH guideline S9 on Nonclinical Evaluation of Anticancer Pharmaceuticals.

Multiple toxicities were seen in the rat and dog repeat-dose toxicity studies based on in-life observations, clinical pathology and/or morphological evaluations. Both the rat and dog responded to the pharmacodynamics effect of copanlisib on glucose homeostasis. Target organs in the repeat-dose studies were the lymphoid and haematopoietic system, liver, kidneys, teeth, bone/femoro-tibial growth plates, heart, and male and female genital systems in the rat and the lymphoid and haematopoietic system, stomach (gastric mucosa) and male genital system in the dog. Effects were dose-dependent.

The spectrum of affected tissues, however, was greater in the rat compared to the dog suggesting that the rat is the more sensitive species.

No NOAEL in the rat and dog repeat-dose studies could be established due to clear adverse effects at all dose levels, that were not reversible within the recovery periods. This is accepted as NOAEL or NOEL are not considered essential to support clinical use of an anti-cancer pharmaceutical.

The blood volume collected at the toxicokinetic sampling was not specified in study report and should be provided.

The repeat-dose studies claimed GLP however discrepancies in that regard were noted:

- QA audits were limited with regard to toxicokinetic, bioanalytical, clinical pathology, pathology and determination of liver enzyme activities studies. Furthermore, the GLP compliance statement was signed several months prior to the QA statement.
- QA audits were limited with regard to toxicokinetic, bioanalytical, clinical pathology, pathology and immunotoxicity investigation studies.
- QA audits were limited with regard toxicokinetic, bioanalytical, clinical pathology, pathology, determination of liver enzyme activities and analytical data of stability and content checks of test substance formulations studies.
- The bioanalytical and toxicokinetic phase reports appeared to be dated and signed electronically. QA audits were limited with regard to toxicokinetic, bioanalytical, determination of glycosylated haemoglobin (Hb Ale), acetoacetic acid (acetoacetate), and D-(-)-3-hydroxybutyric acid (D-(-)-3-hydroxybutyrate) and pathology peer-review studies.

As stated in ICH guideline M3(R2) pivotal studies in the non-clinical setting should be conducted according to the Principles of GLP to ensure uniformity, consistency, reliability, reproducibility, quality, and integrity of data. QA audits in non-clinical studies are necessary to monitor GLP compliance and if these are limited it could result in a study being downgraded from GLP to non-GLP. Therefore, it should be clarified and documented whether the pivotal repeat-dose studies were sufficiently subjected to QA audits in order to be GLP compliant.

Toxicokinetics from the repeat-dose (1 cycle) in rats demonstrated that there were no evidence of sex-related differences in exposure (AUC(0-24) and Cmax) after the treatment 3 as well as in plasma concentrations after treatment 1 and 2. After the 3rd treatment AUC(0-24) and Cmax of copanlisib increased almost proportionally with increase of dose. Overall, the mean exposure was not changed after repeated dosing in all dose groups considering the general high variability within rat infusion studies. Toxicokinetic data from the repeat-dose (multi-cycle) in rats showed there was no evidence of sex-related differences in exposure while AUC(0-24) and Cmax increased dose-proportionally from mid to high dose in females exposure from low to mid dose increased considerably more than dose proportionally. In males a considerable higher than dose-proportional increase in exposure was observed at all dose levels. For all dose groups exposure (AUC(0-24) and Cmax) appeared considerably increased after multiple dosing. Copanlisib was previously shown to concentrate in erythrocytes to higher concentrations than in plasma. The observed haemolysis of plasma samples in the multi cycle rat study might hence have impacted the determination of systemic exposure in this study.

Toxicokinetics

Toxicokinetic data from the repeat-dose (1 cycle) in Beagle dogs determined that there were no gender differences. Exposure [AUC(0-24) and Cmax] to copanlisib increased almost dose-proportionally with increased dose. No significantly changes in mean exposure was seen after repeated administration in any dose group. After the repeat-dose (weekly and multi-cycle) in Beagle dogs there was no evidence

of sex-related differences in exposure. AUC(0-tlast) and Cmax increased proportionally with increase of dose from 0.1 to 1 mg/kg after multiple infusions on Day 99/Day 43. The mean exposure in terms of AUC(0-tlast) and Cmax was not changed after repeated dosing in the 0.1 and 0.3 mg/kg dose groups. In general, toxicokinetic data from the repeat-dose studies in rats and dogs showed that there were no sex-related differences in exposure (AUC(0-24) and Cmax) which increased in an almost dose-proportionally manner. No significantly changes in mean exposure was seen after repeated administration in the dose groups except for the multi-cycle study in rats.

Margins of exposure

Margins of exposure were addressed in a comparison table comparing exposure (C_{max} and AUC) for the pivotal single-cycle and multiple-cycle (also weekly in the dog) rodent and non-rodent toxicity studies with human exposure in cancer patients at the recommended 60 mg dose copanlisib using the population pharmacokinetic model developed for data of clinical study Nos 16349 and 16270A.

For copanlisib, the average maximum plasma concentrations (C_{max}) and the exposure (AUC(0-t_n)) achieved in rats at the highest dose, 6 mg/kg, were approximately 1.2-fold (C_{max}) and approximately 0.7-fold (AUC(0-t_n)), or when corrected for protein binding, approximately 2.7-fold ($C_{max,u}$) and approximately 1.5-fold (AUC(0-$t_{n,u}$) compared to the respective values in cancer patients after a single dose of 60 mg copanlisib. The C_{max} and AUC values at the highest non-severely toxic dose level (HNSTD) in dogs of 2 mg/kg were approximately 0.3-fold, or when corrected for protein binding, approximately 0.8-fold, respectively, compared to the human exposure values.

The doses given in the repeat-dose studies (single- and multiple-cycles) resulted in plasma exposures (maximum plasma concentration and AUC) that were below or in the range of those observed in adult humans in particular for the dog. However, this can be supported as copanlisib is indicated for the treatment of patients with advanced cancer. In addition, more information from the literature is now available on the safety of copanlisib in human patients (Chauhan and Cheson, 2021, Le et al., 2021 and Munoz et al., 2021[1]).

Genotoxicity

The assessment of genotoxic potential of copanlisib was carried out in accordance with the ICH guideline S2(R1) Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use. Copanlisib was studied with respect to gene mutations in bacteria and mammalian cells and chromosomal aberrations *in vivo*. Neither the two *in vitro* tests nor the *in vivo* micronucleus test gave any indication for a mutagenic potential. In conclusion, copanlisib is not considered to be genotoxic which is endorsed.

Carcinogenicity

According to the ICH guideline S9 on Nonclinical Evaluation for Anticancer Pharmaceuticals carcinogenicity studies are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer and thus the omission of carcinogenicity studies can be accepted, as the sought indication is indeed regarding advanced cancer therapy.

Reproductive and developmental toxicity

[1] Chauhan and Cheson. 2021. Copanlisib in the Treatment of Relapsed Follicular Lymphoma: Utility and Experience from the Clinic. Cancer Management and Research. Volume 13: 677-692. Le et al. 2021. Update on the Role of Copanlisib in Hematologic Malignancies. Therapeutic Advances in Hematology. Volume 12: 1-10. Munoz et al. 2021. Copanlisib for the Treatment of Malignant Lymphoma: Clinical Experience and Future Perspectives. Targeted Oncology. Volume 16: 295-308.

No dedicated GLP compliant reproductive toxicity studies were conducted. However, results of repeat-dose toxicity GLP studies revealed adverse effects of copanlisib on male and female reproductive organs in rats and on male reproductive organs in dogs. Embryo-fetal development were assessed in a non-GLP pilot embryo-fetal developmental toxicity study conducted in rats with i.v. bolus administration of copanlisib. Due to severe post implantation loss, and developmental toxicity, including embryo-fetal toxicity and teratogenicity, observed in this rat study, no further studies on developmental toxicity were performed in accordance with ICH guideline S5(R3) on Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals.

Fertility and early embryonic development

No dedicated studies of copanlisib on fertility and early embryonic development were conducted. However, results of repeat dose toxicity studies revealed adverse effects of copanlisib on male and female reproductive organs in rats and on male reproductive organs in dogs.

Adverse effects on male and female reproduction, including a potential effect on fertility, are expected based on morphological findings in the testes, epididymides, prostate and male mammary gland and in the ovaries, uterus and vagina after repeated dosing in the rat toxicity studies and in the testes and epididymides in the longer-term dog toxicity study conducted in adult dogs. In pregnant rats, the radioactivity of [14C]copanlisib penetrated the placental barrier to a low to moderate extent with lower concentrations in the fetuses than in the analogous maternal organs and tissues (exception of brain).

As copanlisib is intended for the use in patients with advanced cancer refractory to treatment the omission of fertility and early embryonic development studies is in accordance with ICH guideline S9 on Nonclinical Evaluation for Anticancer Pharmaceuticals and this is endorsed.

Embryo-fetal development

In a non-GLP rat pilot embryo-fetal developmental toxicity study, maternal toxicity of increasing severity and severe post implantation loss was seen in animals given 0.75 and 3 mg/kg copanlisib. No toxicokinetic evaluation was performed.

The original dose levels of this study, 0.17 mg/kg and 0.69 mg/kg copanlisib dihydrochloride, corresponding to 0.15 mg/kg and 0.6 mg/kg copanlisib were selected based on the results of a previous dose toleration study in rats with copanlisib dihydrochloride with doses of 1.15 mg/kg and 2.3 mg/kg copanlisib dihydrochloride, corresponding to 1 mg/kg and 2 mg/kg copanlisib, which resulted in death (at the 2 mg/kg level), severe signs of maternal toxicity, and total resorptions. Due to an accidental dilution error of the lyophilizate, the doses of 0.86 mg/kg and 3.45 mg/kg copanlisib dihydrochloride, corresponding to 0.75 mg/kg and 3.0 mg/kg copanlisib were administered in this study. This error did not limit the assessment of the results, because the reproductive toxicological endpoints of the study were reached.

Total loss of pregnancy (100% resorption of litter) was observed at the lowest dose tested, 0.75 mg/kg (4.5 mg/m2 body surface; approximately 12% of the recommended human dose, based on body surface area). No females with viable fetuses were evident at the 3 mg/kg dose level. Daily administration of copanlisib during organogenesis in this study resulted in findings of decreased placental weights, decreased number of live fetuses and severely decreased fetal body weights at the 0.75 mg/kg dose level. An increased incidence of fetal external and visceral deviations (mainly shortened umbilical cord, domed head, and flat eye rudiment), and skeletal deviations (retarded ossification at many localizations, increased incidences of fused sternebrae, wavy ribs, 14th ribs, and enlarged fontanelle) and of malformations (mainly hydrocephalus internus, malformations of eyes, heart, major vessels, and skeletal system) were observed at 0.75 mg/kg (4.5 mg/m2 body surface; approximately 12% of the recommended human dose, based on body surface area). No NOAEL was

established as developmental toxicity, including embryo-fetal toxicity and teratogenicity, was seen beginning at the lowest dose tested, 0.75 mg/kg/day copanlisib.

As already described and based on the mechanism of action of copanlisib and its effects on rapidly dividing tissues, adverse effects on development and reproduction are expected. Due to severe post implantation loss, and developmental toxicity, including embryo-fetal toxicity and teratogenicity, observed in the rat pilot embryo-fetal developmental toxicity study, no further studies on developmental toxicity are required according to the ICH guideline S5(R3) on Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals.

Prenatal and postnatal development, including maternal function

In accordance with ICH guideline S9 on Nonclinical Evaluation for Anticancer Pharmaceuticals no dedicated studies of copanlisib on prenatal and postnatal development were conducted and this is endorsed.

Juvenile toxicity

The omission of juvenile animal studies is acceptable since the current indication for copanlisib is for treatment in adults.

Local tolerance

Two GLP and one non-GLP rabbit local tolerance studies were conducted. Local tolerance was also assessed in the repeat-dose studies.

The single intravenous administration of 10 mL of a formulation containing 1.152 mg/mL copanlisib dihydrochloride (infused over 1 hour) into the ear veins of rabbits was associated with slight swelling up to day 4 and slight to moderate reddening at the injection site and of the surrounding tissue up to day 8 which are considered as slight intolerance reaction. Histological examination revealed no compound-related effects. A single paravenous administration of 1.0 mL of the test article caused signs of slight to moderate local irritation at the injection sites in form of slight reddening and swelling and a slight to moderate inflammatory reaction in the subcutaneous and muscular tissues, which were not fully reversible within 8 days. On the basis of these results no severe or irreversible effects are expected in humans after intravenous injection. Paravenous injection is likely to cause slight to moderate transient local reactions, irreversible effects are not expected.

The single intravenous infusion of copanlisib dihydrochloride into the uncongested ear vein was tolerated with minor signs of local irritation. The findings after a single paravenous administration of 1 ml of the test article in rabbits were classified as moderate irritations in all. However, these results indicate that accurate intravenous injection of copanlisib dihydrochloride in humans is necessary to prevent possible local incompatibility reactions due to inadvertent paravenous administration.

A single intravenous administration of 0.5 mL of a formulation containing 1.0 mg/mL copanlisib into the uncongested vein of the ear was tolerated with only slight local irritationat the administration area. On the basis of these results no severe or irreversible effects are expected in humans after intravenous infusion. A single paravenous administration of 1.0 mL of a formulation containing 1.0 mg/mL copanlisib caused signs of mild to moderate local irritation at the injection sites in form of inflammatory infiltrates slight necrosis of muscle fibres (single animal). On the basis of these results no severe or irreversible effects are expected in humans after accidental paravenous injection.

Local tolerance was also assessed in the rat and dog 1-cycle repeat dose i.v. infusion studies using reconstituted drug product diluted with 5% mannitol; pH was maintained at 3.9. There was some evidence of local inflammatory responses along the course of the surgically implanted catheter used for i.v. infusion in rats. The no observed effect level (NOEL) was 2 mg/kg copanlisib in the rat and 0.6

mg/kg copanlisib in the dog. Local tolerance was assessed in the multi cycle rat repeat-dose i.v. infusion study using reconstituted drug product diluted with 0.9% NaCl; the pH was maintained at 3.9. Due to the immunosuppressive effects of the test item, local tolerance along the course of the surgically implanted catheter was reduced in mid and high dose rats. This was partially reversible during the recovery period. In the longer term, weekly and multi-cycle dog repeat-dose i.v. infusion study local findings which exceeded the MTD were observed at the administration site of animals given the high dose of 1.0/0.75 mg/kg/hr/week or 1.0/0.75 mg/kg/hr week cyclically.

In conclusion, accurate intravenous infusion in humans is necessary to prevent possible local incompatibility reactions due to inadvertent paravenous injection. As the clinical route of administration is i.v. the evaluation of local tolerance is considered sufficient and no further studies are required.

Other toxicity studies

Antigenicity

No studies on antigenicity were performed as copanlisib is a non-peptigenic chemical of low molecular weight. This is acceptable, as the risk of anti-drug antibodies formation in patients is considered to be low.

Immunotoxicity

No specific immunotoxicity studies were performed. Findings of immunosuppression resulting in an increased infection rate in repeat-dose studies in rats was further addressed in the multi-cycle rat toxicity study. Immunotoxicological investigations showed decreased splenic cell and B-cell counts in males at 3.0 mg/kg and significantly reduced IgG antibody titre in both males and females at 1.0 and 3.0 mg/kg after the end of treatment that were reversible within the 8-week recovery period.

The approach above is consistent with the ICH guideline S9 on Nonclinical Evaluation for Anticancer Pharmaceuticals where the design components of the general toxicology studies are considered sufficient to evaluate immunotoxic potential.

Dependence

Central nervous depressant effects occurred at high drug plasma concentrations in safety pharmacology studies and were considered secondary to hyperglycaemia. In the single-cycle and multi-cycle rat toxicity studies, clinical examinations and open field observations showed behavioural changes mainly at the dose levels that were poorly tolerated and included mortality. No effects were observed on reflexes in the single-cycle dog toxicity study or in the longer-term dog toxicity study with intermittent dosing regimens of once a week continuously or on a cyclical basis (multi-cycle high dose arm).

It is accepted that no dependency studies were performed.

Metabolites

It is supported that no toxicological studies with copanlisib metabolite dosing were performed.

Studies on impurities

No specific studies for characterization of impurities with regard to systemic toxicity were performed. Two degradation products without structural alert in (Q)SAR, AETQP and 7-hydroxyquinazolinpyramide, are proposed specified above limit of qualification for active substance (ICH Q3A), but below threshold of qualification for drug product (ICH guideline Q3B). Based on the level of AETQP present in copanlisib batches used in toxicity studies, the proposed limit of 0.5% in drug substance is considered toxicologically qualified. 7-hydroxyquinazolinpyramide has not been present in the batches used in

toxicity studies. However, considering the intended patient population, and that 7-hydroxyquinazolinpyramide is limited to below threshold for qualification in the drug product (0.5%), the lack of qualification data for the proposed limit in the drug substance is considered acceptable.

Genotoxic impurities present in the starting materials are 4-(3-chloropropyl)morpholine hydrochloride, 6-nitrovanillin and benzyl-6-nitrovanillin. The impurities are proposed limited to NMT 0.10% in drug substance and NMT 0.20% in drug product (under 'Any unspecified impurities'), above TTC. According to ICH M7(R3), the TTC concept is not considered applicable for drug substances and drug products intended for advanced cancer indications as defined in the scope of ICH guideline S9. In these cases, genotoxic impurities could be controlled at acceptable levels for non-genotoxic impurities, i.e. in accordance with ICH guidelines Q3A and Q3B. Thus, since ICH guideline S9 is applicable for the indications sought, the proposed limits are acceptable from a non-clinical point of view.

To support the characterization of the three starting materials in the synthesis of copanlisib dihydrochloride, the mutagenic potential of the three starting materials - BIB-pyrimidinamine, 4-(3-chloropropyl)morpholine hydrochloride and 2-aminopyrimidine-5-carboxylic acid - used in the synthesis of copanlisib dihydrochloride and of nitrosubstituted aromatic precursors of BIB-pyrimidinamine - benzylnitrovanillin and nitrobenzylimidazoline and the corresponding isomers carrying the nitro group in the 6-position - was evaluated.

BIB-pyrimidinamine was non-mutagenic in a GLP Ames test. 4-(3-chloropropyl)morpholine hydrochloride was mutagenic in GLP Ames test. An in silico assessment of 2-aminopyrimidine-5-carboxylic acid revealed no structural alert for mutagenicity. 6-nitrovanillin and benzyl-6-nitrovanillin were mutagenic in mini Ames screening in all strains tested. On this basis no full GLP Ames test was conducted with either compound. Benzyl-2-nitrovanillin and 6-nitrobenzylimidazolin were mutagenic in GLP Ames tests. Nitrobenzylimidazoline, the last nitroaromatic intermediate in the synthesis chain for BIB-pyrimidinamine was non-mutagenic. In silico assessment of 2-nitrovanillin revealed no structural alert for mutagenicity. No full GLP Ames test was conducted with this compound.

The control strategy for the genotoxic impurities is in line with the ICH guideline M7 on Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, which states that the Threshold of Toxicological Concern concept is clearly not directly applicable in the case of a drug substance and drug product intended for advanced cancer indications as defined in the scope of ICH guideline S9, which is relevant for copanlisib. In this case impurities could be controlled at acceptable levels for non-mutagenic impurities. In consequence the risk calculations in the course of the synthesis of copanlisib were based on an acceptable limit of max. 0.10%, as this is the identification threshold for organic impurities in the ICH guideline Q3A on Impurities in New Drug Substances.

The QA statement and GLP statement of compliance of study report appeared to be dated and signed electronically however this should be documented.

Other studies

Phototoxicty

Due to light absorption in the UV range, the molar extinction coefficient of absorption and tissue distribution, the phototoxic potential of copanlisib dihydrochloride was assessed in the *in vitro* 3T3 Neutral Red Uptake phototoxicity test according to the ICH guideline S10 on Photosafety Evaluation of Pharmaceuticals.

The phototoxic potential of copanlisib dihydrochloride was investigated *in vitro* in mouse fibroblasts (Balb/c 3T3.A31) over a range of concentrations from 0.001 µg/mL to 30 µg/mL in the absence or presence of UV irradiation. Three independent assays with copanlisib dihydrochloride yielded an

average PIF = 0.8. Photo Irritation Factor ≤ 2 predicts "no phototoxicity". Copanlisib dihydrochloride was thus identified as a non-phototoxic compound in the *in vitro* 3T3 NRU phototoxicity test and therefore no direct phototoxicity is anticipated in humans which is endorsed. The concentration range used in the *in vitro* photoxicity test should be justified. More specifically, the high affinity to and retention of copanlisib in pigment-containing tissues demonstrated in rat should be considered and discussed in relation to tested concentration range.

In addition, the GLP statement of compliance and QA statement appeared to be signed electronically however this should be documented.

Haemolytic potential

The haemolytic potential of a test formulation of copanlisib was assessed based on the grade of haemolysis prior to the start of the repeat-dose toxicity studies. Whole blood was drawn from a healthy volunteer with K-EDTA monovettes from the *vena cephalica antebrachii*. The amount of free haemoglobin after the incubations with the test formulations, undiluted and in dilutions of 1:2, 1:10, corresponded to haemoglobin contents in the range of negative control values. Therefore, the hemolysis potential of the test formulation of copanlisib (1 mg/mL) in 5% Mannitol can be considered to be low.

In general, section 4.6 and 5.3 of the SmPC is very elaborate and should be revised and updated according to the guideline on SmPC: *A guideline on Summary of product characteristics (SmPC)* from September 2009. Exact dosing details in mg/kg should be avoided. Section 4.6: In the section on women of childbearing potential, the duration of use of contraception must be justified. For breastfeeding, a contraindication should be considered, in view of the toxic nature of the drug, which is also common for kinase inhibitors in general.

3.2.4. Ecotoxicity/environmental risk assessment

An Environmental Risk Assessment was submitted as part of a market authorization application for Aliqopa (copanlisib), 60 mg (administered as a single agent on an intermittent basis i.v. over 1 hour on Days 1, 8, and 15 of a 28-day cycle, on an intermittent dosing schedule) and followed the CHMP guidance EMEA/CHMP/SWP/4447/00 entitled; "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" published 01 June 2006.

Phase I

Copanlisib is an ionisable compound and log D_{OW} values as a function of pH covering an environmentally relevant pH-range ranging from pH 4 to 9 were determined (pH 4 log P_{OW} = < -4.0, pH 7 log P_{OW} = 1.37 and pH 9 log P_{OW} = 1.44). The flask-shaking method was used to determine the partition coefficient of copanlisib at pH 4. Copanlisib was partitioned between n-octanol and aqueous buffer solutions. The copanlisib concentration in each phase after equilibration was determined by HPLC. At pH 7 and pH 9, no experimental determination was possible due to the very low water solubility at these pH values. Therefore, the partition coefficients were calculated from the ratio of the solubilities in n-octanol and in the corresponding buffer solutions.

The log D_{OW} of copanlisib at pH 7 was lower than 4.5 therefore, it is not to be further screened for persistence, bioaccumulation and toxicity. However, it was noted that this value was calculated from the ratio of the solubility in n-octanol and in the corresponding buffer solution due to low water

solubility. In addition, the determination of the log D_{OW} values was not conducted at three pH values ranging from pH 5 to 9 but from 4 to 9. This deviation should be justified.

The PEC_{SW} of copanlisib was estimated to 0.032 µg/L above the action limit of 0.01 µg/L thus the compound was further assessed in environmental fate and ecotoxicological effects studies.

Phase II Tier A

Environmental fate

Adsorption/desorption using a batch equilibrium method (OECD 106) determined that dissolved copanlisib can be expected to partly adsorb to the sewage sludge in sewage treatment operations due to a log K_{OC} value of up to 3.96 in sewage sludge. Furthermore, a log K_{OC} value of up to 6.39 in soils indicated a high binding of copanlisib to terrestrial soils.

The biodegradability of copanlisib in the manometric respiration test (OECD 301) demonstrated that the compound was not readily biodegradable (no degradation occurred after 28 days) therefore a study on transformation in aquatic/sediment systems had to be performed.

A test of aerobic and anaerobic transformation in aquatic sediment systems (OECD 308) indicated that copanlisib is primarily distributed to the sediment compartment and not degraded. As a consequence of the aquatic-sediment test, a sediment toxicity test was performed in Tier B. Since the octanol/water partition coefficient indicates a no relevant bioaccumulation potential, i.e. K_{OW} <1000, no study on bioaccumulation in fish had to be performed in Tier B. Because the adsorption coefficient K_{OC} was >10000, terrestrial studies had to be performed in Tier B. The study does not fulfil the quality criteria according to OECD TG 308 because the mass balance of 90% has not been achieved and temperature and organic carbon content exceeded the maximum permissible values. Furthermore, results as described in Q 9 iii of EMA/CHMP/SWP/44609/2010 Rev. 1 were not available because of limited extraction efficiency. The selection of a suitable extraction method is not presented in a comprehensible way. A higher extraction efficiency was shown for 0,1M Na OH solution, but was not carried out for all samples or considered in the evaluation. Finally, no DT50 values for water, sediments and whole systems were derived.

The conclusion that "copanlisib is irreversibly bound to the non-extractable fraction (no quantification or qualification were conducted) and not degradable" does not appear to be scientifically justified in view of the considerable deficiencies in the study design.

The applicant is asked for the conduction of a new study according to OECD 308 using the proposed extraction scheme by Löffler/ Ternes et al. (2020) or other extractions schemes with harsh steps (e.g. Schäffer et al., 2018).

References:
Loeffler, D., Hatz, A., Albrecht, D., Marvin, F., Hogeback, J., Ternes, T.A., 2020. Determination of non-extractable residues in soils: Towards a standardised approach. Environmental Pollution 259, 113826.
Schaeffer, A., Kästner, M., Trapp, S., 2018. A unified approach for including non-extractable residues (NER) of chemicals and pesticides in the assessment of persistence. J. Environ. Sci. Eur

Environmental effects analysis

Green algae showed no effect on growth up to the solubility limit of copanlisib (0.4 mg/L at pH 7.7 to 8) (OECD 201), while activated sludge from a municipal sewage treatment plant was not inhibited in the respiration activity when incubated at nominal loading of 100 mg/L (limit test), which was much higher than the solubility limit (OECD 209). In the test over 21 days, on reproduction with Daphnia magna the NOEC for reproduction (number of off-spring) was 1.3 µg/L, the LOEC was 3.6 µg/L in the

reproduction test (OECD 211). The chronic toxicity in fish showed that copanlisib has effects on survival of fish (fathead minnow) at concentrations from 3.53 µg/L onwards. Thus, the overall no observed effect concentration (NOEC) was 1.19 µg/L, the lowest observable effect concentration (LOEC) was 3.53 µg/L (OECD 210). The assessor does not agree with the conclusion on OECD 210: an overall NOEC (according to the study protocol) of 0.3 µg/L is reported (survival of fry); however, in the ERA 1.19 µg/L (survival at day 29pf) is used for PNEC derivation. A risk for surface water arises by using a PNEC of 0.03 µg/L in Phase II Tier A. The applicant is asked to revise the risk assessment for surface water by considering 0.3 µg/l for PNEC derivation.

Furthermore, in recent applications the current OECD guidelines should be used. The OECD 210 was updated in 2013. The study plan should have been followed this updated version. The study shows deficiencies masking a potential growth effect. According to the actual OECD guideline, a minimum of 18 mm length in control fish for the species used, fathead minnow is recommended. Instead the control fish in this test do not exceed 11 mm, which clearly would mask potential exposure related growth effects. This effect was fortified in this study, due to the high mortality in the two highest concentration, where less fish had more space and access to food. Consequently, these fish displayed a better growth rate and grew faster than the control fish. These effects, too small control fish and less fish in the highest exposure concentration clearly mask a potential growth effect, the only sublethal endpoint in this test. As a risk is identified and for animal welfare reasons, the applicant is not asked to conduct a new test.

The $PEC_{SURFACEWATER}/PNEC_{WATER}$ ratio for surface water was determined to 0.2 indicating that copanlisib is unlikely to represent a risk to the aquatic environment. The $PEC_{GROUNDWATER}/PNEC_{GROUNDWATER}$ was assessed to 0.06 indicating that it is unlikely that copanlisib represents a risk to groundwater. The $PEC_{SURFACEWATER}/PNEC_{MINCROORGANISMS}$ ratio was calculated as (0.0032 x 10) µg/L / 4.4µg/L = 0.007, indicating no risk for the waste water treatment plant.

Phase II Tier B

Extended effects analysis

The study on sediment toxicity of copanlisib was performed on the midge larvae Chironomus riparius according to the guideline OECD 218 and the NOEC for copanlisib was determined to ≥100 mg/kg. The NOEC based on standard sediment was determined to ≥666 mg/kg and the $PEC_{SEDIMENT}$ to =920.74 µg/kg and based on calculations no risk for sediment was assumed. The calculation of $PEC_{SEDIMENT}$ from the equation is not fully understood and should be clarified.

Terrestrial environmental fate and effects analysis

A base set of tests investigating biodegradation in soil, toxicity to soil invertebrates and acute effects on terrestrial plants and microorganisms was conducted.

The acute earthworm test was conducted according to the guideline OECD 207 and the NOEC was determined to be ≥1000 mg/kg. The effects of copanlisib on the metabolic activity of soil microorganisms were determined according to OECD Guideline 216. The NOEC for nitrate transformation in soil was determined to be 1000 mg/kg. The NOEC for nitrate N-formation in soil on day 28 was 500 mg/kg soil dry weight. Thus, the overall NOEC was 500 mg/kg. The effects of copanlisib on the mortality and reproduction of *Folsomia candida* in artificial soil were determined in a laboratory study according to the guideline OECD 232 and the NOEC for mortality was determined to be ≥ 560 mg/kg and the NOEC for reproduction was determined to be 35 mg/kg. The phytotoxicity of the test item copanlisib to three terrestrial plant species was determined in a seedling emergence test over a period of 21 days according to guideline OECD 208. After 21 days no test item related

phytotoxic effects were determined for all tested plant species at the limit test concentration 1000 mg/kg soil dry weight. Thus, the NOEC was ≥1000 mg/kg. The aerobic transformation of [14C] copanlisib in 4 different natural soils was determined over a test period of 120 days according to the guideline OECD 307. It was concluded that no significant transformation of copanlisib in soils is expected, but a formation of non-extractable residues to a very high degree within a short time frame after application can be anticipated.

The exposure of copanlisib in soil was determined by a PECSOIL/PNECSOIL ratio of 0.002, thus indicating no risk for the soil compartment.

In conclusion, the environmental risk of copanlisib was evaluated in a Phase II Tier A and B assessment and the compound is unlikely to represent a risk for surface water, ground water, microorganisms, sediments and soil. Copanlisib has no potential for bioaccumulation, but is bound in sediments as non-extractable residue.

The QA statement and GLP statement of compliance in the GLP reports of studies appeared to be signed electronically however this should be documented.

3.2.5. Discussion on non-clinical aspects

Pharmacology

Copanlisib was shown to be a PI3K specific inhibitor, most potently against the α and δ isoforms (IC50 values of 0.5 and 0.7 nM), but approximately 10-fold less of the α, β and γ isoforms (IC50 3.7 and 6.4nM).

Anti-proliferative effects were tested *in vitro* against many tumour cell lines, of various origin (breast, ovary, prostate, colon, lung, brain, kidney, melanoma, pancreas, fibrosarcoma, NHL, AML, multiple myeloma, biliary tract. More specifically against haematological cancers, cell lines representing AML. ALL, CLL, CML, NHL, and myeloma were tested, where copanlisib was compared to idelalisib. In general, copanlisib showed lower IC50 values than idelalisib.

In CLL samples, the combination of idelalisib and copanlisib with CD20+ Mab (either Rituximab or obinutuzumab) was more direct cytotoxic compared to PI3K inhibitor alone, with obinuztuzumab appearing more potent than rituximab.

The *in vivo* pharmacology studies showed that copanlisib effectively inhibited tumour growth of xenograft models in nude mice and athymic rats. Furthermore, intermittent dosing regimens were more effective in inhibiting tumour growth compared to continuous administration, hence the clinical dosing regimen appears to be supported by the nonclinical *in vivo* PD studies.

Non-clinical data on haematological malignancies confirm antiproliferative effects of copanlisib on DLBCL and CLL cell lines *in vitro* and in a xenograft model of DLBCL *in vivo*. Further, copanlisib appears more potent than idelalisb in these models.

According to the Nonclinical Overview, clinical samples from FL and DLBCL patients indicated that high PI3Kα expression was more prevalent in DLBCL that FL (60% vs 18%, respectively). This difference in PI3Kα expression could be a contributing factor for the observed beneficial effect of the PI3Kδ inhibitor idelalisib in FL patients, but not in a Phase I study in DLBCL patients, and for the antiproliferative effect of copanlisib on DLBCL cell lines *in vitro* and in a DLBCL xenograft model *in vivo*.

Taken together, differences in PI3Kα expression levels between NHL models could affect the antiproliferative effect of copanlisib. Pharmacodynamic effects of copanlisib has been demonstrated in

DLBCL and CLL cells *in vitro*, and in DLBCL xenograft modes *in vivo*. No data on MZL have, however, been submitted, although cell lines for MZL are available. Further, no discussion has been provided addressing the relevance of presented results for MZL. The applicant is therefore requested to address the relevance of studies on DLBCL and CLL for the indications sought for Aliqopa.

The lowest active dose in the *in vivo* pharmacology studies in rats and mice supported by separate PK studies and determined fraction unbound was used and compared to mean human exposure at the dose of 60 mg. To be able to compare across species and dosing regimens, $AUC_{(0\text{-}168h)}$ during the first week was used. It is acknowledged that unbound AUCs appear in a similar range. Hence, from a non-clinical point of view the 60 mg dose can be considered relevant.

In order to characterise secondary pharmacology, secondary pharmacology screen of a range of receptors, enzymes and ion channels as well as a targeted screening of kinase profiles were performed – however, these two screening studies appear to have limitations with respect to target selection and relevance of the results and target selection should be further addressed by the applicant.

Safety pharmacology was addressed with regards to effect of treatment with copanlisib on vital organ functions (central nervous system (CNS), cardiovascular system [including electrocardiogram (ECG)], respiratory system) as well as on supplemental organ systems (haematology and blood coagulation, gastrointestinal function, renal function, metabolism [glucose, lipids], platelet aggregation Several findings were made at exposures within the range expected in human patients: vasoconstriction and hypertension, enhanced insulin and glucose levels, impaired glucose tolerance, reduced gastrointestinal motility, increased renal volume and electrolyte excretion, and CNS depressant effects. Some of these effects (hypertension, hyperinsulinemia, hyperglycaemia) showed signs of a ceiling effect; can be explained by inhibition of PI3K dependent signalling pathways; and are well-known from the clinical setting. The CNS depressant (and most other) effects seen likely reflect severe hyperglycaemia, and has typically not been seen in humans where great focus has been paid on avoiding severe hyperglycaemia. Such effects seen in rats at high doses included piloerection, ptosis, salivation, splayed limbs, backward walking, stereotypic chewing, hypoactivity, hypothermia, decreased nocifensive responsiveness, reduced muscle tone, and signs of mild haemoconcentration. As PI3kinase inhibitors could contribute to drug-induced QT prolongation and arrhythmias by increasing cardiac late sodium current. This effect may need a chronic exposure and thus, the QT prolongation might not be addressed appropriate during the pre-clinical testing. The applicant is asked to comment on this aspect One of the most common adverse effects in the clinical studies is hyperglycaemia. Rats in the repeat-dose study showed increased HbA1c in the high dose groups indicating that this effect is also present in the rat. However, in the repeat-dose toxicity study in the dog, HbA1c remained normal.

Pharmacokinetics

Pharmacokinetics and toxicokinetics from pivotal toxicology studies of copanlisib were carried out in accordance with Good Laboratory Practice (GLP) consistent with the guideline S3A Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies.

In the course of the non-clinical development different liquid chromatography-tandem-mass spectrometry assays were developed and validated. A bioanalytical method for quantitation of copanlisib performed according to GLP was validated and presented to support the pharmacokinetic, toxicokinetic and toxicity assessments in non-GLP pharmacokinetic and GLP toxicology studies in relevant animal species including mice, rats, dogs and monkeys. All validation criteria were met for all parameters in this study. It is unclear whether the validation method to support bioanalysis and toxicokinetics in the pivotal repeat-dose study was carried out according to the principles of GLP. It is

stated in the report that the study was conducted to GLP however no GLP certificate, QA statement or GLP compliance statement were provided. The GLP status of the validation method should be clarified The validation of the liquid scintillation counting method to assess the radioactivity in body fluids, organs, tissues and in excreta should be provided

The assessment of copanlisib pharmacokinetics following a single i.v. dose in rats and dogs demonstrated that exposure for both Cmax and AUC was roughly dose-proportional. The plasma clearance of copanlisib was moderate to high in rats, dogs and monkeys (1.57 - 6.04 L/(h × kg)). The volume of distribution was generally very high in all investigated species (7 - 32 L/kg). Except in mice elimination of copanlisib occurred with moderate to long half-lives (t1/2: between 4 and 17 hours). See further toxicokinetic studies in repeat-dose toxicity.

Protein binding of copanlisib was low across all species including mice, rat, dog and monkey (free fractions were between 10 and 48% compared to 15.8% in human plasma) as assessed by equilibrium dialysis. Copanlisib was distributed from plasma into blood cells of rat, dog and humans to a considerable extent (CBlood/CPlasma: 2.06, 3.01 and 1.74, respectively). The free fractions (fu) of the metabolite M-1 ranged between 20 and 56% compared to 20% in human plasma. There was no saturation of plasma protein binding of copanlisib and metabolite M-1 within the investigated pharmacological and toxicological relevant concentration range (about 100 - 10000 µg/L). The investigations on plasma protein binding and plasma/blood cell distribution of copanlisib and metabolite M-1 indicated that there was no risk for saturation of plasma protein binding and plasma/blood cell distribution.

Assessment of copanlisib tissue distribution was conducted in male and female albino rats (Wistar) as well as in male pigmented rats (Long Evans) and consisted of quantitative whole-body autoradiography (radioluminography). Copanlisib was distributed rapidly to organs and tissues following intravenous administration of 1 mg/kg [14C]copanlisib. The radioactivity concentrations were higher in the majority of organs and tissues in comparison with blood. Among others, high radioactivity concentrations were determined in the kidneys as well as in the lymphatic tissues including spleen, thymus and lymph nodes. The testes and the accessory genital glands (prostate, epididymides, seminal vesicles) contained higher radioactivity concentrations than blood. [14C]Copanlisib radioactivity penetrated the blood brain barrier to a moderate extent (brain/blood AUC(0-24) ratio of 24%). The distribution patterns of radioactivity were virtually identical in both sexes. Radioactivity showed high affinity for melanin-bearing tissues including pigmented skin and eye wall after intravenous administration of [14C]copanlisib to the pigmented Long Evans rats. The high radioactivity concentrations determined in the lymphatic tissues including spleen and lymph nodes indicated high affinity of the compound to the potential pharmacological target organs and tissues. Conclusions on the distribution pattern between sexes was based on only two female Wistar rats. In addition, organ and tissue distribution in pigmented rats did not include any female animals.

14C]Copanlisib was administered as a single i.v. dose to pregnant Wistar rats to investigate the distribution and elimination of radioactivity in maternal and fetal organs and tissues by means of quantitative whole-body autoradiography. the radioactivity of [14C]copanlisib penetrated the placental barrier to a low to moderate extent.

The distribution in organs and tissues and the placental transfer of copanlisib was only investigated in the rat.

Some non-GLP study reports appeared to be dated and signed electronically however this should be documented.

In vitro investigations revealed that enzymatic activities of major cytochrome P 450 (CYP) and uridin-diphosphat glucuronosyltransferase (UGT) isoforms as well as dihydropyrimidine dehydrogenase (DPD) (study No A50878 were not affected in the presence of copanlisib or metabolite M-1. Some study reports appeared to be dated and signed electronically however this should be documented.

Copanlisib was the predominant component in plasma with > 84% of AUC of total following i.v. administration to mice, rats, dogs, and humans.

The morpholinone derivative M-1 was the only relevant circulating metabolite in rat and human plasma. The ratio M-1/total radioactivity was about 10% in rat plasma and about 5% in human plasma. Therefore, metabolite M-1 was considered as a minor human plasma metabolite according to ICH guideline M3(R2) (2) because it contributed to less than 10% total systemic exposure. Metabolite M-1 was only occasionally present in mouse plasma, whereas in dog plasma besides copanlisib no circulating metabolites were observed.

A balanced excretion of unchanged drug and oxidative biotransformation products was observed in rats (about 40% and 60%, respectively) and humans (about 50% and 50%, respectively. In dogs, elimination of copanlisib was dominated by oxidative biotransformation (> 80%) and less pronounced by unchanged excretion (< 20%).

In studies only male or female animals were selected. A justification for not including both sexes in these studies should be provided.

[14C]Copanlisib radioactivity was mainly excreted via the biliary/fecal route after i.v. administration to rats, dogs and humans. Approximately 10% of the administered radioactivity were excreted by the renal route in rats and dogs. Renal radioactivity excretion was more pronounced in humans with about 22% of dose. In rats, there was a considerable direct secretion of the radioactivity in the gastrointestinal tract amounting to 26.9% of the administered radioactive dose within 24 hours. Excretion of radioactivity was slower in humans compared to rats and dogs.

In lactating rats, following a single i.v. administration of [14C]copanlisib radioactivity was secreted into the milk of lactating rats to a low extent. It is not known whether copanlisib is excreted into human milk however it cannot be excluded based on the animal data.

A battery of *in vitro* assays evaluating the potential effect of copanlisib and its minor metabolite M-1 on transporter test systems (substrate or inhibitor), UGT inhibition and CYP induction and inhibition suggested that clinically relevant drug interactions with copanlisib or the metabolite M-1 was minimal.

Study reports appeared to be dated and signed electronically however this should be documented.

Toxicology

The rat and Beagle dog were selected as the main test species in the pivotal toxicology studies for the evaluation of copanlisib, because they were expected to be responsive to the pharmacological mode of action which was confirmed in the pilot studies by the pattern of toxicity. Both species showed a human-like metabolite pattern *in vitro* in hepatocytes and adequate exposure after intravenous injection. The toxicological profile of copanlisib for the sought therapeutic indications was characterised in a single-dose study conducted in rats in addition to repeat-dose studies in rats for single-cycle (1/week x 3 weeks) and multi-cycle (3 or 4 (1/week x 3 weeks + 1 week off) cycles) and in dogs for single-cycle (1/week x 3 weeks) and multi-cycle (3 or 4 (1/week x 3 weeks + 1 week off) cycles).
All pivotal repeat-dose studies were conducted to the principles of GLP according to the ICH guideline M3(R2) and the duration of the repeat-dose (multi-cycle/weekly) systemic toxicity studies (3 months)

was in line with the expectation for an anti-cancer pharmaceutical for patients with advanced disease refractory to treatment as outlined in the ICH guideline S9.
The non-clinical toxicology programme of copanlisib also included a pilot embryo-fetal developmental toxicity study, genotoxicity studies and studies addressing specific questions including phototoxicity, hemolytic potential, toxicity of impurities and local tolerance.

In the GLP rat single-dose toxicity study i.v. administration of copanlisib induced clear signs of intolerance reactions in male and female rats, which were transient (occurrence within 1 hour after administration) at the low dose of 10.0 mg/kg and were not all reversible within the 3-week observation period at higher doses. The LD50 of copanlisib in male and female rats after a single i.v. administration was 20.0 mg/kg. The GLP certificate was missing in the study report and should be made available.

Multiple toxicities were seen in the rat and dog repeat-dose toxicity studies based on in-life observations, clinical pathology and/or morphological evaluations. Both the rat and dog responded to the pharmacodynamics effect of copanlisib on glucose homeostasis. Target organs in the repeat-dose studies were the lymphoid and haematopoietic system, liver, kidneys, teeth, bone/femoro-tibial growth plates, heart, and male and female genital systems in the rat and the lymphoid and haematopoietic system, stomach (gastric mucosa) and male genital system in the dog. Effects were dose-dependent. Most histological findings in the rat and dog repeated-dose toxicity studies were reversible or partially reversible.

The spectrum of affected tissues, however, was greater in the rat compared to the dog suggesting that the rat is the more sensitive species.

No NOAEL in the rat and dog repeat-dose studies could be established due to clear adverse effects at all dose levels, that were not reversible within the recovery periods. This is accepted as NOAEL or NOEL are not considered essential to support clinical use of an anti-cancer pharmaceutical.

Toxicokinetic data from the repeat-dose studies in rats and dogs showed that there were no sex-related differences in exposure (AUC(0-24) and Cmax) which increased in an almost dose-proportionally manner. No significantly changes in mean exposure was seen after repeated administration in the dose groups except for the multi-cycle study in rats.

The doses given in the repeat-dose studies (single- and multiple-cycles) resulted in plasma exposures (maximum plasma concentration and AUC) that were below or in the range of those observed in adult humans in particular for the dog. However, this can be supported as copanlisib is indicated for the treatment of patients with advanced cancer. In addition, more information from the literature is now available on the safety of copanlisib in human patients (Chauhan and Cheson, 2021, Le et al., 2021 and Munoz et al., 2021[2]).

The blood volume collected at the toxicokinetic sampling was not specified in study report and should be provided.

The repeat-dose studies claimed GLP however discrepancies in that regard were noted:

[2] Chauhan and Cheson. 2021. Copanlisib in the Treatment of Relapsed Follicular Lymphoma: Utility and Experience from the Clinic. Cancer Management and Research. Volume 13: 677-692. Le et al. 2021. Update on the Role of Copanlisib in Hematologic Malignancies. Therapeutic Advances in Hematology. Volume 12: 1-10. Munoz et al. 2021. Copanlisib for the Treatment of Malignant Lymphoma: Clinical Experience and Future Perspectives. Targeted Oncology. Volume 16: 295-308.

- Study: QA audits were limited with regard to toxicokinetic, bioanalytical, clinical pathology, pathology and determination of liver enzyme activities studies. Furthermore, the GLP compliance statement was signed several months prior to the QA statement.
- Study: QA audits were limited with regard to toxicokinetic, bioanalytical, clinical pathology, pathology and immunotoxicity investigation studies.
- Study: QA audits were limited with regard toxicokinetic, bioanalytical, clinical pathology, pathology, determination of liver enzyme activities and analytical data of stability and content checks of test substance formulations studies.
- Study: The bioanalytical and toxicokinetic phase reports appeared to be dated and signed electronically. QA audits were limited with regard to toxicokinetic, bioanalytical, determination of glycosylated haemoglobin (Hb Ale), acetoacetic acid (acetoacetate), and D-(-)-3-hydroxybutyric acid (D-(-)-3-hydroxybutyrate) and pathology peer-review studies.

As stated in ICH guideline M3(R2) pivotal studies in the non-clinical setting should be conducted according to the Principles of GLP to ensure uniformity, consistency, reliability, reproducibility, quality, and integrity of data. QA audits in non-clinical studies are necessary to monitor GLP compliance and if these are limited it could result in a study being downgraded from GLP to non-GLP. Therefore, it should be clarified and documented whether the pivotal repeat-dose studies were sufficiently subjected to QA audits in order to be GLP compliant.

Genotoxicity studies were carried out in accordance with the ICH guideline S2(R1) and copanlisib showed no genotoxic potential.

No carcinogenicity studies were conducted as the sought indication of copanlisib was for advanced cancer therapy in agreement with ICH guideline S9.

In accordance with ICH guideline S9 no fertility and early embryonic and prenatal and postnatal development studies of copanlisib were performed. No juvenile studies were carried out as the current indication for copanlisib is for treatment in adults. Despite the fact that no dedicated GLP compliant reproductive toxicity studies were conducted results of repeat-dose toxicity GLP studies revealed adverse effects of copanlisib on male and female reproduction in the testes, epididymides, prostate and male mammary gland and in the ovaries, uterus and vagina after repeated dosing in the rat toxicity studies and in the testes and epididymides in the longer-term dog toxicity study conducted in adult dogs.

Embryo-fetal development were assessed in a non-GLP pilot embryo-fetal developmental toxicity study conducted in rats with i.v. bolus administration of copanlisib. Due to severe post implantation loss, and developmental toxicity, including embryo-fetal toxicity and teratogenicity, observed in this rat study, no further studies on developmental toxicity were performed in accordance with ICH guideline S5(R3).

Local tolerance studies in rabbits showed that no severe or irreversible effects are expected in humans after intravenous infusion. Paravenous injection was likely to cause slight to moderate transient local reactions. Thus, accurate intravenous infusion in humans is necessary to prevent possible local incompatibility reactions due to inadvertent paravenous injection. In the repeat-dose toxicity studies with i.v. infusion local tolerance effects with signs of irritation were seen in rats and dogs.

No studies on antigenicity were performed as copanlisib is a non-peptigenic chemical of low molecular weight. Therefore, the risk of anti-drug antibodies formation in patients is considered to be low.

Findings of immunosuppression resulting in an increased infection rate in repeat-dose studies in rats was further addressed in the multi-cycle rat toxicity. Immunotoxicological investigations showed decreased splenic cell and B-cell counts in males and significantly reduced IgG antibody titre in both males and females after the end of treatment that were reversible within the 8-week recovery period.

The approach above is consistent with the ICH guideline S9 where the design components of the general toxicology studies are considered sufficient to evaluate immunotoxic potential.

No dedicated dependency studies were performed. Overall, it was concluded that copanlisib was not likely to present a risk of physical dependence or a meaningful risk of an abuse potential at clinically relevant exposure, which is supported.

Morpholinone metabolite M-1 was the only relevant circulating metabolite in rat and human plasma and showed similar pharmacologically activity to copanlisib. Metabolite M-1 was evaluated as a minor metabolite in humans according to ICH guideline M3(R2) because it contributed to < 10% of total systemic exposure.

Two degradation products without structural alert in (Q)SAR, AETQP and 7-hydroxyquinazolinpyramide, are proposed specified above limit of qualification for active substance (ICH Q3A), but below threshold of qualification for drug product (ICH guideline Q3B). Based on the level of AETQP present in copanlisib batches used in toxicity studies, the proposed limit of 0.5% in drug substance is considered toxicologically qualified. 7-hydroxyquinazolinpyramide has not been present in the batches used in toxicity studies. However, considering the intended patient population, and that 7-hydroxyquinazolinpyramide is limited to below threshold for qualification in the drug product (0.5%), the lack of qualification data for the proposed limit in the drug substance is considered acceptable.

Genotoxic impurities present in the starting materials are 4-(3-chloropropyl)morpholine hydrochloride, 6-nitrovanillin and benzyl-6-nitrovanillin. The impurities are proposed limited to NMT 0.10% in drug substance and NMT 0.20% in drug product (under 'Any unspecified impurities'), above TTC. According to ICH M7(R3), the TTC concept is not considered applicable for drug substances and drug products intended for advanced cancer indications as defined in the scope of ICH guideline S9. In these cases, genotoxic impurities could be controlled at acceptable levels for non-genotoxic impurities, i.e. in accordance with ICH guidelines Q3A and Q3B. Thus, since ICH guideline S9 is applicable for the indications sought, the proposed limits are acceptable from a non-clinical point of view.

No concern regarding haemolytic potential, phototoxicity or impurities were identified. The QA statement and GLP statement of compliance of study reports appeared to be dated and signed electronically however this should be documented. The concentration range used in the *in vitro* phototoxicity test should be justified. More specifically, the high affinity to and retention of copanlisib in pigment-containing tissues demonstrated in rat should be considered and discussed in relation to tested concentration range. In addition, the GLP statement of compliance and QA statement appeared to be signed electronically however this should be documented.

The environmental risk of copanlisib was evaluated in a Phase II Tier A and B assessment. Based on the data the compound is not a PBT substance and not expected to pose a risk to the environment. In addition, copanlisib should be used according to the precautions stated in the SmPC in order to minimise any potential risks to the environment (e.g. "*Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment*").

In the environmental risk assessment:

1. The log DOW of copanlisib at pH 7 was lower than 4.5 therefore, it is not to be further screened for persistence, bioaccumulation and toxicity. However, it was noted that this value was calculated from the ratio of the solubility in n-octanol and in the corresponding buffer solution due to low water solubility. In addition, the determination of the log DOW values was not conducted at three pH values ranging from pH 5 to 9 but from 4 to 9. This deviation should be justified.

2. The assessed study does not fulfil the quality criteria according to OECD TG 308 because the mass balance of 90% has not been achieved and temperature and organic carbon content exceeded the maximum permissible values. Furthermore, results as described in Q 9 iii of EMA/CHMP/SWP/44609/2010 Rev. 1 were not available because of limited extraction efficiency. The selection of a suitable extraction method is not presented in a comprehensible way. A higher extraction efficiency was shown for 0,1M Na OH solution, but was not carried out for all samples or considered in the evaluation. Finally, no DT50 values for water, sediments and whole systems were derived.

   The conclusion that "copanlisib is irreversibly bound to the non-extractable fraction (no quantification or qualification were conducted) and not degradable" does not appear to be scientifically justified in view of the considerable deficiencies in the study design.
   The applicant is asked for the conduction of a new study according to OECD 308 using the proposed extraction scheme by Löffler/ Ternes et al. (2020) or other extractions schemes with harsh steps (e.g. Schäffer et al., 2018).

   References:
   Loeffler, D., Hatz, A., Albrecht, D., Marvin, F., Hogeback, J., Ternes, T.A., 2020. Determination of non-extractable residues in soils: Towards a standardised approach. Environmental Pollution 259, 113826. https://doi.org/10.1016/j.envpol.2019.113826
   Schaeffer, A., Kästner, M., Trapp, S., 2018. A unified approach for including non-extractable residues (NER) of chemicals and pesticides in the assessment of persistence. J. Environ. Sci. Eur.

   The CHMP does not agree with the conclusion on OECD 210: an overall NOEC (according to the study protocol) of 0.3 µg/L is reported (survival of fry); however, in the ERA 1.19 µg/L (survival at day 29pf) is used for PNEC derivation. A risk for surface water arises by using a PNEC of 0.03 µg/L in Phase II Tier A. The applicant is asked to revise the risk assessment for surface water by considering 0.3 µg/l for PNEC derivation. Furthermore, in recent applications the current OECD guidelines should be used. The OECD 210 was updated in 2013. The study plan should have been followed this updated version. The study shows deficiencies masking a potential growth effect. According to the actual OECD guideline, a minimum of 18 mm length in control fish for the species used, fathead minnow is recommended. Instead the control fish in this test do not exceed 11 mm, which clearly would mask potential exposure related growth effects. This effect was fortified in this study, due to the high mortality in the two highest concentration, where less fish had more space and access to food. Consequently, these fish displayed a better growth rate and grew faster than the control fish. These effects, too small control fish and less fish in the highest exposure concentration clearly mask a potential growth effect, the only sublethal endpoint in this test. As a risk is identified and for animal welfare reasons, the applicant is not asked to conduct a new test.

3. The calculation of $PEC_{SEDIMENT}$ from the equation is not fully understood and should be clarified.
4. The QA statement and GLP statement of compliance in the GLP reports of studies appeared to be signed electronically however this should be documented.
5. Section 4.6 and 5.3 of the SmPC is very elaborate and should be revised and updated according to the guideline on SmPC: *A guideline on Summary of product characteristics (SmPC)* from September 2009. In general, exact dosing details in mg/kg should be avoided. Section 4.6: In the section on women of childbearing potential, the duration of use of contraception must be justified. For breastfeeding, a contraindication should be considered, in view of the toxic nature of the drug, which is also common for kinase inhibitors in general.

3.2.6. Conclusion on non-clinical aspects

Overall, the primary pharmacodynamic studies provided adequate evidence that copanlisib is a PI3K inhibitor against all the four PI3K isoforms (α, β, γ, and δ). The *in vivo* pharmacology studies showed that copanlisib effectively inhibited tumour growth of xenograft models. Furthermore, intermittent dosing regimens were more effective in inhibiting tumour growth compared to continuous administration, hence the clinical dosing regimen appears to be supported by the nonclinical *in vivo* PD studies. It was also shown that the combination of a CD20+ mAb and copanlisib showed a higher inhibition of tumour growth compared to either treatment alone.

From the pharmacokinetic point of view, the rat and dog were the most relevant species for non-clinical efficacy and safety studies of copanlisib. The pharmacokinetic data after single i.v. dosing for copanlisib in rats and dogs demonstrated that exposure for both Cmax and AUC was roughly dose-proportional. The plasma clearance of copanlisib was moderate to high in rats, dogs and monkeys. The volume of distribution was generally very high in all investigated species. Except in mice elimination of copanlisib occurred with moderate to long half-lives. Protein binding was low across all species including in mice, rat, dog and monkey. Copanlisib was distributed from plasma into blood cells of rat, dog and humans to a considerable extent. In rats, copanlisib showed remarkable distribution into most organs and tissues with the exception of brain. *In vitro* enzymatic activities of major cytochrome P and uridin-diphosphat glucuronosyltransferase isoforms as well as dihydropyrimidine dehydrogenase were not affected in the presence of copanlisib or metabolite M-1. Copanlisib was the predominant component in plasma with > 84% of AUC of total following i.v. administration to mice, rats, dogs, and humans. The morpholinone derivative M-1 was the only relevant circulating metabolite in rat and human plasma and it was evaluated as a minor metabolite. A balanced excretion of unchanged drug and oxidative biotransformation products was observed in rats and humans. In dogs, elimination of copanlisib was dominated by oxidative biotransformation and less pronounced by unchanged excretion. Copanlisib was mainly excreted via the biliary/fecal route after i.v. administration to rats, dogs and humans. Approximately 10% of the administered copanlisib was excreted by the renal route in rats and dogs. Transplacental transfer and milk excretion studies in rats showed copanlisib penetrated the placental barrier and was secreted into the milk of lactating rats to a low extent, respectively. A battery of *in vitro* assays also suggested that clinically relevant drug interactions with copanlisib and metabolite M-1 was unlikely.

Overall, the toxicology programme of copanlisib revealed no major concerns. The toxicity studies supporting the market authorization of copanlisib for the treatment of patients with advanced cancer refractory to other treatment was performed according to appropriate ICH guidelines. Multiple toxicities were seen in the rat and dog repeat-dose toxicity studies. Target organs were the lymphoid and haematopoietic system, liver, kidneys, teeth, bone/femoro-tibial growth plates, heart, and male and female genital systems in the rat and the lymphoid and haematopoietic system, stomach (gastric mucosa) and male genital system in the dog. Effects were dose-dependent. Toxicokinetic data from the repeat-dose studies in rats and dogs showed that there were no sex-related differences in exposure (AUC(0-24) and Cmax) which increased in an almost dose-proportionally manner. Copanlisib was not considered to be genotoxic. Developmental toxicity, including embryo-fetal toxicity and teratogenicity was seen after treatment with copanlisib. Based on local tolerance studies no severe or irreversible effects are expected in humans after i.v. injection. Copanlisib was found to be non-phototoxic. The environmental risk assessment of copanlisib in a Phase II Tier A and B demonstrated that the compound is unlikely to represent a risk for surface water, ground water, microorganisms, sediments and soil. Copanlisib has no potential for bioaccumulation, but is bound in sediments as non-extractable residue.

In conclusion, no major objections were identified in the non-clinical dossier, however a number of other concerns have been raised which need to be sufficiently addressed before approval of copanlisib can be supported from a non-clinical perspective.

3.3. Clinical aspects

Tabular overview of clinical studies

Table: Clinical studies included in the clinical pharmacology documentation

Table 1–1 Clinical studies of copanlisib with PK variables

Study no (EudraCT/NCT no) No of centers and countries (Status)	Design/ Copanlisib dose and schedule	Study population	Number of treated subjects Total	NHL	Main outcomes
Phase 1 studies in cancer patients					
	Dose Escalation Studies				
12871 (NCT00962611) 3 centers in the US (completed; LPLV: 23 FEB 2016)	FIH: Open-label, uncontrolled, multi-center; dose escalation: 0.1 to 1.2 mg/kg; intermittent schedule (Days 1, 8, and 15 of a 28-day treatment cycle)	Cancer patients with advanced ST or NHL	57	9	Tumor response, basic PK, PD, MTD, and safety
	PD Study				
16790 (2013-004746-42) 10 centers in 3 EU countries (completed; LPLV: 04 OCT 2016)	Open-label, uncontrolled, multi-center, PD; 0.4 and 0.8 mg/kg and 45 and 60 mg; intermittent schedule (Days 1, 8, and 15 of a 28-day treatment cycle)	Cancer patients with selected ST or NHL	63	33	PK-PD relationship, safety
	Asian populations studies – ethnicity, dose escalation				
15205 (NCT01404390) 1 center in Japan (completed; LPLV: 12 JUL 2012)	Uncontrolled, open-label, non-randomized 0.4 or 0.8 mg/kg; intermittent schedule (Days 1, 8, and 15 of a 28-day treatment cycle)	Japanese cancer patients with advanced or refractory ST	10	0	Tumor response, PK, MTD and safety
17792 (NCT02342665) 13 centers in Japan (primary completion; cut-off: 20 FEB 2020)	Open-label, uncontrolled, single-arm, 45 and 60 mg; intermittent schedule (Days 1, 8, and 15 of a 28-day treatment cycle)	Japanese patients with relapsed/ refractory iNHL (B-cell)	25	25	Safety, efficacy, PK, QoL, biomarker
16866 (NCT03498430) 1 center in China (completed; LPLV: 02 JUN 2020)	Open-label, single-center; 60 mg flat dose on Days 1, 8, and 15 of a 28-day treatment cycle	Chinese patients with relapsed iNHL	13	13	PK, safety, efficacy
	Combination studies with chemotherapy in cancer patients				
12874 (NCT01411410) 2 centers in the US (completed; LPLV: 22 OCT 2014)	Multi-center, open-label; 0.6 or 0.8 mg/kg; intermittent schedule (Days 2, 9, and 16 of a 28-day treatment cycle) and weekly dosing in combination with paclitaxel	Cancer patients with advanced or refractory ST	55	0	Safety, recommended Phase 2 dose, PK, MTD

(Table continued)

Table 1–1 Clinical studies of copanlisib with PK variables

Study no (EudraCT/NCT no) No of centers and countries (Status)	Design/ Copanlisib dose and schedule	Study population	Number of treated subjects Total	NHL	Main outcomes
12875 (NCT01460537) 3 centers in the US (completed; LPLV: 20 JUL 2015)	Multi-center, open-label; 0.6 and 0.8 mg/kg; intermittent schedule (Days 1, 8, and 15 of a 28-day treatment cycle) in combination with gemcitabine; intermittent schedule (Days 1 and 8 of a 21-day treatment cycle) in combination with gemcitabine/cisplatin	Cancer patients with advanced ST; biliary tract cancer expansion cohort	50	0	Tumor response, PK, MTD and safety
12876 (2010-024082-45) 8 study centers in 3 countries: EU, US (completed; LPLV: 13 APR 2014)	Multi-center, open-label; dose-escalation (0.2–0.8 mg/kg); intermittent schedule (Days 1, 8, and 15 of a 28-day treatment cycle) and weekly dosing in combination with MEK inhibitor refametinib given continuously or 4 days on / 4 days off	Cancer patients with advanced ST	64	0	Tumor response, PK, MTD, and safety
Drug interaction studies (CYP3A4 inhibitor/inducer) and QT/QTc in cancer patients and healthy volunteers					
16270 (NCT02253420) 5 centers in Canada and the US (completed; Arm A LPLV: 21 AUG 2017, Arm B LPLV: 13 AUG 2019)	Open-label, non-randomized, 2 arms (Arm A: 12 and 60 mg copanlisib with itraconazole, Arm B: 60 mg copanlisib with rifampin and cardiovascular safety); intermittent schedule (Days 1, 8, and 15 of a 28-day treatment cycle)	Cancer patients with advanced ST or NHL	Arm A 12 mg: 10 60 mg: 16 Total: 26 Arm B: 25	Arm A: 0 Arm B: 2	Effect of CYP 3A4 inhibitor or inducer on the PK of copanlisib, cardiovascular safety
19951 (NCT03655301) 1 center in the US (completed; LSLV: 12 NOV 2018)	Open-label, non-randomized, single-center, single-arm; single dose of 60 mg copanlisib with metformin	Healthy volunteers	13	0	Effect of copanlisib on metformin PK and PD, safety of copanlisib

(Table continued)

Table 1–1 Clinical studies of copanlisib with PK variables

Study no (EudraCT/NCT no) No of centers and countries (Status)	Design/ Copanlisib dose and schedule	Study population	Number of treated subjects Total	NHL	Main outcomes
Phase 1 study in healthy volunteers - mass balance study					
16353 (2013-002544-90) 1 center in The Netherlands (completed; LSLV: 21 APR 2014)	Single-center, open-label, single IV dose of 12 mg copanlisib labeled with 2.76 MBq (75 µCi) of [^{14}C]copanlisib	Healthy male volunteers	6	0	Metabolism, excretion, mass balance, safety, tolerability, and PK
Phase 1 study in non-cancer subjects with hepatic and renal impairment					
18041 (2016-004561-51) 2 centers in Germany and Romania (completed; LSLV: 13 MAR 2020)	Open-label, non-randomized, parallel group, multi-center single dose of 12 mg copanlisib First part: Severe renal and moderate hepatic impairment Second part: Severe hepatic impairment	Healthy subjects and subjects with impaired renal and hepatic function	30	0	PK, safety and tolerability in subjects with impaired hepatic or renal function
Phase 2 studies with PK/PD and biomarker analysis in cancer patients					
16349 Part A (2012-002602-52) 41 centers in 10 countries: EU, Canada, US (completed; LPLV: 13 AUG 2018)	Open-label, uncontrolled, 0.8 mg/kg (maximum 65 mg) intermittent schedule (Days 1, 8, and 15 of a 28-day treatment cycle)	Patients with iNHL, CLL, and aggressive NHL	84	84	Efficacy, safety, PK, biomarkers, cardiovascular safety (LVEF/QTc sub-study in 20 patients)
16349 Part B CHRONOS-1 (2012-002602-52) 81 centers in 24 countries: US, Canada, Europe, Asia Pacific, Russia, Israel, Australia, New Zealand (primary completion 2016; follow-up cut-off: 20 FEB 2020)	Open-label, uncontrolled 60 mg Intermittent schedule (Days 1, 8, and 15 of a 28-day treatment cycle)	Patients with iNHL	142	142	Efficacy, safety, PK, biomarkers and quality of life
(Table continued)					
Phase 3 study with efficacy, PK, and biomarker analysis in cancer patients					
17067 CHRONOS-3 (2013-003893-29) 186 centers in 37 countries: US, Europe, Asia Pacific, Latin America (primary completion; cut-off: 31 AUG 2020)	Randomized (2:1), double-blind, copanlisib + rituximab vs. placebo + rituximab; 60 mg Intermittent schedule: Days 1, 8, and 15 of a 28-day treatment cycle in combination with rituximab given weekly during the first 28-day cycle (Cycle 1) and then on Day 1 of Cycles 3, 5, 7 and 9	Patients with 2nd line relapsed/refractory iNHL	Total: 453 Copa/R: 304 Pbo/R: 149	Total: 453 Copa/R: 304 Pbo/R: 149	Efficacy, safety, PK, biomarkers, and QoL

CLL = Chronic lymphocytic leukemia; Copa/R = Copanlisib/rituximab; CYP = Cytochrome P450; FIH = First-in-human; iNHL = Indolent non-Hodgkin's lymphoma; IV = Intravenous; LPLV = Last patient, last visit; LSLV =

Table 1–1 Clinical studies of copanlisib with PK variables

Study no (EudraCT/NCT no) No of centers and countries (Status)	Design/ Copanlisib dose and schedule	Study population	Number of treated subjects Total	NHL	Main outcomes

Last subject, last visit; LVEF = Left ventricular ejection fraction; MEK = Mitogen-activated protein kinase; MTD = Maximum tolerated dose; NHL = Non-Hodgkin's lymphoma; PD = Pharmacodynamics; PK = Pharmacokinetics; Pbo/R = Placebo/rituximab; QoL = Quality of life; QTc = QT interval corrected for heart rate; ST = Solid tumors

3.3.1. Pharmacokinetics

The pharmacokinetic (PK) and drug-drug interaction (DDI) properties of copanlisib, were investigated in three Phase I studies in healthy subjects and subjects with impaired hepatic/renal function (single dose) and eleven Phase I & II studies conducted in subjects with solid tumours or NHL and in one Phase III study in patients with r/r NHL. Further, population PK (popPK) exercises were used to inform clinical development. The main popPK model included pharmacokinetic data from three clinical studies in patients and is used to describe copanlisib PK, explore the effect of covariates, provide a rationale for the flat dosing regimen, derive dose recommendations in severe hepatic impairment and estimate exposures for exposure-response (ER) analysis (efficacy, safety, QTc). To investigate the metabolism, active transport, protein binding and drug interaction potential of copanlisib, several *in vitro* studies were conducted.

The proposed dose of copanlisib is 60 mg administered as a 1-hour intravenous infusion on Days 1, 8, and 15 of a 28-day treatment cycle as monotherapy or in combination with rituximab.

Methods

A validated LC-MS/MS method was used for determination of copanlisib in human plasma. Data of the active metabolite M1 was also collected in several clinical studies. An unknown number of urine samples were analysed for copanlisib and M-1 in several clinical studies. All samples were analysed within the demonstrated stability period.

PK parameters in the clinical studies with dense sampling were calculated using non-compartmental methods and WinNonlin (Certara). PopPK model development was conducted using nonlinear mixed-effects modelling with NONMEM (ICON Development Solutions). All other preparation, analysis and visualisation of data was done using R. NONMEM and R were also used for NLME modelling of concentration-QTc relationships.

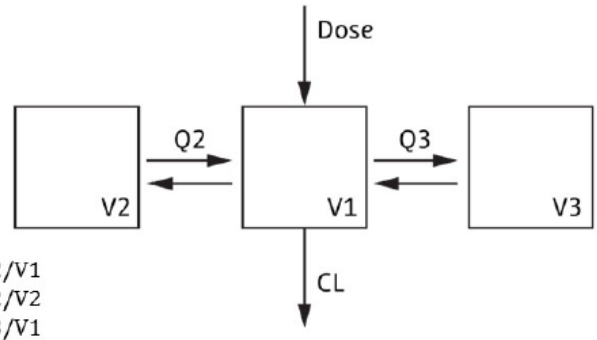
The exposure-response analysis of progression-free survival was performed using the semiparametric Cox proportional hazards methodology. The exposure-response analyses of the objective response rate and treatment-emergent adverse events were performed using logistic regression.

Statistical analyses were mainly performed using SAS. The Wilcoxon signed-rank test was used for evaluation of concentration-QTc effects.

Population PK

The structural model from preliminary popPK analyses of copanlisib was a three-compartment model with linear clearance from the central compartment (Figure 10-3).

Figure 10-3: Structure of final model (Run048_cov)



$K_{12} = Q2/V1$
$K_{21} = Q2/V2$
$K_{13} = Q3/V1$
$K_{31} = Q3/V3$
$D1 = DUR_{OBS} \cdot \theta_{INF}$
$CL = CL_{TV} \cdot \left(1 + \theta_{ALBU\_CL} \cdot (ALBU - 3.8)\right) \cdot \exp(\eta_1)$
$V2 = V2_{AGE<35} \cdot \left(1 + \theta_{AGE\_V2} \cdot (AGE - 35) \cdot B\right) \cdot \exp(\eta_2)$ where B=0 when AGE<35, else B=1
$V3 = V3_{AGE<35} \cdot \left(1 + \theta_{AGE\_V3} \cdot (AGE - 35) \cdot B\right) \cdot \exp(\eta_3)$ where B=0 when AGE<35, else B=1

CL, clearance; K, distribution rate constant; Q2, inter-compartmental clearance for first peripheral compartment; Q3, inter-compartmental clearance for second peripheral compartment; V1, volume of distribution for central compartment; V2, volume of distribution for first peripheral compartment; V3, volume of distribution for second peripheral compartment; D1, modelled duration of infusion; DUR_{obs}, observed infusion duration; θ_{INF}, parameter describing factor by which observed infusion duration is modified; ALBU, serum albumin concentration (g/dL); CL_{TV}, estimated CL for a patient with median Value of ALBU; θ_{ALBU_CL}, parameter describing influence of ALBU on CL; AGE, age of patient (years); $V2_{AGE<35}$, estimated V2 for a patient with AGE<35; θ_{AGE_V2}, parameter describing influence of AGE on V2; $V3_{AGE<35}$, estimated V3 for a patient with AGE<35; θ_{AGE_V3}, parameter describing influence of AGE on V3.

The main popPK model (18641) used to support the MAA was built using PK data obtained through intensive and sparse sampling in three studies 12871, 15205 and 16349 part A, which were conducted in patients with advanced or refractory solid tumour, CLL or NHL (including aggressive NHL and iNHL). The model building dataset consisted of 1608 observations in 123 cancer patients (females 59%) following weight-based dosing of copanlisib. The majority were whites (72.1%). The model was externally tested using data from the three studies 16349 part B, 16790 and 16270 arm A (976 observations in 174 patients, all received 60 mg flat dosing).

The final popPK model (run048_cov) contained three significant covariate relationships: age on V2, age on V3 and albumin concentration on CL. The final parameter estimates for copanlisib are shown in Table 3-10. Data of the active metabolite M1 was collected in several clinical studies. M1 was not included in the main popPK model.

Table 3–10 Population PK meta-analysis - parameter estimates for the final model

Parameter	Unit	Estimate	RSE [%]	LLCI	ULCI	Description
Fixed effects (THETA)						
CL_{TV}	L/h	18.9	5.7	16.8	21.0	Clearance for patient with median albumin concentration
V1	L	44.0	6.7	38.2	49.8	Volume of distribution of central compartment
Q2	L/h	54.7	5.2	49.1	60.3	Inter-compartmental clearance between central / first peripheral compartment
$V2_{AGE<35}$	L	37.7	24.1	19.9	55.5	Volume of distribution of first peripheral compartment for patient with age<35
Q3	L/h	57.3	3.0	53.9	60.7	Inter-compartmental clearance between central / second peripheral compartment
$V3_{AGE<35}$	L	437	13.2	324	550	Volume of distribution of second peripheral compartment for patient with age<35
θ_{INF}	-	0.839	4.2	0.770	0.908	Parameter that modifies observed infusion duration
θ_{ALBU_CL}	$(g/dL)^{-1}$	0.234	19.8	0.143	0.325	Parameter describing the linear influence of albumin concentration on CL
θ_{AGE_V2}	$Year^{-1}$	0.052	36.0	0.0153	0.0887	Parameter describing the piecewise linear influence of patient age on V2
θ_{AGE_V3}	$Year^{-1}$	0.0199	37.3	0.00534	0.0345	Parameter describing the piecewise linear influence of patient age on V3
Random effects[a]: Inter-individual variability (OMEGA)						
CL (ω^2)	-	0.233	13.9	0.169	0.297	Inter-individual variability on CL
CL (CV)	%	51.2		43.0	58.8	
CL (Shrinkage)	%	16.1				
V2 (ω^2)	-	0.572	24.0	0.304	0.841	Inter-individual variability on V2
V2 (CV)	%	87.9		59.4	115	
V2 (Shrinkage)	%	24.9				
V3 (ω^2)	-	0.163	25.3	0.0822	0.244	Inter-individual variability on V3
V3 (CV)	%	42.1		29.3	52.5	
V3 (Shrinkage)	%	27.0				
Random effects: Inter-occasion variability (OMEGA)						
CL (ω^2)	-	0.0511	19.2	0.0318	0.0704	Inter-occasion variability on CL
CL (CV)	%	22.9		18.0	27.0	
Residual error (SIGMA)						
Resid1 (σ^2)	-	0.463	5.03	0.417	0.509	Additive residual error of model predictions
Resid1 (CV)	%	68.0		64.6	71.3	(on natural log scale) during infusion
Resid2 (σ^2)	-	0.0564	3.24	0.0528	0.0600	Additive residual error of model predictions
Resid2 (CV)	%	23.7		23.0	24.5	(on natural log scale) post infusion

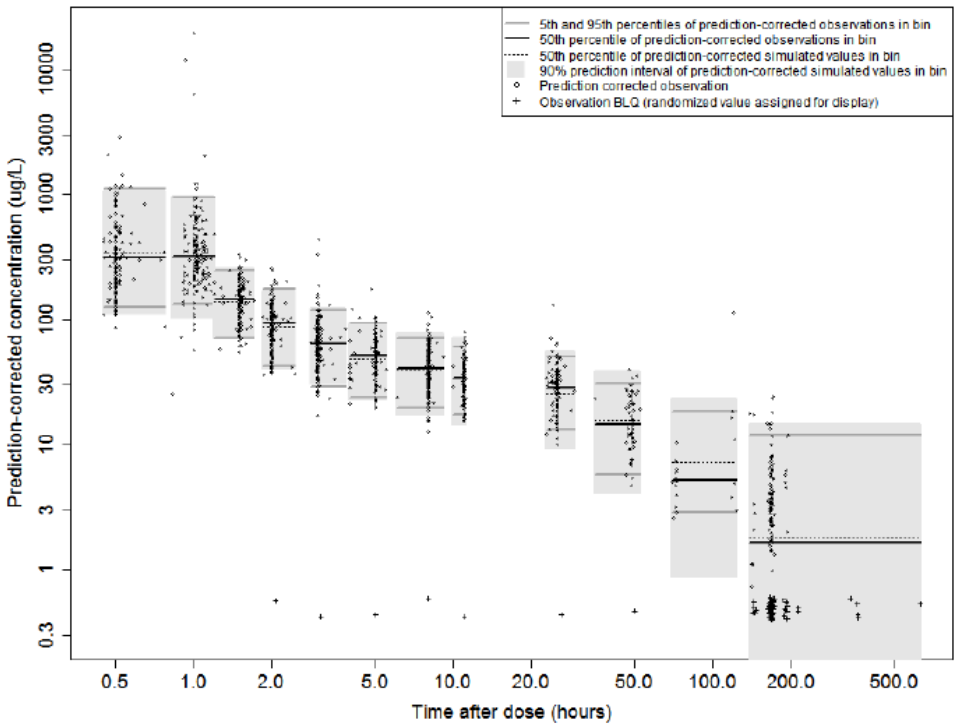
LLCI = Lower limit of 95% confidence interval (estimate - 1.96·SE); PK = Pharmacokinetic; RSE = Relative standard error (100·SE/estimate); SE = Standard error; ULCI = Upper limit of 95% confidence interval (estimate + 1.96·SE).

a: The coefficient of variation (CV) is calculated as 100·SQRT(EXP($OMEGA^2$)-1) and 100·SQRT($SIGMA^2$). The confidence intervals of CV are derived through transformation of confidence intervals of $OMEGA^2$ and $SIGMA^2$. Eta shrinkage is calculated as 100·(1-standard deviation of individual eta estimates/ω).

Source: Module 5.3.3.5, Report R-11088, Table 10-7

IIV on CL, V2 and V3 were estimated to be 53.1%C, 110% and 48.0%, respectively, prior to inclusion of covariates. After inclusion of covariates, 51.2%, 87.9% and 42.1%, respectively, remained unexplained. IOC on CL was reduced from 23.4%CV to 22.9% from base to final model.

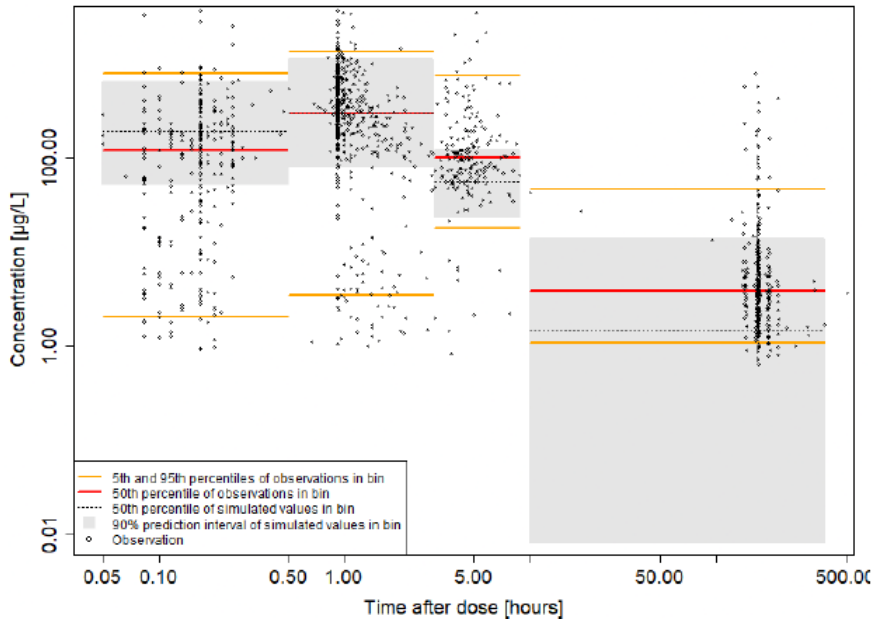
Figure F-7: Prediction-corrected Range VPC for final model



44% of observations in final time after dose bin are <LLOQ and 5th percentile of prediction-corrected observations cannot be calculated. Hence the lower horizontal grey line in final bin is not shown.

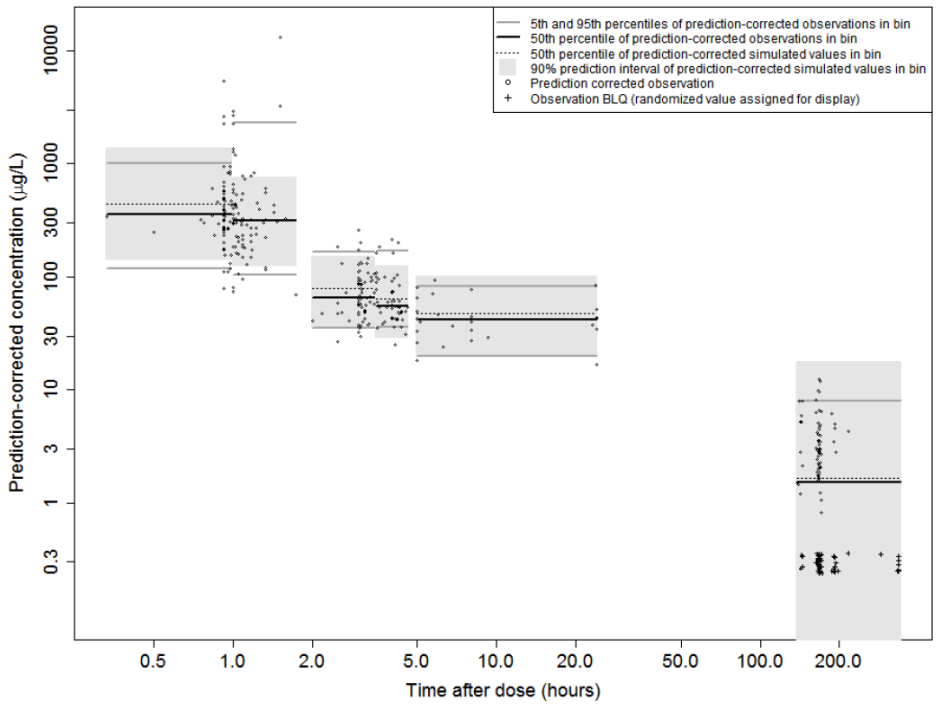
The PK data collected in pivotal studies, the ongoing Phase III Study 17067 (60 mg flat dose regimen, 1434 observations in 289 patients) and Phase II study 16349 part B (0.8 mg/kg or 60 mg, 411 observations 124 patients), were overlaid with model predicted concentrations in a VPC (Figures below).

Figure 13-1: Range VPC comparing measured copanlisib plasma concentrations and predictions by the existing popPK model.



Prediction of copanlisib exposure in patients from study 17067 using main popPK model (18641).

Figure F-15: Prediction-corrected Range VPC for final model applied to data from study 16349 Part B



46% of observations in final time after dose bin are <LLOQ and 5th percentile of prediction-corrected observations cannot be calculated. Hence the lower horizontal grey line in final bin is not shown.

Prediction of copanlisib exposure in patients from study 16349-part B using main popPK model (18641).

Exposure-response models

Separate exposure-response analyses were conducted for data collected in studies CHRONOS-1 (16349 Part B) and CHRONOS-3 (17067). The E-R relationships were evaluated for efficacy and safety in three data sets for each study: a combined data set, the follicular lymphoma (FL) and the marginal zone lymphoma (MZL) data sets. The methodology for evaluation of E-R relations was similar for both studies. The exposure metrics were calculated using the latest Pop PK model: AUC (0-168) and Cmax after the 3rd weekly dose of 60 mg copanlisib. Additionally, time-varying exposure variables were used in initial monotherapy E-R analyses (average copanlisib plasma concentration). For efficacy, graphical evaluation was performed using Kaplan-Meier plots of PFS by exposure quartiles. Covariates were evaluated for their influence by univariate analysis followed by multivariate analysis using Cox-PH models. The Cox-PH models were qualified by calculating Schoenfeld (test for violation of the proportionality assumption) and Deviance (test of linear covariate relationships) residuals and by estimating the statistical power using the individual hazard ratios achieved after bootstrapping (n=1000) and univariate Cox analysis.

For evaluation of ORR and safety events (5% incidence), multivariate logistic regression analyses were employed eliminating a covariate one at a time from a full model ($p < 0.01$). Effect on ORR (or safety event) was evaluated by a final univariate logistic regression for exposure.

Exposure-QTc modelling

Combined C-QTc analyses phase 1 and 2 studies

A preliminary assessment of potential QTc effect was conducted using all ECG measurements of data from phase 1 and phase 2 studies 12871, 15205, 16349, and 16790 which included 285 paired concentration-ΔQTc observations from 126 patients.

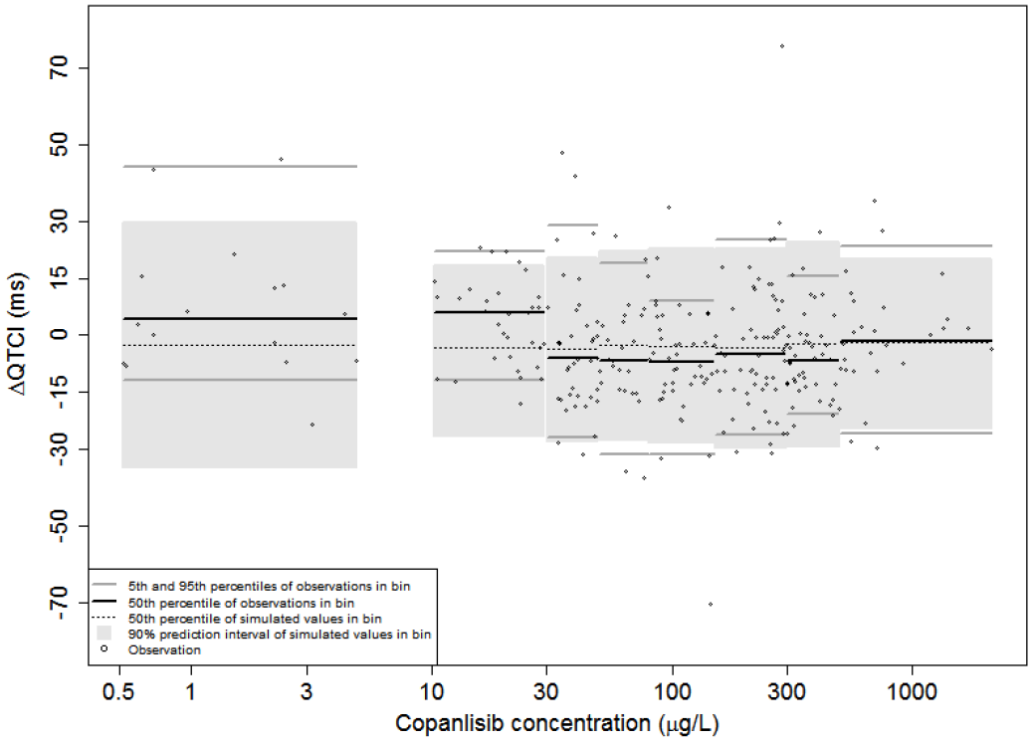
An individualised heart rate correction was achieved using mixed-effects modelling. None of the tested covariate relationships were found to significantly influence the SLOPE parameter, therefore the final model for the copanlisib plasma concentration-ΔQTc relationship was the base model, Run023 (Table 10-11).

Table 10-11: Parameter estimates together with standard errors and confidence intervals for the base model for concentration-ΔQTc relationship (Run023)

Parameter	Unit	Estimate	RSE [%][a]	LLCI[b]	ULCI[c]	Description
Fixed effects (THETA)						
INT	ms	-2.55	45.5	-4.82	-0.276	Estimate of ΔQTcI when copanlisib concentration is zero and when measurement hour is not 14:00 or 15:00
P14	ms	-9.23	45.6	-17.5	-0.978	Estimate of ΔQTcI when copanlisib concentration is zero and when measurement hour is 14:00
P15	ms	-10.6	41.6	-19.2	-1.95	Estimate of ΔQTcI when copanlisib concentration is zero and when measurement hour is 15:00
SLOPE	ms·mg/L	1.18	181	-3.00	5.36	Linear influence of copanlisib concentration on ΔQTcI
NREP_PAR	–	0.732	35.9	0.217	1.25	Parameter describing the increase in variance of residual error for observations comprising ≤2 replicate measurements
CYC_PAR	–	0.838	36.3	0.242	1.43	Parameter describing the increase in variance of residual error for observations in treatment cycle 3
Residual error (SIGMA)						
Resid1 (σ^2)	ms^2	141	10.6	112	170	Additive residual error

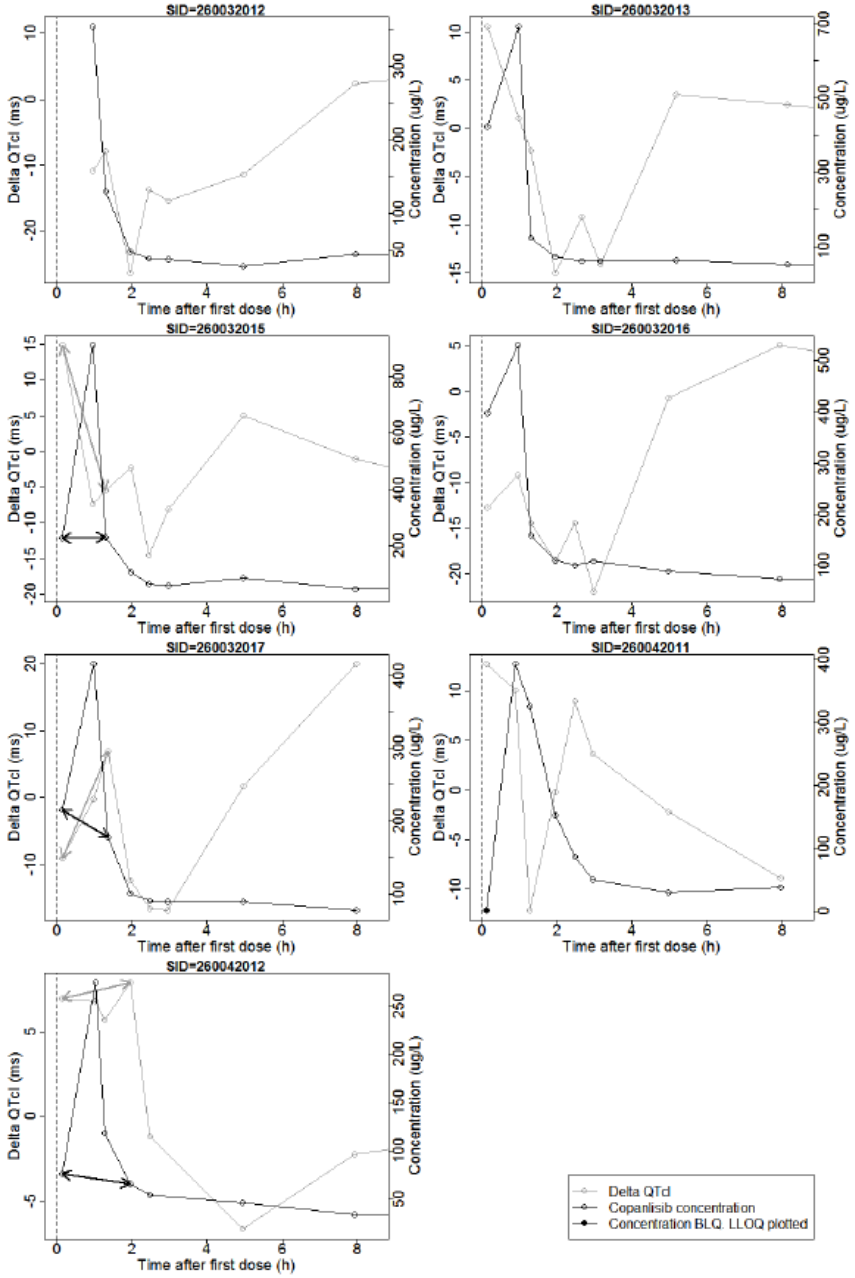
Model structure is given by Eq. 11
[a] RSE = relative standard error (100·SE/|estimate|)
[b] LLCI = lower limit of 95% confidence interval (estimate - 1.96·SE)
[c] ULCI = upper limit of 95% confidence interval (estimate + 1.96·SE)

Figure F-2: Range VPC for final model



The number of patients with dense data for evaluation of hysteresis was low (n=7) and data was collected on Day 1 of treatment.

Figure 10-3: Plots of ΔQTcI and copanlisib concentration versus time after first dose for the 7 patients in study 16270 Arm B

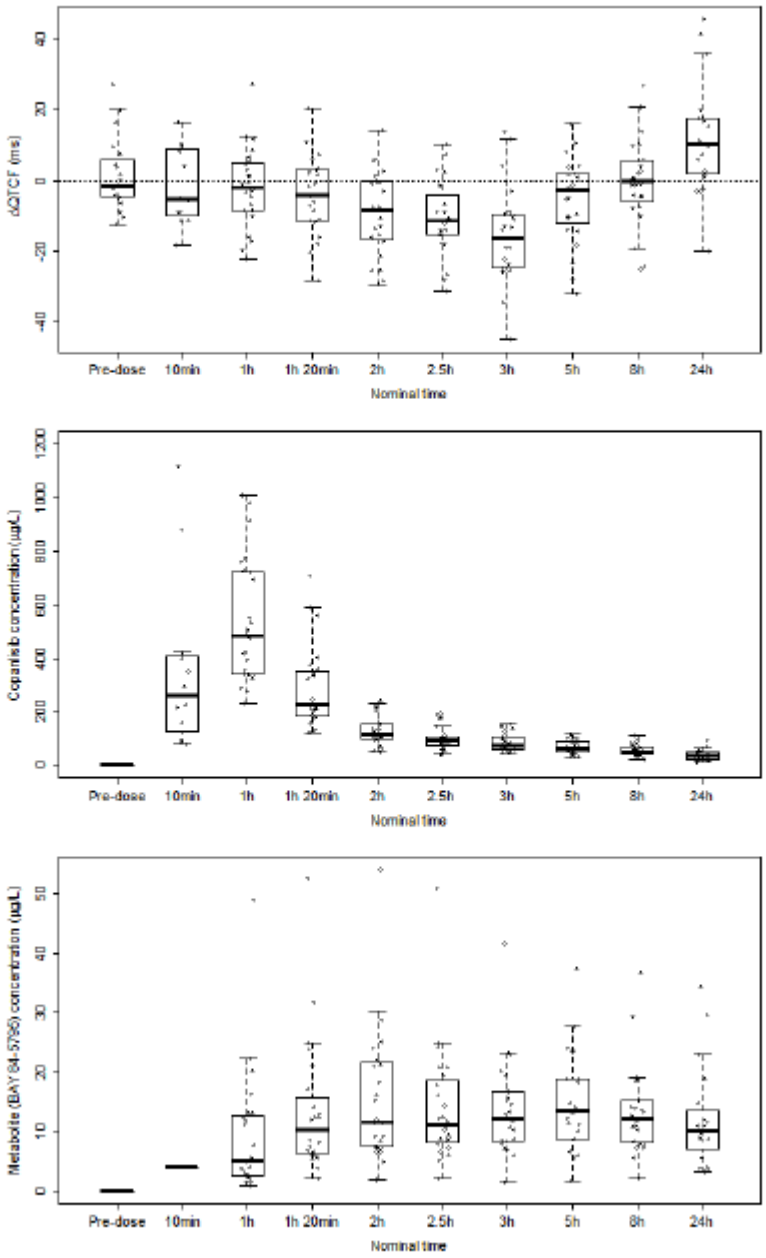


Black double-headed arrows link concentration observations during the infusion with the closest observation post-infusion. Gray double-headed arrows link ΔQTcI observations from same time as the concentration observations that are linked by black double-headed arrows.

Dedicated cardiovascular safety study (16270 Arm B)

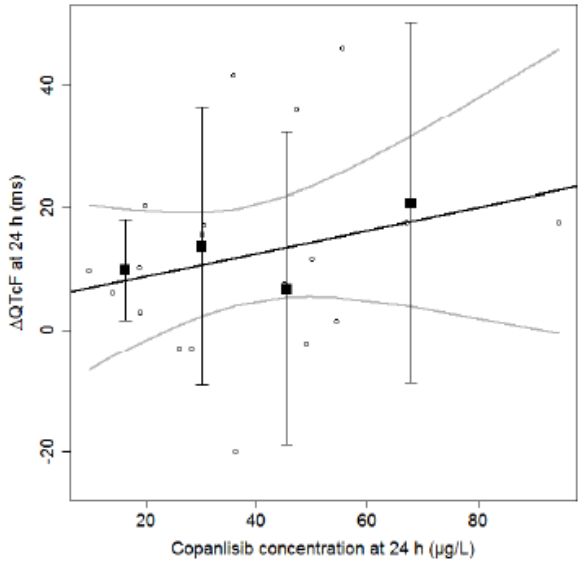
Dense ECG and time-matched PK data of copanlisib and the metabolite M-1 (BAY84-5795) were collected from 25 patients in the cardiovascular safety cohort (Arm B) of clinical study 16270. Data was collected from pre-first infusion (baseline) to up to 24 hours post-start of infusion. The ECG data was corrected for heart rate using Fridericia correction method. A decrease in HR was noticed over the first 2.5 hours but returned to baseline after 24 hours. The largest ΔQTcF were detected at the latest data collection time-point of 24 hours post-start of infusion.

Figure 9-12: Box and whisker plots of ΔQTcF, copanlisib concentration and BAY 84-5795 concentration stratified by nominal time



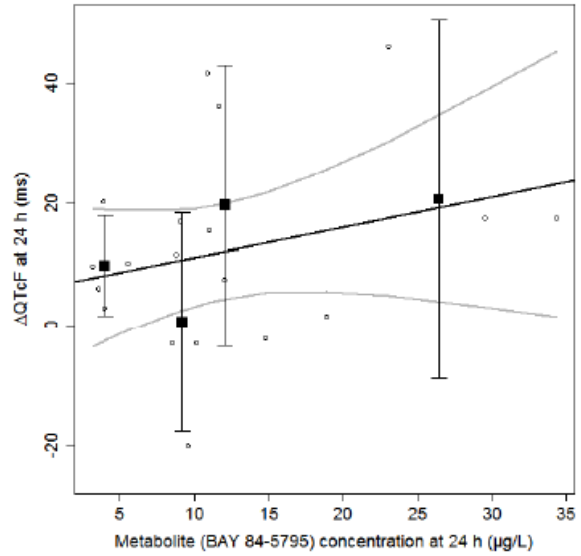
Bold horizontal lines show medians, box shows range between first and third quartile, lower and upper whiskers extend to the lowest and highest data points which are within 1.5 times the inter-quartile range of the first and third quartiles respectively.

Figure 9-13: Plot of ΔQTcF at 24 h versus copanlisib concentration at 24 h



Open circles: Individual data
Closed squares: x=mean of each quartile of copanlisib concentration.
y=mean ΔQTcF in each quartile of copanlisib concentration.
Error bars: 95% CI around mean ΔQTcF from each quartile of copanlisib concentration.
Black line: Linear regression model.
Grey lines: 95% CI around linear regression model.

Figure 9-14: Plot of ΔQTcF at 24 h versus BAY 84-5795 concentration at 24 h



Open circles: Individual data
Closed squares: x=mean of each quartile of BAY 84-5795 concentration.
y=mean ΔQTcF in each quartile of BAY 84-5795 concentration.
Error bars: 95% CI around mean ΔQTcF from each quartile of BAY 84-5795 concentration.
Black line: Linear regression model.
Grey lines: 95% CI around linear regression model.

Table 9-5: Linear regression statistics for relationship between ΔQTcF at 24 h and various exposure variables

Exposure variable	Estimated slope [unit]	LLCI[a]	ULCI[b]	R^2	p-value
Concentration of copanlisib at 24 h	0.185 [ms·L/µg]	-0.201	0.571	0.0567	0.3264
Concentration of BAY 84-5795 at 24 h	0.498 [ms·L/µg]	-0.425	1.42	0.0708	0.2710
Cmax of copanlisib	0.00544 [ms·L/µg]	-0.0261	0.0369	0.0078	0.7199
Cmax of BAY 84-5795	0.577 [ms·L/µg]	-0.0887	1.24	0.1644	0.0850
Copanlisib AUC_{0-24}	0.00567 [ms·L/µg·h]	-0.00762	0.0190	0.0455	0.3807
BAY 84-5795 AUC_{0-24}	0.0336 [ms·L/µg·h]	-0.00922	0.0764	0.1389	0.1161
Concentration of copanlisib at 24 h + Concentration of BAY 84-5795 at 24 h	0.139 [ms·L/µg]	-0.137	0.414	0.0623	0.3029
Concentration of BAY 84-5795 at 24 h/ Concentration of copanlisib at 24 h	41.8 [ms]	-72.9	157	0.0336	0.4524
Copanlisib AUC_{0-24} + BAY 84-5795 AUC_{0-24}	0.00574 [ms·L/µg·h]	-0.00499	0.0165	0.0697	0.2747
BAY 84-5795 AUC_{0-24} / Copanlisib AUC_{0-24}	83.7 [ms]	-49.6	217	0.0936	0.2028

[a] Lower limit of the 95% confidence interval around estimated slope
[b] Upper limit of the 95% confidence interval around estimated slope

C-QTc analysis Japanese phase I study 17792

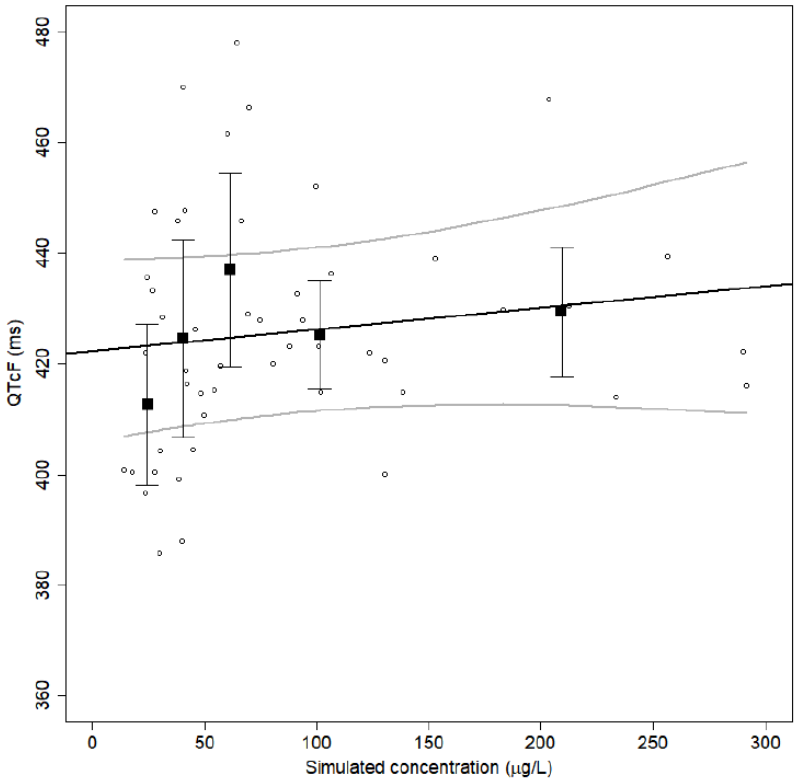
In the Japanese study 17792, 25 subjects contributed 278 copanlisib concentrations. The PK data was collected within the time interval: 0.08 h to 168 h after start of first infusion. ECG data was also collected with more dense data until 24 h on Day 1 and followed up to end of treatment. No ECG data was collected on C1D2. Since the ECG and PK data was not time-matched, the latest Pop PK model was used to predict the copanlisib concentrations at the time of ECG-measurement. No baseline QT data was collected; hence the ΔQTc could not be evaluated. The metabolite M-1 was also measured in Study 17792 at the same time-points as copanlisib, but no C-QTc analysis of M-1 was performed.

Table 9-9: Summary statistics of QTcF stratified by nominal time point

Statistic	n	Minimum	Maximum	Median	Arithmetic mean	Arithmetic SD
Baseline/Screening	25	386.35	453.51	412.94	414.28	17.90
C1D1 1 h 20 min	10	400.06	468.00	426.05	428.00	18.48
C1D1 2h 30 min	10	388.04	452.14	425.62	423.71	16.56
C1D1 5 h	10	385.72	466.53	417.46	418.68	20.41
C1D1 8 h	10	396.62	461.83	423.68	424.65	22.35
C1D1 24 h	10	400.44	478.27	434.49	434.07	27.69
C1D8	10	377.95	446.40	419.13	417.79	19.24
C2D22	19	393.18	519.42	414.54	426.02	27.98
C3D1	7	388.04	460.13	423.00	422.02	22.28
C5D22	8	392.27	441.86	424.01	421.16	16.16
C6D1	7	367.93	454.41	412.11	413.01	28.16
Later visits[a]	20	354.46	445.48	408.69	411.73	19.78
End of treatment	17	348.45	443.46	405.94	401.54	22.88

[a] Measurements recorded at later cycles than those described above.

Figure 9-13: Linear correlation of QTcF with predicted copanlisib plasma concentrations during C1D1 in study 17792

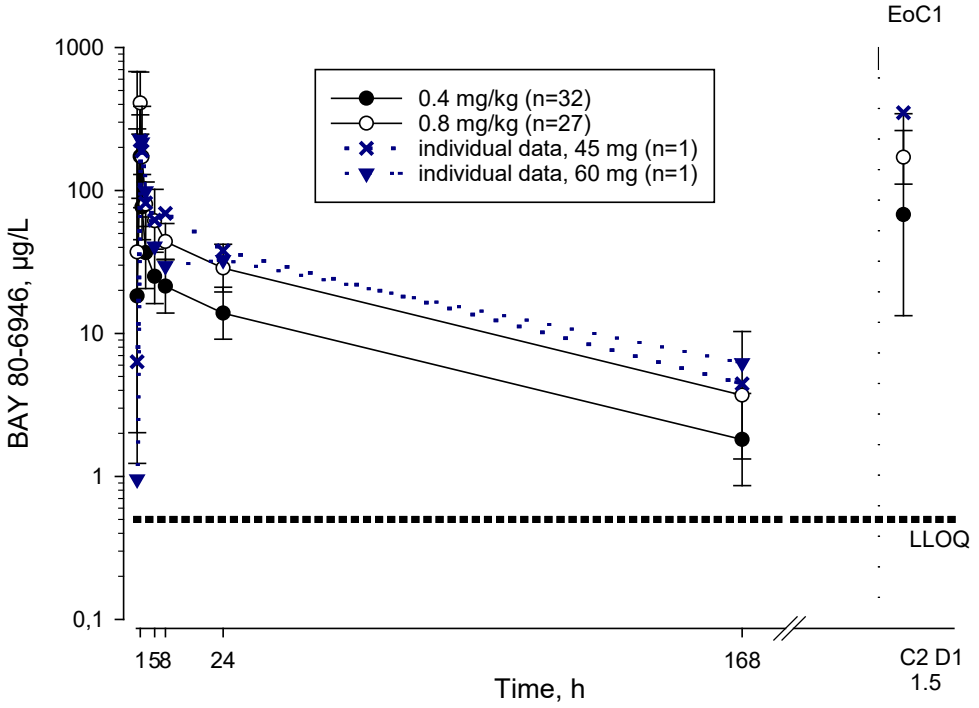


Open circles depict pairs of QTcF and model-predicted copanlisib plasma concentrations at the time of the ECG measurement. The copanlisib plasma concentrations were divided into quintiles and the closed squares depict the mean QTcF at the mean plasma concentration within each quintiles, along with 90% confidence intervals for QTcF. A linear model was fit to the QTcF and concentration data (black line, with grey curves depicting the 90% prediction interval). QTcF does not show a significant linear correlation with predicted copanlisib plasma concentrations (P-value = 0.356).

ADME

The product is intended for intravenous administration and the bioavailability is therefore 100% and Cmax is reached at the end of infusion.

Figure –1 Study 16790 - Geometric mean (StD) concentration-time profiles of copanlisib in plasma after a 1-h IV infusion of copanlisib on C1D1 and C2D1 at dose levels of 0.4 mg/kg and 0.8 mg/kg and individual data at dose levels of 45 mg and 60 mg (PKS)



CXDY = Cycle X, Day Y; EoC1 = End of Cycle 1, IV = Intravenous; LLOQ = Lower limit of quantitation (0.5 µg/L); n = Number of patients; PKS = Pharmacokinetic analysis set; StD = Standard deviation.

Following an IV infusion, copanlisib was rapidly distributed throughout the body with plasma concentration-time profiles showing three distinct phases. The mean volume of distribution (Vz) of copanlisib is large [871 L (range: 423 to 2150L], suggesting that copanlisib is widely distributed in tissues. The CBlood/CPlasma ratio of copanlisib was 1.71 and 1.28 for the metabolite M1, indicating a higher distribution of copanlisib into blood cells than in plasma. Consequently, the plasma protein binding is low (fu=15.8%).

Elimination pathways of copanlisib are unchanged excretion into urine and feces and hepatically via CYP3A4. In the mass balance study, approximately 86 % of the administered dose was recovered with 64 % in faeces and 22 % in urine. Unchanged copanlisib represented approximately 30 % of the administered dose in faeces and 15 % in urine, respectively. Metabolites resulting from oxidation metabolism accounted for 41 % of the administered dose.

The terminal half-life is 39.1 h (range: 14.6 to 82.4 h). The apparent clearance (CL) is 17.9 L/h (range: 7.3 to 51.4 L/h).

Metabolite M1 was the only metabolite observed in plasma covering about 5% of total radioactivity with similar pharmacological activity compared to the parent compound.

Biotransformation of copanlisib is mediated by CYP3A4 (>90% of metabolism) and to a minor extent by CYP1A1 (<10% of metabolism). Copanlisib is a substrate of P-gp and BCRP, but was not identified as a substrate of MATEs, OCTs, OATs or OATPs.

The terminal phase half-life of of the pharmacologically active metabolite M1 is similar to that of the parent drug substance.

In Study 16270 Arm A, exposure data was given of both parent and M-1 after a single dose of 12 mg or 60 mg copanlisib. Based on AUC0-168h, the metabolic ratio can be estimated to about 33% or 17% after 12 mg or 60 mg copanlisib, respectively, which indicate that M-1 is not a minor metabolite.

Dose proportionality and time dependency

Dose linearity both alone and as a combination therapy has been demonstrated in the relevant dose range between 0.1 and 1.2 and 0.2 to 0.8 mg/kg, respectively. The proposed dose is 60 mg (corresponding to 0.8 mg/kg for a 75kg subject).

No accumulation was observed after once weekly dosing when comparing PK on Cycle 1 Days 1 and 15 and Cycle 3 Day 15 in study 12871.

Variability

The inter-individual variability across studies was 40.8% for AUC (0-25) and 65.4% for Cmax in patients (CV%) at steady-state.

Target and special populations

Most data describing the PK of copanlisib were obtained in cancer patients (Table in section 3.3 above). Only study 16353 (human mass balance) and study 19951 (drug interaction study with metformin) were conducted in healthy subjects. The PK of copanlisib was studied in non-cancer subjects with impaired hepatic or renal function.

Impaired renal function

The effect of severe renal impairment on the PK of copanlisib was evaluated in a dedicated single-dose study (12 mg) in non-cancer subjects. The renal clearance of copanlisib was reduced in subjects with severe renal impairment compared to subjects with normal renal function, while geometric mean clearance was similar (32.11 and 34.51 L/h). Cmax was lower in subjects with severe renal impairment (31.77 µg/L) compared to healthy subjects (49.20 µg/L). Mean exposure and mean t1/2 were comparable.

The popPK analysis of patients with normal renal function (35.8%), mild (35%) or moderate (27.6%) renal impairmen indicated that mild to moderate renal impairment does not affect copanlisib clearance.

Impaired hepatic function

The effect of moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment on the PK of copanlisib was evaluated in a dedicated single-dose study (12 mg) in non-cancer subjects. The geometric mean of total copanlisib Cmax and AUC increased 1.38-fold and 1.71-fold, respectively, in subjects with moderate hepatic impairment (Child-Pugh B) and 1.44-fold and 2.71-fold, respectively, in subjects with severe hepatic impairment (Child-Pugh C) compared to subjects with normal hepatic function. The geometric mean unbound AUC (AUCu) of copanlisib was increased by 1.23-fold and 3.77-fold, respectively, in subjects with moderate and severe hepatic impairment.

The popPK analysis of 47 patients with mild hepatic impairment (total bilirubin [TB] ≤ULN and AST >ULN or TB >1 to 1.5 × ULN and AST any value) at baseline and 250 patients with normal hepatic function (TB ≤ULN and AST ≤ULN) revealed no statistically significant effect on copanlisib CL.

Other special populations

The potential impact of age (22-90 years), gender (59% females), body weight (41 to 130 kg), ethnicity (72% whites vs 18% other), creatinine clearance, renal and hepatic impairment, albumin, and geographical region on copanlisib PK was investigated in the popPK analysis. Increasing age was associated with a higher peripheral volume of distribution, and increasing albumin was associated with a higher clearance (see Table 3-10 above). The popPK analysis did not identify age, including elderly age, as a significant covariate influencing copanlisib clearance.

Interactions

Based on *in vitro* studies, it was concluded that copanlisib has a low risk of causing drug-drug interactions through inhibition or induction of CYP enzymes and transporters, except for MATE2-K. Copanlisib was found to be a potent inhibitor of MATE2-K *in vitro*. The clinical relevance of the inhibitory potential of copanlisib on MATE2-K has been evaluated in a human study, indicating no relevant effect of the co-administration of copanlisib on the exposure of metformin.

The effect of itraconazole on copanlisib PK was assessed in a clinical study. AUC increased 1.53-fold (+53%) at therapeutic dose of copanlisib, after co-administration with itraconazole. No substantial change in copanlisib Cmax was observed.

Also, the effect of rifampin on copanlisib PK was assessed. The induction of CYP3A4 relevantly affected the plasma exposure of copanlisib as the geometric mean AUC of copanlisib following co-administration with rifampin decreased by 60% compared to copanlisib alone. The geometric mean Cmax showed no substantial change after copanlisib was co-administered with rifampin. The SmPC reflects this adequately.

Copanlisib has been combined in clinical studies with four chemotherapeutic agents and one targeted agent, including paclitaxel, gemcitabine, gemcitabine / cisplatin, and refametenib. There was no evidence of clinically meaningful PK interactions between copanlisib and gemcitabine, cisplatin (a MATE2-K substrate), paclitaxel (a CYP2C8 substrate), and refametenib (a CYP3A4 substrate).

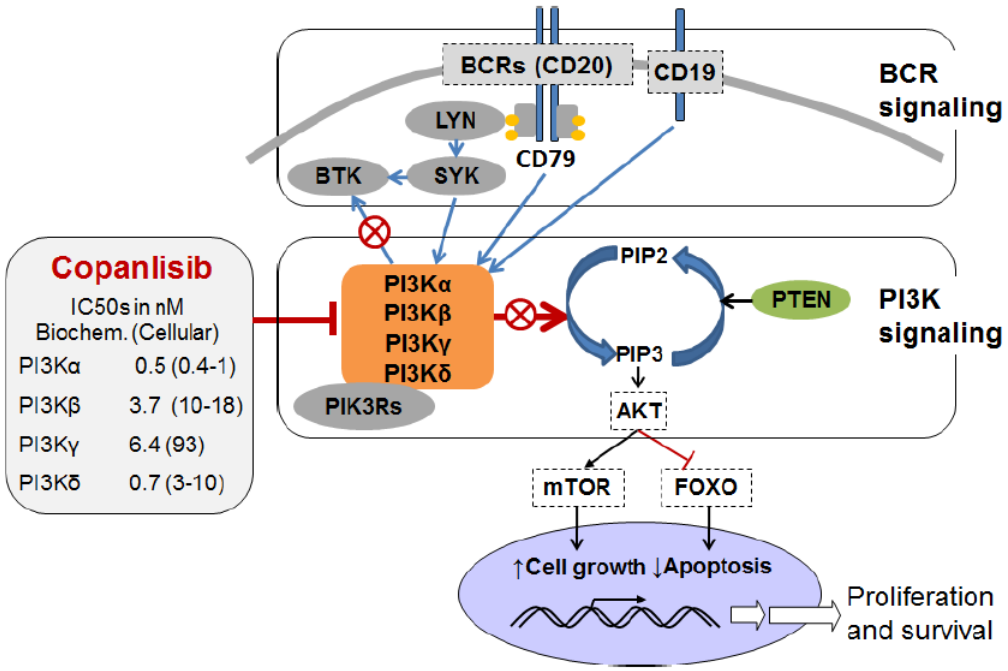
3.3.2. Pharmacodynamics

Mechanism of action

Copanlisib is a potent pan-class I phosphatidylinositol 3-kinase (PI3K) inhibitor against all four PI3K isoforms (α, β, γ, and δ).

Pharmacodynamic biomarkers were used for demonstration of on-target activity. Plasma glucose, insulin, and C-peptide were used as PD markers for activity mediated by PI3K in association with glucose metabolism.

Figure 1–1 PI3K signaling pathways in tumor growth and B-cell malignancies

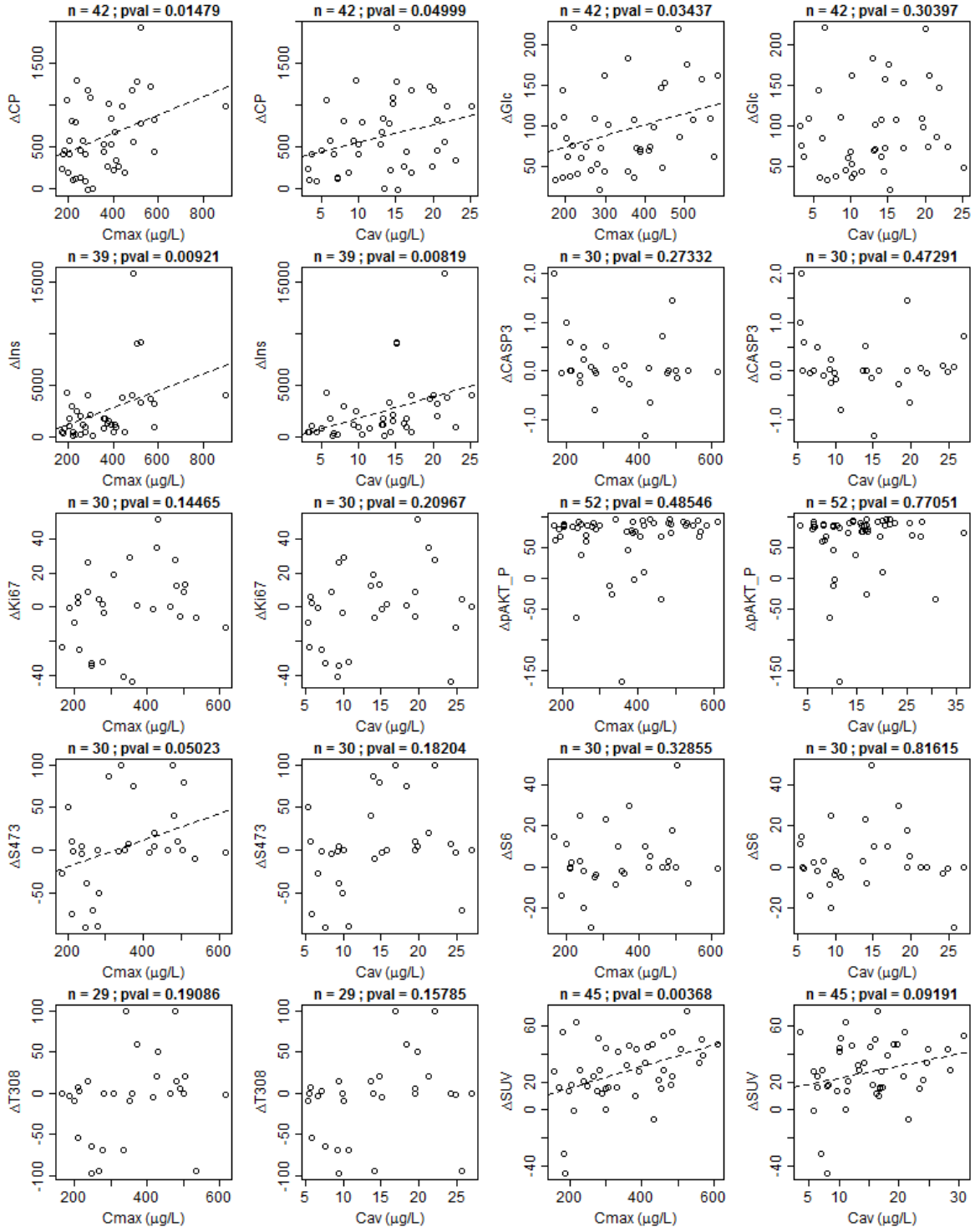


AKT = Protein kinase B; BCR = B-cell receptor; BTK = Bruton's tyrosine kinase;
PI3K = Phosphatidylinositol 3-kinase; PIK3R = PI3K regulatory subunit;
PIP2 = Phosphatidylinositol bisphosphate; PIP3 = Phosphatidylinositol trisphosphate;
PTEN = Phosphatase and tensin homolog

Results from surrogate tissue and tumour tissues from study 16790 were used to demonstrate the on-target inhibition of the PI3K pathway by copanlisib metabolic markers reflecting indirect PD. In study 16790, treatment with copanlisib was associated with transient modulation of blood glucose with corresponding changes in C-peptide and insulin in a dose-dependent manner (0.8 mg/kg > 0.4 mg/kg, **Figure 1-2**).

No predictive biomarker has been identified for copanlisib in NHL that would be appropriate for patient selection.

Figure 1-2: Study 16790 - Plots of various PD markers against exposure variables



The exposure variable (Cmax or Cav) is plotted on the X-axis. The % change from baseline in the PD marker is plotted on the Y-axis. Positive numbers on the Y-axis indicate the anticipated direction of change: a reduction for all PD markers except for ΔCASP3, ΔGlc (glucose), ΔIns (insuline), and ΔCP (C-peptide) where positive numbers indicate an increase. 'n' denotes the number of patients (symbols) in the scatter plot and 'pval' denotes the Pearson's p-value. Regression lines with intercept are only shown when $p < 0.1$.

QT

Based on the meta-analysis of copanlisib exposure and QTc interval across 5 clinical studies in 307 patients (see methods section of this assessment report) and the cardiac safety assessment as part of the integrated safety analysis of 514 patients treated with copanlisib monotherapy, copanlisib does not prolong the QT or QTc interval. There was no statistically significant relationship between copanlisib concentration and change in QTc from baseline.

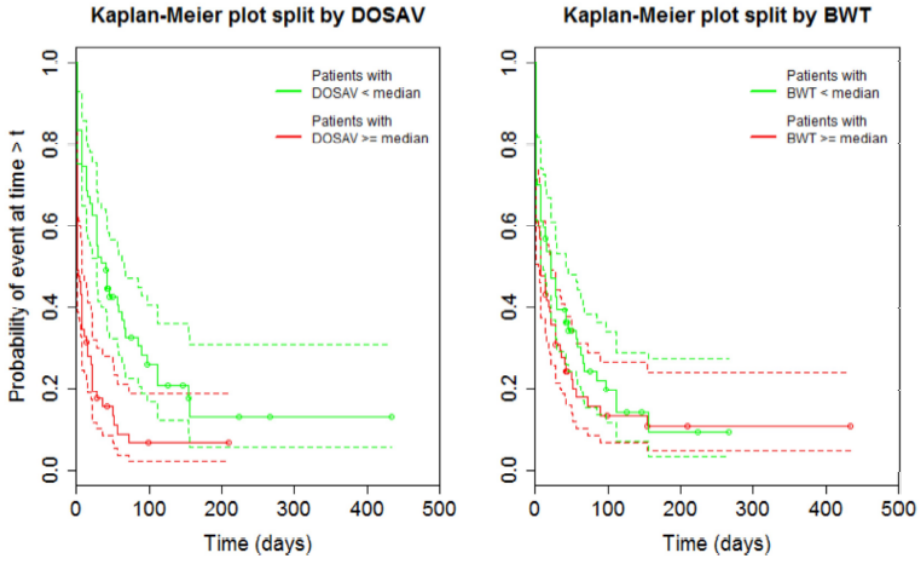
At the proposed recommended dose of 60 mg of copanlisib in cancer patients, no large changes (i.e., greater than 20 ms) in the mean QTc interval (QTcF, QTcB, and QTcI) from baseline were detected at any time point across C1D1, C3D1, and C6D1 from pre-dose to 24 h post dosing in study 16270 B.

No pharmacodynamic drug interaction studies were carried out.

Switch to fixed dose

In a dose-finding study, copanlisib was administered to patients with advanced cancer. The MTD was determined at 0.8 mg/kg in study 12871 (equivalent to approximately 60 mg absolute dose). The switch from body weight-based dosing at the MTD (0.8 mg/kg) to fixed dosing of 60 mg was based on population PK and dose-response analyses. The population PK analysis did not identify a significant effect of body weight on copanlisib exposure (see section 3.3.1). A preliminary TTE analysis of available safety data was conducted to select a fixed dose that would match the benefit/risk profile of the actual weight-based dosing schedules used to date. Safety data of 134 patients in study 12871 (57 patients, 0.1 to 1.2 mg/kg), study 15205 (10 patients, 0.4 and 0.8 mg/kg) and study 16349 Part A (67 patients, 0.8 mg/kg) were used (actual starting total dose: 2 mg to 93 mg; median dose of 54 mg). The preliminary TTE analyses revealed that body weight had no significant effect on the probability of safety events (right panel in Figure 3–13).

Figure 3–13 Model-free assessment of Grade ≥3 events



The panels show Kaplan-Meier plots and their 95% confidence intervals for the first observed Grade ≥3 event in each patient in their respective half of the data file which was split at the median of the average dose rate (DOSAV, left) and body weight (BWT, right). Censored events are indicated by small circles.
Source: Module 5.3.4.2, Report R-11194, Figure 7

The same dosing schedule (1-h IV infusion on Days 1, 8, and 15 of a 28-day treatment cycle) was used throughout clinical development, except in studies 12874, 12875 and 12876 investigating various chemotherapy combination therapies.

Exposure-response relationships

Exposure-efficacy in monotherapy

Initially, the relationship between copanlisib exposure and efficacy endpoints used time-varying copanlisib plasma exposure variables and was assessed using data from the efficacy analysis from 152 patients diagnosed with FL or MZL (study 12871, N=6; study 16349 Part A, N=19; and study 16349 Part B, N=127). The exposure-efficacy analysis by PTTE modeling used one more patient in study 16349 Part A, resulting in 153 patients in total.

There was no significant exposure-response relationship for any of the efficacy endpoints (ORR, PFS, DOR) in studies 12871 and 16349.

As disease progression, AEs, and copanlisib dosage adjustment influenced the exposure, causal relationships between exposure and responses may have been obscured or even reversed. Therefore, the relationship between copanlisib exposure and the efficacy endpoint PFS was re-assessed using updated data (MAY 2020) from patients with iNHL in study 16349 Part B. Three analysis data sets were used: all patients (N=143), patients with FL (N=104), and patients with MZL (N=23). Copanlisib AUC(0-168)nd and Cmax,nd were tested as time-invariant plasma exposure variables.

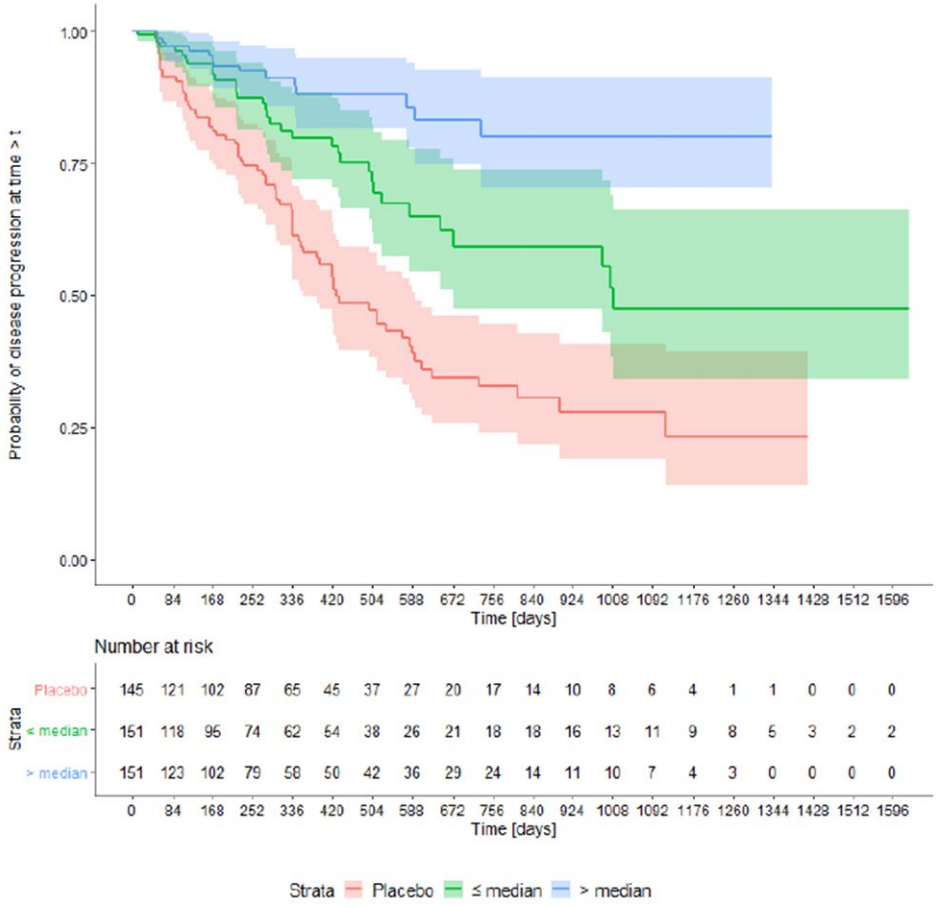
The exposure-response efficacy analysis of PFS in all patients of study 16349 Part B did not identify any relationship between covariates related to demographics, prior treatments, disease status, histology, and PFS. Furthermore, no association between copanlisib exposure [AUC(0168),nd] and Cmax,nd] and PFS was found, whether considering all patients, only FL patients, or only MZL patients.

Exposure-efficacy in combination with rituximab

Study 17067 was a Phase 3, randomised, double-blind, placebo-controlled, two-arm study evaluating the efficacy and safety of 60mg copanlisib in combination with rituximab in patients with relapsed indolent B-cell non-Hodgkin's lymphoma (iNHL) - CHRONOS-3. 458 patients were randomised in a 2:1 ratio to study treatment (307 patients to copanlisib/rituximab [Copa/R] and 151 patients to placebo/rituximab [Pbo/R]). Of these, 304 patients in the Copa/R arm and 149 patients in the Pbo/R arm received at least one dose of study treatment.

The exposure-response analysis for efficacy focused on the two study endpoints PFS and ORR. For all iNHL patients in study 17067, a multivariate analysis of PFS did not identify any relationship between covariates related to demographics, prior treatments, disease status, and PFS. An association between a larger area under the copanlisib plasma concentration-time curve and a higher maximum plasma concentration [AUC(0-168)nd and Cmax,nd] and longer PFS was found (Figure 3–29). Equivalent analyses including only patients with FL or only patients with MZL did not find any association between copanlisib exposure and PFS.

Figure 3–29 Kaplan-Meier plot of progression-free survival in the total analysis data set stratified by AUC(0-168)$_{nd}$ - branch trial 17679



AUC(0-168)$_{nd}$ = Area under the plasma concentration-time curve from 0 to 168 h after three nominal doses of 60 mg copanlisib.
Kaplan-Meier survival curves with 95% confidence intervals and risk table for progression-free survival in the total analysis data set, stratified by patients with simulated AUC(0-168)$_{nd}$ above the median (blue) or equal to or below the median (green) or patients in the placebo treatment arm (red).
Source: Module 5.3.4.2, Report R-13388, Figure 5-7

A logistic regression analysis of ORR in the total analysis data set found a relationship with treatment arm (copanlisib vs. placebo), but no additional influence of covariates related to demographics, prior treatments, disease status, or histology. Beyond treatment, no further influence of copanlisib plasma exposures was found. In the FL analysis data set, a small disease burden (lesions <7 cm) was found to be influential besides treatment, but copanlisib exposure played no role. In the MZL analysis data set, neither covariates nor treatment nor copanlisib exposure showed an influence on ORR.

Exposure-safety in monotherapy

Initially, the relationship between time-variant copanlisib exposure to selected AEs of all grades including the MedDRA preferred terms hyperglycaemia and hypertension was assessed using data from the pooled safety analysis from 152 patients diagnosed with FL or MZL (study 12871, N=6; study 16349 Part A, N=19; and study 16349 Part B, N=127).

The initial combined exposure-response analysis of Phase 1 and Phase 2 studies found no significant exposure-response relationship between copanlisib exposure and selected safety endpoints such as hyperglycaemia, hypertension, thrombocytopenia, mucositis, and rash after administration of 60 mg copanlisib. Higher copanlisib exposure did not increase the risk of lung infections (including pneumonitis) or neutropenia (any Grade, Grade ≥2, Grade ≥3). Higher copanlisib exposure was not

associated with the risk of dose reductions, interruption or permanent discontinuations. This earlier analysis was again superseded by an updated analysis avoiding time-varying exposure covariates.

The re-analysis of exposure-response for safety events of study 16349 Part B focused on the following endpoints: first occurrence of any grade TEAE of hyperglycaemia, hypertension, diarrhoea, nausea, fatigue, lung infections (including pneumonitis), or neutropenia. For each safety endpoint a separate Cox Proportional Hazards analysis of time-invariant exposure variables with selected covariates was performed. The analysis revealed an association between North American patients and increased incidence of nausea and fatigue. These relationships were apparent in the entire population and for FL patients only. An increased likelihood of hypertension for patients older than 65 years and an increased likelihood of fatigue in MZL patients was also found when considering the entire population. No significant association between copanlisib exposure and any safety event was identified for any study population analysed.

Exposure-safety in combination with rituximab

The exposure-response analysis for safety in study 17067 focused on the following endpoints: first occurrence of any grade (and of Grade 3 and higher in a separate analysis) TEAE of hyperglycaemia, hypertension, diarrhoea, nausea, fatigue, lung infections (including pneumonitis), or neutropenia. Multivariate logistic regression analyses of TEAEs in the total analysis data set found an association of copanlisib treatment with hyperglycaemia, hypertension, diarrhoea, and neutropenia, but copanlisib plasma exposures were not influential. Besides treatment, the geographic region China was associated with an increased risk of hyperglycaemia, hypertension, lung infection, and neutropenia. Additionally, the region Japan was found to have an increased risk of neutropenia. High rituximab exposure and high levels of glycated hemoglobin (Hb1Ac) also contributed to an increased risk of hyperglycaemia. A low ECOG performance score and being female were found to be associated with a higher risk of nausea, and low neutrophil count increased the risk of lung infection (including pneumonitis) and neutropenia.

Similar associations were identified in the analysis data sets for FL and for MZL.

3.3.3. Discussion on clinical pharmacology

The clinical pharmacology assessment included in the application was based on several clinical studies examining single-dose and multiple-dose PK of copanlisib in patients with solid tumours (ST) and NHL as well as the single-dose PK in healthy subjects, mass balance/absorption, distribution, metabolism, and excretion (ADME), drug interactions and impact of renal and hepatic impairment in non-cancer subjects. In addition, a popPK model was used to estimate population PK parameters and to generate exposures for ER analysis. Overall, the outlined PK/PD study programme for copanlisib is considered comprehensive.

Bioanalysis

Overall, the bioanalytical method and within study validation conducted in support of copanlisib clinical development is considered acceptable, with a few exceptions due to missing documentation.

Population PK

Copanlisib population PK was described by nonlinear mixed-effects models with a 3-compartment structure. The main model supporting the MAA contained data from studies 12871, 15205 and 16349-part A (mg/kg dosing). The popPK model has been used to describe PK, identify covariates with impact on PK, generate exposure data for ER efficacy and safety analysis, support a fixed dose regimen and to simulate exposure to support dose recommendation in severe hepatic impairment. The model is of

moderate to high regulatory impact if used to inform dose recommendations, however it is not considered fit for this purpose. The main model is developed based on limited information, is primarily data driven rather than based on biological plausibility and has remaining unexplained variability, which restricts its usefulness to descriptive purposes. There are moderate to high variation in copanlisib PK, but currently the patients who could potentially benefit from dose adjustments cannot be accurately identified. The switch from weight-based dosing to the 60 mg flat dose needs further justification. The model failed to accurately predict the observed data in study 17067 (60 mg flat dose regimen), except around 1-hour post-infusion start. A new popPK model should be developed based on a larger PK data set for a thorough evaluation of all covariates, including weight effects following flat 60 mg dosing. It is questioned wether the active metabolite M-1 can be regarded as a minor metabolite and the PK of M1 should be evaluated at the population level.

QTc

Assessment of potential QTc effect of copanlisib was performed using modelling trough 3 different C-QTc analyses. First, a preliminary assessment of potential QTc effect was conducted using all ECG measurements of data from phase 1 and phase 2 studies 12871, 15205, 16349, and 16790 followed by a dedicated cardiovascular safety study (16270 Arm B) and a c-QTc analysis of data from the Japanese phase 1 study 17792. The largest ΔQTcF were detected at the latest data collection time-point of 24 hours post-start of infusion. A possible further prolongation after 24h cannot be ruled out. Exploratory plots of copanlisib concentrations and M-1 concentrations against ΔQTcF suggest that copanlisib itself might not cause QTc prolongation, as Tmax was reached already at 1 hour, unless there is a time delay of effect (hysteresis). The plasma time-profile of M-1 reached a maximum about 2 hours post-start of infusion with decline >8 hours. Baseline was not reached after 24 hours indicating a longer half-life of M-1 and thus different PK of M-1 compared to copanlisib. A negative study as defined by the ICH E14 criteria is an upper one-sided 95% CI of QTc prolongation effect <10 ms. The applicant should justify the use of a cut off of 20ms. The potential of copanlisib to induce QT prolongation cannot be disregarded based on this study. It should be discussed whether a new QT study, or intensive ECG monitoring in later-stage trials to obtain further information on the frequency of marked QT prolongation >8-24 h post dose, is warranted (as recommended in ICH E14 Q&As (R3).

ADME

The product is intended for intravenous administration and the bioavailability is therefore 100% and Cmax is reached at the end of infusion. Following an IV infusion, copanlisib was rapidly distributed throughout the body with plasma concentration-time profiles showing three distinct phases. The mean volume of distribution (Vz) of copanlisib is large [871 L (range: 423 to 2150 L], suggesting that copanlisib is widely distributed in tissues. The CBlood/CPlasma ratio of copanlisib was 1.71 and 1.28 for M1, indicating a higher distribution of copanlisib into blood cells than in plasma. Consequently, the plasma protein binding is low.

Elimination pathways of copanlisib are unchanged into urine and feces and hepatically biotransformation of copanlisib is mediated by CYP3A4 (>90% of metabolism) and to a minor extent by CYP1A1 (<10% of metabolism). Copanlisib is a substrate of P-gp and BCRP. A concern has been raised regarding the concentrations of copanlisib used in the *in vitro* assays evaluating substrate characteristics towards hepatic uptake transporters. M1 is the only relevant metabolite with similar pharmacological activity compared to the parent compound. The applicant concludes that M-1 is no major metabolite as it represented about 5% (range 1.6-12%) of total radioactivity in plasma. However, the percent M-1 of total radioactivity appears to be calculated based on AUC of total radioactivity (AUC(0-$t_{last,rad}$)) in which $t_{last,rad}$ ranged between 24 and 96h, and AUC of M-1 (AUC(t_{last})) in which t_{last} ranged between 8 and 36h, i.e. considerably shorter. It would therefore seem likely that the calculated percentages M-1 of total radioactivity are underestimated, and the applicant should

elaborate on the estimation of these percentages to justify the statement that M-1 can be considered a minor metabolite. The half-life of M1 should be mentioned in section 5.2 of the SmPC. The terminal half-life of copanlisib is 39.1 h (range: 14.6 to 82.4) h. The apparent clearance (CL) is 17.9 L/h (range: 7.3 to 51.4) L/h.

Dose linearity both alone and as a combination therapy has been demonstrated in the relevant dose range between 0.1 and 1.2 and 0.2 to 0.8 mg/kg respectively based on graphical depiction of dose-normalised data. The applicant should also present a scatterplot of absolute dose administered vs. AUC and Cmax. Further, dose proportionality should also be statistically evaluated across the studied range of absolute doses, preferably using a power function regression. The proposed dose is 60 mg (corresponding to 0.8 mg/kg for a 75kg subject). No accumulation was observed after once weekly dosing.

Inter-individual variability for AUC and Cmax was moderate to high, while no information on intra-individual variability was found in the dossier. The applicant is asked to provide those data for both parent drug and active metabolite.

Target population

PK parameters of copanlisib were generally comparable between healthy volunteers and cancer patients based on the observed means and range of systemic exposure following single dosing.

Special populations

The potential impact of various intrinsic factors, including age, gender, race, and body weight as well as renal or hepatic impairment populations have been examined by the use of popPK analyses. In addition, a dedicated clinical study has examined the PK of copanlisib in patients with impaired hepatic and impaired renal function. The dose used was only 1/5 of the the recommended dose. While it is acknowledged that a conservative approach minimises patient risks, the applicant should justify the transferability of the results to the higher dose. Exposure, clearance and half-life were comparable in subjects with severe renal impairment compared to subjects with normal renal function despite the renal clearance being reduced in subjects with severe renal impairment. Results of the popPK analysis support that mild to moderate renal impairment does not affect copanlisib clearance.

The geometric mean of total copanlisib Cmax and AUC increased 1.38-fold and 1.71-fold, respectively, in subjects with moderate hepatic impairment (Child-Pugh B) and 1.44-fold and 2.71-fold, respectively, in subjects with severe hepatic impairment (Child-Pugh C) compared to subjects with normal hepatic function. The popPK revealed no statistically significant effect of mild hepatic impairment on copanlisib CL. Dose recommendations in patients with hepatic impairment are based on results from simulations using the existing popPK model. The model is not fit for this purpose as there are not sufficient information on the moderate to severe hepatic impairment categories in the PK data set on which the model is built. Furthermore, the unbound exposure of copanlisib was not taken into account in the simulations. The applicant should propose dose recommendations in patients with hepatic impairment based on results from the dedicated PK study, taking into consideration the observed differences in unbound fraction of copanlisib.

The results from the popPK analysis point to no clinically significant differences in the PK parameters across subjects based on gender, bodyweight, or age. There are insufficient data on ethnicity/race to conclude on any impact on copanlisib PK. The weight range in the clinical studies is wide and a fixed dose as proposed is considered acceptable. However, the popPK analysis should be repeated using a larger dataset. The applicant should fill out the table regarding the available PK data on the elderly.

Interactions

Copanlisib metabolism is mediated by CYP3A4 (>90%) and to a minor extent by CYP1A1 (<10%). In addition, copanlisib is a substrate of P-gp and BCRP. The drug-drug interaction studies showed that copanlisib PK is affected by strong inhibitors (53% increase in AUC) and inducers of CYP3A4 (60% decrease in AUC). The applicant concludes that no dose adjustment is needed when copanlisib is coadministered with CYP3A4 inhibitors based on the lack of association found between copanlisib exposure and occurrence of Grade 3 AEs in the exposure-response analyses. However, the knowledge of exposure-response relationships is currently considered too limited to draw this conclusion. The applicant is asked to propose a dosing regimen for patients concomitantly treated with strong CYP3A4 inhibitors with the highest probability of achieving equivalent systemic exposure to patients not treated with CYP3A4 inhibitors. Further, it is unclear how the applicant has been able to discriminate between the cause of the increase, as itraconazole is classified not only as a strong CYP3A4 inhibitor but also as a P-gp/BCRP transporter inhibitor and copanlisib was found to be a substrate of P-gp and BCRP *in vitro*. The applicant should justify the proposed metabolic pathway of the AUC increase and explain how possible interactions with P-gp and BCRP are handled.

Copanlisib has been combined in clinical studies with four chemotherapeutic agents and one targeted agent, including paclitaxel, gemcitabine, gemcitabine / cisplatin, and refametenib. There was no evidence of clinically meaningful PK interactions between copanlisib and gemcitabine, cisplatin (a MATE2-K substrate), paclitaxel (a CYP2C8 substrate), and refametenib (a CYP3A4 substrate).

Some concerns have been raised regarding the potential of copanlisib to act as an inducer of CYP enzymes and an inhibitor of P-gp based on results from *in vitro* studies.

Copanlisib is a potent pan-class I phosphatidylinositol 3-kinase (PI3K) inhibitor against all four PI3K isoforms (α, β, γ, and δ). Plasma glucose, insulin, and C-peptide were used as PD markers for activity mediated by PI3K in association with glucose metabolism.

Switch to fixed dose

The popPK model was used to support a switch from body weight-based to fixed dosing due to the lack of a significant effect of body weight on copanlisib exposure. However, this model has been questioned and the switch to flat 60 mg dosing regimen for copanlisib is thus not yet considered justified. The applicant also justifies the fixed dosing with a model-free assessment, where there was no apparent relationship between body weight and Grade 3+ adverse events. This could support the fixed-dose regimen. Of note, the applicant's analysis of average dose (DOSEAV) and Grade 3+ adverse events display an apparent dose-response relationship for safety (left panel in Figure 3-13 in section 3.3.2). From a safety point of view, this may suggest that a lower starting dose level than 60 mg would lead to reduced toxicity.

Exposure response

Overall, the ER analyses have limitations due to the underlying clinical data. The majority of subjects started therapy on the MTD, and only data from subjects starting at 0.8 mg/kg or flat 60 mg dosing were utilised in the ER analyses. The subsequent plasma exposure-ranges are therefore narrow, which limits the possibility to quantify how efficacy and safety endpoints potentially change in relation to different dose- and exposure levels.

Monotherapy

The applicant has presented two different ER analyses. Initially, exposure-response was investigated with time-variant exposure. There was no significant exposure-response relationship for any of the efficacy endpoints (ORR, PFS, DOR) in the combined Phase 1 and 2 studies. The same, i.e. no

significant exposure-response relationship between copanlisib exposure and selected safety endpoints such as hyperglycaemia, hypertension, thrombocytopenia, mucositis, and rash was found after administration of 60 mg copanlisib. Higher copanlisib exposure did not increase the risk of lung infections (including pneumonitis) or neutropenia (any grade, Grade ≥2, Grade ≥3). Higher copanlisib exposure (Cmax or Cavg) was not associated with the risk of dose reductions, delays, or discontinuations. Thus, the recommended dose reduction in case of toxicity as described in section 4.2 of the SmPC is not pharmacologically substantiated.

As pointed out by the applicant, for the time-variant exposure metric the causal relationships between exposure and responses may have been obscured or even reversed, limiting the impact of the analyses. In the repeat analysis with time-invariant exposure, there was no association between exposure and PFS over the investigated exposure range for copanlisib monotherapy. It has not been found an updated analysis with ORR as endpoint in the dossier. The applicant is requested to conduct such an analysis with time-invariant copanlisib exposure.

No significant association between time-invariant copanlisib exposure and any safety event was identified for any study population analysed. However, the exposure-safety analyses are limited by few subjects and narrow exposure range and cannot be used to rule out associations between exposure and the investigated adverse events.

Co-treatment with rituximab

The exposure-response analyses show conflicting results, depending on co-treatment and which efficacy endpoint was used. The results for combination therapy indicate that patients with low plasma exposure achieve shorter PFS. The interindividual variability in plasma exposure is high, and patients with high clearance could potentially benefit from individual dose adjustments to achieve a target plasma exposure, i.e. therapeutic drug monitoring (TDM). However, a target plasma exposure has not been defined. Copanlisib at the recommended starting dose was poorly tolerated, as indicated by high rates of dose modifications and discontinuations (see 3.3.7. Clinical safety). Taken together, the optimal dose or target exposure is not well characterised. The applicant should describe their planned efforts to optimise copanlisib dosing in MZL, and other potential indications, as well as discuss whether there should be different dose modifications with and without rituximab.

A logistic regression analysis of ORR in combination therapy found a relationship with treatment arm (copanlisib vs. placebo), but no influence of copanlisib plasma exposures. This could indicate that plasma exposure is at, or above the plateau for tumour response, and could also indicate that remaining on treatment over time could be more influential for efficacy than the actual doses given. Therefore, the applicant should investigate the relationship between time-invariant exposure and copanlisib treatment discontinuation and dose modifications (reduction and interruptions). This should be done for both copanlisib monotherapy and combination therapy with rituximab. In contrast exposure-efficacy as well as exposure-safety relationships could be shown in phase 3 study 17067 with the same dose given concomitantly with rituximab.

Conclusions on clinical pharmacology

The clinical pharmacology programme consists of a multitude of clinical studies and popPK analyses. Most studies were conducted in the target population of cancer patients and the pharmacology package is considered adequate. No major objections were identified with respect to the clinical pharmacology. However, before approval of the medicinal product, several issues remain to be solved regarding the use of a flat dose regimen, effects of body weight, DDI potential, dose recommendations in patients with hepatic impairment and potential delayed C-QTc effect. The PK/PD of the active metabolite M1 is not adequately characterised.

Few investigated dose levels in the clinical trials and subsequent narrow exposure ranges leave the dose-response and exposure-response relationships to a large extent undescribed. The proposed start dose is at the MTD, and it is unknown whether a lower start dose would lead to similar efficacy, but is expected to provide better safety profile.

3.3.4. Clinical efficacy

Table 2–1 Overview of clinical studies supporting efficacy of copanlisib in combination treatment and monotherapy

Study no. (NCT / EudraCT no.) Region (No of countries, No of centers) Study status (cut-off date)	Design Copanlisib dose and schedule	Study population	No. of patients included in the efficacy analysis	Main outcomes Reference
Phase 3 combination study in iNHL				
17067 – CHRONOS-3 (pivotal study) (NCT02367040 / EudraCT: 2013-003893-29) Asia, Australia, Europe, New Zealand, North America (Mexico and the US), Russia, South Africa, and South America (37 countries,186 study centers) Primary completion (cut-off 31 AUG 2020), ongoing	*A Phase III, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of copanlisib in combination with rituximab in patients with relapsed iNHL – CHRONOS-3*			
	Randomized (2:1), double-blind, placebo-controlled (Copa/R vs. Pbo/R), two-arm Combination therapy: Copanlisib (or placebo) 60 mg IV Days 1, 8, and 15 of a 28-day treatment cycle Rituximab 375 mg/m^2 IV weekly during Cycle 1 (on Days 1, 8, 15, and 22), and on Day 1 of Cycles 3, 5, 7, and 9	Patients with relapsed iNHL after one or more prior lines of therapy	Total (copanlisib vs. placebo): 458 (307 vs. 151) FL: 275 (184 vs. 91) MZL: 95 (66 vs. 29) SLL: 50 (35 vs.15) LPL/WM: 38 (22 vs.16)	Efficacy, safety, tolerability Module 5.3.5.1, Report PH-41310
Phase 2 monotherapy studies in NHL [-]				
16349 Part B – CHRONOS-1 (pivotal study) (NCT01660451 / EudraCT: 2012-002602-52) US, Canada, Europe, Asia Pacific, Russia, Israel, Australia, New Zealand (24 countries, 81 study centers) Primary completion 2016 (follow-up cut-off: 20 FEB 2018), ongoing	*Open-label, uncontrolled Phase II trial of intravenous PI3K inhibitor BAY 80-6946 in patients with relapsed, indolent or aggressive NHL (Part B: indolent patients only)*			
	Open-label, uncontrolled, single-arm Monotherapy: 60 mg IV [b] Days 1, 8, and 15 of a 28-day treatment cycle	Patients with relapsed or refractory iNHL after at least two prior lines of therapy	Total: 142 iNHL: 141 FL: 104 MZL: 23 Other iNHL: 14	Efficacy, safety Module 5.3.5.2, Report PH-38670 Module 5.3.5.2, Report PH-40438

Study no. (NCT / EudraCT no.) Region (No of countries, No of centers) Study status (cut-off date)	Design Copanlisib dose and schedule	Study population	No. of patients included in the efficacy analysis	Main outcomes Reference
16349 Part A (NCT01660451 / EudraCT: 2012-002602-52) US, Canada, Europe (10 countries, 41 study centers) Completed, LPLV 13 AUG 2018	Open-label, uncontrolled, parallel group Monotherapy: 0.8 mg/kg IV Days 1, 8, and 15 of a 28-day treatment cycle	Patients with relapsed or refractory iNHL, aNHL, or CLL after at least two lines of therapy	Total: 51 aNHL and 33 iNHL/CLL CLL:13 iNHL: 20 ○ FL: 16 ○ MZL: 3 ○ Other iNHL:1	Efficacy, safety Module 5.3.5.2, Report PH-37856 Module 5.3.5.2, Report PH-38458 Module 5.3.5.2, Report PH-38661 Module 5.3.5.2, Report PH-40792
Phase 1b/2 monotherapy study in iNHL				
17792 (NCT02342665) Japan (13 study centers) Primary completion 2018 (follow-up cut-off: 20 FEB 2020), ongoing	*Open-label, uncontrolled, single-arm, Phase Ib/II study of intravenous copanlisib in Japanese patients with iNHL relapsed after or refractory to standard therapy*			
	Open-label, uncontrolled, single-arm Monotherapy: 45 and 60 mg IV Days 1, 8, and 15 of a 28-day treatment cycle	Japanese patients with relapsed or refractory iNHL	Total: 25 (all iNHL)	Safety (efficacy was a further objective) Module 5.3.3.3, Report PH-39332 Module 5.3.3.3, Report PH-40185 Module 5.3.3.3 Report PH-41437

Study no. (NCT / EudraCT no.) Region (No of countries, No of centers) Study status (cut-off date)	Design Copanlisib dose and schedule	Study population	No. of patients included in the efficacy analysis	Main outcomes Reference
Phase 1 monotherapy studies in NHL or solid tumors				
16866 (NCT03498430) China (one study center) Primary completion (cut-off: 06 AUG 2019) [c] Completed, LPLV 02 JUN 2020	*An open label, Phase I study of copanlisib to evaluate the pharmacokinetics, safety and tolerability in Chinese patients with relapsed iNHL*			
	Open-label, uncontrolled, non-randomized, single-arm Monotherapy: 60 mg IV Days 1, 8, and 15 of a 28-day treatment cycle	Chinese patients with relapsed iNHL		Safety, tolerability, PK, tumor response Module 5.3.3.3, Report PH-40801 Module 5.3.3.3, Report PH-41608 [c]
12871 (NCT00962611) US (three study centers) Completed, LPLV 23 FEB 2016	*An open-label Phase I dose-escalation study to evaluate the safety, tolerability, pharmacokinetics, maximum tolerated dose, and biomarker response after intravenous administration of weekly BAY 80-6946 to patients with advanced cancer*			
	Open-label, uncontrolled, multi-center Monotherapy: Dose-escalation cohorts (0.1–1.2 mg/kg IV) MTD expansion cohorts: 0.8 mg/kg IV Diabetic cohort: 0.4 mg/kg IV Days 1, 8, and 15 of a 28-day treatment cycle	Dose-escalation cohort: cancer patients with advanced solid tumors MTD expansion cohorts: patients with NHL or solid tumors Diabetic cohort: patients with solid tumors	Total: 49 NHL: 9 FL: 6 (DLBCL:3)	MTD, safety, tolerability, PK, biomarkers, pharmacodynamics, efficacy Module 5.3.3.2, Report PH-37433 (amended as of 15 NOV 2016)

Study no. (NCT / EudraCT no.) Region (No of countries, No of centers) Study status (cut-off date)	Design Copanlisib dose and schedule	Study population	No. of patients included in the efficacy analysis	Main outcomes Reference

aNHL = Aggressive non-Hodgkin's lymphoma; CLL = Chronic lymphocytic leukemia; Copa = Copanlisib; CSR = Clinical Study Report; DLBCL = Diffuse large B-cell lymphoma; FL = Follicular lymphoma; iNHL = Indolent non-Hodgkin's lymphoma; IV = Intravenous; LPL = Lymphoplasmacytoid lymphoma; LPLV = Last patient last visit; MTD = Maximum tolerated dose; MZL = Marginal zone lymphoma; NHL = Non-Hodgkin's lymphoma; No. = Number; Pbo = Placebo; PI3K = Phosphatidylinositol 3-kinase; PK = Pharmacokinetics; QoL = Quality of life; R = Rituximab; SCE = Summary of Clinical Efficacy; SLL = Small lymphocytic lymphoma; US = United States; WM = Waldenström macroglobulinemia

a: Study 17322 (CHRONOS-2) was originally a randomized, placebo-controlled Phase 3 study of copanlisib vs. placebo conducted in iNHL patients. The study enrollment was prematurely stopped due to low recruitment, the study was unblinded, and patients in the placebo arm were crossed over to copanlisib and continue to be treated and followed-up for safety only. The study has not reached primary completion, and neither a clean database nor a CSR are available for the study. Therefore, it will not be included in this SCE. As of 31 AUG 2020, 25 patients have been treated with copanlisib and 5 patients were ongoing with treatment in the study.

b: Twelve patients were enrolled and assigned to a 0.8 mg/kg dose before Protocol Amendment 4, which introduced the 60 mg dose, became effective (Module 5.3.5.2, Report PH-40438, Section 9.2.2.1.3).

c: After primary completion, a CSR addendum of the three ongoing patients was prepared (LPLV: 02 JUN 2020). The SCE presents data from the primary CSR (Module 5.3.3.3, Report PH-40801), as the clinical follow-up of the three remaining patients did not change the conclusions on efficacy.

Dose-response studies and main clinical studies

Selection of MTD (0.8 mg/kg) and fixed dose (60 mg)

The MTD was determined to be 0.8 mg/kg in the dose-escalating, dose-finding, first-in-man, Phase 1 study 12871.

According to the applicant, the lack of a significant effect of body weight on copanlisib exposure in the population PK modeling analysis supported the switch from body weight-based (0.8 mg/kg) to fixed dosing (60 mg). For details, please refer to clinical pharmacology sections 3.3.1 and 3.3.3.

See also the clinical pharmacology section 3.3.2 for comments.

Main studies

- **Study 17067 (CHRONOS-3):** A phase 3, randomised, double blind, placebo-controlled study of copanlisib in combination with rituximab in patients with relapsed iNHL
- **Study 16349 Part B:** A Phase 2, open-label, uncontrolled, single-arm study of copanlisib as a single agent in patients with B-cell iNHL, relapsed or refractory after at least two prior lines of therapy

Study 17067 (CHRONOS-3) – combination therapy:

Methods

Study Participants

Patients were recruited from 186 study centres in 37 countries located in: Asia, Australia, Europe, New Zealand, North America (Mexico and the US), Russia, South Africa, and South America.

Inclusion criteria

The main inclusion criteria for the study were:

- Histologically confirmed diagnosis of iNHL in CD20-positive patients with histological subtype limited to:
    - FL Grade 1-2-3a
    - SLL with absolute monoclonal lymphocyte count $<5 \times 10^9$/L at study entry
    - LPL/WM
    - MZL (splenic, nodal, or extranodal)
- Patients must have had 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 were allowed. A previous regimen is defined as one of the following: at least 2 months of single-agent therapy (less than 2 months of therapy is allowed for patients who responded to single-agent rituximab, rituximab biosimilars, or anti-CD20 monoclonal antibody); at least 2 consecutive cycles of polychemotherapy; autologous transplant; radioimmunotherapy. Previous exposure to PI3K is acceptable (except to copanlisib) provided there is no resistance (see also exclusion criterion 40). Patients with prior intolerance to PI3K inhibitors other than copanlisib are eligible.
- Non-WM patients must have had at least one bi-dimensionally measurable lesion (that had not been previously irradiated) according to Cheson 2014 criteria. For patients with splenic MZL this requirement could have been restricted to splenomegaly alone since that is usually the only manifestation of measurable disease.
- Patients affected by WM who did not have at least one bi-dimensionally measurable lesion in the baseline radiologic assessment must have had measurable disease, defined as presence of IgM paraprotein with a minimum IgM level $\geq 2 \times$ upper limit of normal and positive immunofixation test.
- ECOG performance status ≤ 2 (ECOG: Eastern Cooperative Oncology Group).
- Life expectancy of at least 3 months
- Availability of fresh tissue and/or archival tumour tissue for central pathology (obtained within 5 years of the consent date) at Screening.
- Left ventricular ejection fraction (LVEF) $\geq$ 45%.
- Patients must either:
    - have had a progression-free and treatment-free interval of $\geq$12 months after completion of the last rituximab-containing treatment

OR

- be considered unfit to receive chemotherapy on reason of age, concomitant morbidities, and/or residual toxicity from previous treatments, or unwillingness to receive chemotherapy. These patients must also have had a progression-free and treatment-free interval of ≥6 months after completion of the last rituximab-containing treatment. Patients in whom chemotherapy is contraindicated are defined by one of the following features:

  o Age ≥ 80 years

  o Age < 80 years and at least 1 of the following conditions:

  - at least 3 grade 3 CIRS-G comorbidities (see Appendix 14.7)

  OR

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

Neither of the two patient cohorts (≥12 months since last rituximab containing therapy and for the unfit/unwilling ≥6 months) were refractory to rituximab [defined as stable disease (SD) after or progressive disease (PD) during or within six months of rituximab-containing treatment], and thus the efficacy of Copa/R in these patients is unknown.

Exclusion criteria

The main exclusion criteria for the study were:

- FL Grade 3b or transformed disease, or chronic lymphocytic leukaemia.
- History or concurrent condition of interstitial lung disease and/or severely impaired lung function.
- Known lymphomatous involvement of the central nervous system.
- Congestive heart failure > New York Heart Association (NYHA) class 2.
- Patients with haemoglobin A1c (glycosylated haemoglobin) (HbA1c) >8.5% at screening.
- Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis or pulmonary embolism within 3 months before the start of study treatment.
- Known history of human immunodeficiency virus infection.
- Hepatitis B (HBV) or hepatitis C (HCV). Patients positive for hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb) were eligible if they were negative for HBV-DNA, these patients should have received prophylactic antiviral therapy. Patients positive for anti-HCV antibody were eligible if they were negative for HCV-RNA.
- Patients with seizure disorder requiring medication.
- Patients with evidence or history of bleeding diathesis. Any haemorrhage or bleeding event ≥ CTCAE Grade 3 within 4 weeks prior to the start of study treatment.
- Cytomegalovirus (CMV) infection. Patients who were CMV polymerase chain reaction (PCR) positive at baseline were not eligible.

- Any illness or medical conditions that are unstable or could jeopardise the safety of patients and their compliance in the study. (*Exclusion criterion 26)*
- Ongoing immunosuppressive therapy.
- Anti-arrhythmic therapy (beta blockers or digoxin are permitted).
- Use of strong inhibitors of CYP3A4 is prohibited from Day -14 of Cycle 1 until the Safety follow up visit (see Appendix 14.1).
- Use of strong inducers of CYP3A4 is prohibited from Day -14 of Cycle 1 until the Safety follow up visit (see Appendix 14.1).
- Documented evidence of resistance to prior treatment with idelalisib or other PI3K inhibitors defined as: (*Exclusion criterion 40)*

  ☐ No response (response defined as partial response [PR] or complete response [CR]) at any time during therapy, or

  ☐ Progression (PD) after any response (PR/CR) or after stable disease within 6 months from the end of the therapy with a PI3K inhibitor.
- Prior treatment with copanlisib.

Patients with HbA1c > 8.5% at study start were excluded. Patients with congestive heart failure >NYHA class 2 or on anti-arrhythmic therapy (other than beta blockers or digoxin) were excluded.

Treatments

- Combination of the study drug copanlisib and rituximab, administered as combination therapy. Copanlisib was administered before rituximab
- Combination of placebo and rituximab

Copanlisib (60 mg) or placebo was administered intravenously (IV) (over approximately 1 h) on Days 1, 8, and 15 of each 28-day cycle.

Rituximab (375 mg/m^2) was administered weekly during Cycle 1 on Days 1, 8, 15, and 22, and then on Day 1 of Cycles 3, 5, 7, and 9.

Rituximab monotherapy is a standard treatment option for patients with relapsed iNHL in clinical practice and has been the comparator in several studies seeking to improve treatment outcomes in patients with iNHL. The indication for rituximab in follicular lymphoma (FL) includes treatment in combination with chemotherapy in untreated patients, as monotherapy in the maintenance setting and in patients who are chemoresistant or in their second or subsequent relapse. Rituximab monotherapy in second or third line is also an option according to the ESMO guideline for FL.

Objectives

The objectives are generally agreed:

The primary objective of this study was:

- 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 had 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 were unwilling to receive chemotherapy/for whom chemotherapy was contraindicated due to age, comorbidities, and/or residual toxicity

The secondary objectives of this study were to evaluate:

- The following characteristics of patient-reported disease-related physical 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 were to evaluate:

- Pharmacokinetics
- Biomarkers
- Patient-reported outcomes (PRO)/ Health-related quality of life (HRQoL)

Outcomes/endpoints

Primary endpoint: PFS

Secondary endpoints:

- ORR
- DOR
- CR
- Time to progression
- OS
- Time to deterioration in DRS-P
- Time to improvement in DRS-P

Randomisation and blinding (masking)

Randomisation

Resulting from the combination of the 4 stratification factors (FL vs. other iNHL, >12 months progression-free interval vs Unfit/Unwilling to receive chemotherapy, +/- bulky disease, +/- previous treatment with PI3K inhibitors) patients will be randomised into 16 different strata. The randomization must be performed up to maximum 72 h before the first dose of study treatment.

The study was originally planned with 1:1 randomization but was modified to 2:1 randomization in Amendment 1 (23 Jan 2015). In this Amendment, the stratification factors were changed to comprise iNHL histology; treatment-free interval after rituximab treatment vs contraindication for chemotherapy, presence of bulky disease and prior exposure to PI3K inhibitors. In Amendment 9, the definition of stratification factor related to entry criteria was adjusted (2 Feb 2018).

From a clinical point of view the stratification factors 1, 3, and 4 are relevant although in hindsight previous treatment with PI3K inhibitors could have been omitted given there were only three patients in this group. Stratification factor 2 is also clinically relevant although the "Unfit/Unwilling" group will have to be characterised in detail.

The wording of the inclusion criteria stratification factor was changed during the course of the study, and it is not mutually exclusive (a patient can fulfil both conditions at the same time). The applicant defined in the Amendment 9 that "*In case a patient fulfils both entry criteria the preferential*

assignment should be for the group labelled as "unwilling/unfit to receive chemotherapy" providing a resolution to a possible impasse". This approach is not considered adequate since the stratum should be exclusive to allow a proper treatment comparison. The applicant is asked to provide information about how many patients fulfilled both conditions for the stratification factor inclusion criteria and to present an additional analysis for PFS and ORR where the patients who fulfilled both conditions (≥12 months and unwilling/unfit) are included in the other stratum category.

Blinding

The study was double-blinded and measures were in place to minimise potential unblinding. This is acceptable. Unintended unblinding during the study could nevertheless occur due to injection related reactions and hyperglycaemia reactions in the copanlisib arm.

Sample size

The original sample size for the study was 567 patients, which was reduced to 450 patients in Protocol Amendment 9 (2 Feb 2018). The sample size calculations were again updated in Amendment 10 (8 Oct 2019). The required number of PFS events was reduced from 288 to 190. The changes were made based on the results reported by the AUGMENT study Leonard et al., 2019).

According to the applicant, assuming a median PFS of 23 months for copanlisib + rituximab arm and 14 months for placebo + rituximab arm, a hazard ratio of 0.61 would be detected with 89 % power when including 190 PFS events. To assure a sufficient number of patients in each stratum, the applicant included a non-binding requirement on the required number of PFS events in each stratum.

The sample size calculations seem adequate.

Statistical methods

The **primary analysis population** used for the efficacy analyses is the FAS, where all randomised patients are included. This is agreed.

The **primary efficacy endpoint** is independent-review-based PFS. The difference in PFS between the treatment arms was tested using a stratified log-rank test with stratification factors: "iNHL histology" and "entry criterion". The hazard ratio was calculated using a stratified Cox model with the same stratification factors used for the log-rank test. Kaplan-Meier estimates were presented. Censoring was assumed to be non-informative.

The implementation of a log-rank test and a Cox model to analyse PFS are endorsed. The applicant presented a sensitivity analysis with all the stratification factors, which yielded similar results to those reported for the primary analysis.

Exploratory analyses of PFS

- Analysis of concordance and discordance between radiological progression evaluation by central blinded review and by investigator assessment during the blinded study phase will be performed via cross tabulations in FAS for overall and for each treatment group.
- To assess the impact of the stratification variables, Kaplan-Meier curves and median PFS times by treatment groups will be estimated.

The EMA guideline regarding PFS in oncology studies encourages the following censoring rules: "outcome data should be collected according to the intended schedule of assessment and the date of progression or recurrence should be assigned based on the time of the first evidence of objective

progression or recurrence regardless of violations, discontinuation of study drug or change of therapy ” [Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man - methodological consideration for using progression-free survival (PFS) or disease-free survival (DFS) in confirmatory trials; EMA/CHMP/27994/2008/Rev.1, esp. Appendix 1]. In addition, the assumption of non-informative censoring is likely not to be fullfiled since patients who changed to another anti-cancer therapy or discontinued the study before a centrally declared PFS event or experienced a PFS event after missing two or more consecutive assessments could have a different risk than the patients who remained in the study.

It is acknowledged that the applicant has submitted a sensitivity analysis that challenges the non-informative censoring rules and results of the sensitivity analyses were concordant with those presented for the primary analysis. However, the numbers of censored events per censoring rule has not been presented, making assessment of the impact of the different censoring rules on the result difficult.

Therefore, the applicant is asked to clarify whether progression dates were collected after study drug discontinuation due to other reasons than PD. If this is the case, the applicant should submit supplementary PFS analyses where date of progression or recurrence is assigned based on the time of the first evidence of objective progression or recurrence regardless of violations, discontinuation of study drug or change of therapy (treatment policy estimand). The applicant should also repeat the sensitivity analyses 1 to 6 using the actual progression date regardless of study drug discontinuation. In all cases, the number and percent in each event and censoring sub-category should be presented for assessment.

The first **secondary endpoint ORR** was tested using the Cochran-Mantel-Haenszel test, stratified for the same stratification factors as used for PFS. Patients with missing or non-evaluable assessment were included in the denominator. The method to calculate the confidence interval had not been clarified in the SAP.

If a patient has no post-baseline tumour assessment available (or no post-baseline laboratory/clinical tests available for WM patients without radiologically measurable lesion(s)), i.e. the overall best response assessment is missing, the patient will be non-evaluable (NE), but will be included into denominator for calculation of objective tumour response rate (ORR) and complete response rate (CRR).

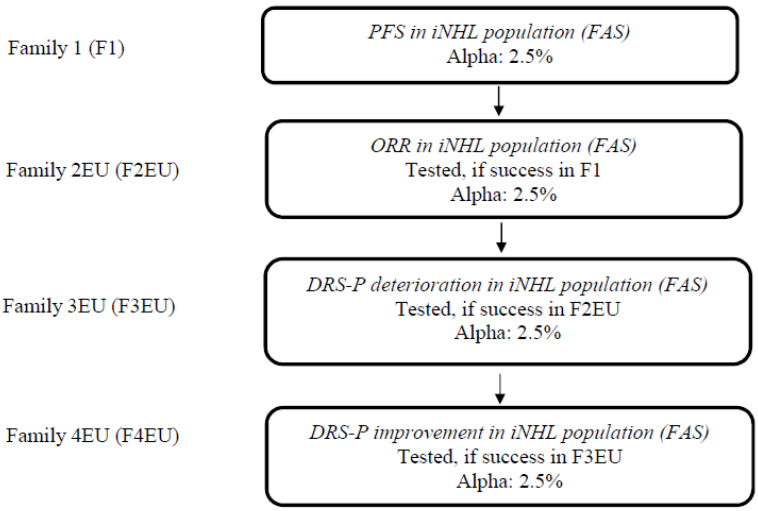
The **secondary endpoints DRS-P deterioration and improvement** were analysed in the same manner as PFS. Non-informative censoring was also assumed.

The assumption of non-informative censoring in DRS-P endpoints is not agreed since patients who initiated a new anti-cancer therapy or discontinued the study prematurely may not be well represented by the patients who remained in the study. The handling of missing data is not fully understood. According to the applicant it seems that 80% of the questions should be addressed to get a valid score. The consequences of this approach on the results are not known. However, since this endpoint is not statistically significant, this issue will not be pursued.

Confirmatory statistical test strategy

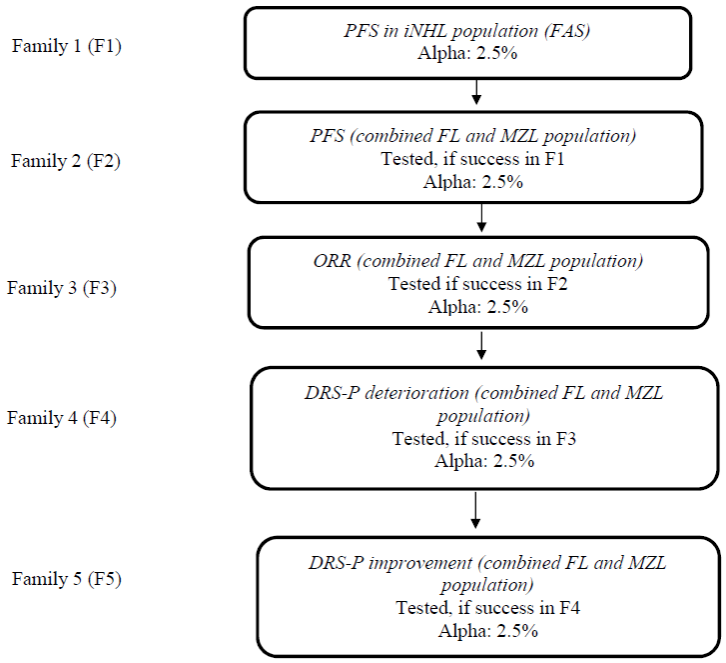
Separate statistical test strategies will be conducted for the United States and Europe as outlined below.

Figure 6–2: Confirmatory Test Strategy Based on Four Test Families for Europe



Source: SAP

Figure 6–1: Confirmatory Test Strategy Based on Five Test Families for United States



Source: SAP

A hierarchical approach was implemented to control the type I error due to multiple endpoints. This is endorsed. Different hierarchies were used in the MAA for EU and for US. Given the study results, this has no practical implications since the hypotheses for PFS and ORR were rejected for both populations (iNHL and FL and MZL) and DRS-P progression could not be rejected.

No **interim analysis** was performed for Study 17067. A blinded safety review was performed after the first 30 patients were recruited, which did not impact the results of the study.

Versions of the SAP were implemented to follow the changes made to the protocol. The latest version is SAP final The main changes are related to changes to the sample size and definition of the stratification factors. Those changes were addressed in the sample size and randomization sections. The other changes made to the SAP are not considered to affect the interpretation of the results.

An additional Statistical Analysis Plan was implemented.

Results

Participant flow

A total of 652 patients were screened for the study (i.e., signed ICF) between 03 AUG 2015 (first patient first visit) and 17 DEC 2019 (last patient first visit). The database cut-off date for the primary completion analyses was 31 AUG 2020.

A total of 458 patients were randomly assigned in a 2:1 ratio to study treatment: 307 patients to Copa/R and 151 patients to Pbo/R. Of the randomised patients, nearly all (Copa/R: 99.0% and Pbo/R: 98.7%) received at least one dose of the study drug treatment.

Of these 458 iNHL patients, 95 patients had MZL. 66 MZL patients were randomised to the Copa/R arm and 29 to the Pbo/R arm.

In the CSR, it appears that baseline diagnosis is by local assessment. In particular, the CSR states that "Analyses for histological subpopulations (FL, MZL, SLL, and LPL/WM) were performed based on the diagnosis of cancer histology by investigator assessment, unless otherwise specified". The applicant is asked to clarify whether the baseline diagnoses were also verified by a central laboratory and whether there were any discrepancies between the two diagnosis assessments, especially in light of the significant difference between local and central baseline diagnosis in CHRONOS-1.

Table 8–1 Patient disposition in the total iNHL study population (FAS)

Study period		Total N=652 n (%)
Enrolled (signed ICF) [a]		**652**
Screening		
Completed screening and randomized to treatment		458 (70.2)
Premature discontinuation of screening		194 (29.8)
AE		2 (0.3)
Death		1 (0.2)
Failure to meet randomization criteria		13 (2.0)
Screening failure [b]		156 (23.9)
Withdrawal by patient		22 (3.4)
Study period	**Copanlisib/ rituximab N=307 n (%)**	**Placebo/ rituximab N=151 n (%)**
Randomized/assigned to treatment	**307 (100.0)**	**151 (100.0)**
No study drug administered	3 (1.0)	2 (1.3)
Study treatment		
Started treatment [c]	304 (99.0)	149 (98.7)
Ongoing with treatment	70 (22.8)	29 (19.2)
Discontinued treatment	234 (76.2)	120 (79.5)

AE = Adverse event; COVID-19 = Coronavirus disease 2019; FAS = Full analysis set; ICF = Informed Consent Form; iNHL = Indolent non-Hodgkin's lymphoma; N = Total number of patients (100%); n = Number of patients with event

a: Number of patients enrolled is the number of patients who signed the informed consent.

b: Screening failure = Patient signed informed consent but did not meet inclusion criteria/met exclusion criteria.

c: Three patients were randomized to the placebo/rituximab arm but received at least one dose of copanlisib by mistake. These patients were included in the copanlisib/rituximab arm in the analysis of safety variables (Table 14.1.1/9).

Source: Table 14.1.1/3, Table 14.1.1/4

There were a number (269/458=58.7%) of deviations classified as important, including 53 instances where inclusion/exclusion criteria were not met but patient entered treatment. It is also noted that the deviations did not lead to exclusion from the efficacy data analysis, and the applicant is invited to

discuss the classification used for deviations (important, major, minor), as well as criteria for what constituted a deviation necessitating exclusion of data.

Emergency unblindings are accepted. Some procedure-related records were omitted in the initial release of the clinical database due to a database error. It is agreed that efficacy and safety analyses are not considered to be affected.

Baseline data

Table 8–4 Demographics and baseline characteristics in the total iNHL study population and histological subpopulations (FAS)

	Total iNHL N=458		MZL N=95	
	Copanlisib/ rituximab N=307	Placebo/ rituximab N=151	Copanlisib/ rituximab N=66	Placebo/ rituximab N=29
Gender, n (%)				
Male	153 (49.8)	85 (56.3)	33 (50.0)	12 (41.4)
Female	154 (50.2)	66 (43.7)	33 (50.0)	17 (58.6)
Age (years)				
Median	63.0	62.0	65.5	63.0
Age category (years), n (%)				
<65	167 (54.4)	88 (58.3)	30 (45.5)	17 (58.6)
≥65	140 (45.6)	63 (41.7)	36 (54.5)	12 (41.4)
Geographic Region 2, n (%) [b]				
North America	15 (4.9)	3 (2.0)	3 (4.5)	1 (3.4)
Asia Pacific	125 (40.7)	50 (33.1)	21 (31.8)	7 (24.1)
Rest of the world	167 (54.4)	98 (64.9)	42 (63.6)	21 (72.4)
History of diabetes, n (%)				
Yes	45 (14.7)	22 (14.6)	13 (19.7)	2 (6.9)
No	262 (85.3)	129 (85.4)	53 (80.3)	27 (93.1)
History of hypertension, n (%)				
Yes	114 (37.1)	53 (35.1)	35 (53.0)	11 (37.9)
No	193 (62.9)	98 (64.9)	31 (47.0)	18 (62.1)

AST = Aspartate aminotransferase; BMI = Body mass index; BP = Blood pressure; FAS = Full analysis set; FL = Follicular lymphoma; iNHL = Indolent non-Hodgkin's lymphoma; Max = Maximum; Min = Minimum; MZL = Marginal zone lymphoma; N = Total number of patients (100%); n = Number of patients with event; StD = Standard deviation; ULN = Upper limit of normal;

a: Geographic Region 2 was used for sensitivity analysis of PFS and subgroup analysis of selected efficacy variables only; Asia Pacific includes China, Japan, Korea, Taiwan, Hong Kong, Malaysia, Singapore, Thailand, Vietnam, and Philippines.

The applicant is asked to discuss the baseline disease status of the patients in the control and treatment arms. (see Table below). The applicant should provide an additional analysis adjusting for time from initial diagnosis to randomization and Ann Arbor Stage. The applicant is also asked to provide data on how long the progression-free and treatment-free intervals from last treatment where in the two arms in the MZL population.

Table 8–5 Baseline cancer characteristics in the total iNHL study population and histological subpopulations (FAS)

	Total iNHL N=458		MZL N=95	
	Copanlisib/ rituximab N=307	Placebo/ rituximab N=151	Copanlisib/ rituximab N=66	Placebo/ rituximab N=29
Most recent histology of lymphoma [a], n (%)				
FL	184 (59.9)	91 (60.3)	-	-
Grade 1	56 (18.2)	31 (20.5)	-	-
Grade 2	88 (28.7)	40 (26.5)	-	-
Grade 3a	40 (13.0)	20 (13.2)	-	-
MZL	66 (21.5)	29 (19.2)	66 (100.0)	29 (100.0)
Extranodal	24 (7.8)	11 (7.3)	24 (36.4)	11 (37.9)
Nodal	25 (8.1)	12 (7.9)	25 (37.9)	12 (41.4)
Splenic	17 (5.5)	6 (4.0)	17 (25.8)	6 (20.7)
SLL	35 (11.4)	15 (9.9)	-	-
LPL/WM	22 (7.2)	16 (10.6)	-	-
Progression-free and treatment-free interval of at least 12 months after completion of the last rituximab-containing treatment, n (%)	247 (80.5)	121 (80.1)	49 (74.2)	22 (75.9)
Unfit or unwilling to receive chemotherapy, n (%) [c]	60 (19.5)	30 (19.9)	17 (25.8)	7 (24.1)
Presence of bulky disease, n (%)				
Yes	45 (14.7)	21 (13.9)	8 (12.1)	5 (17.2)
No	262 (85.3)	130 (86.1)	58 (87.9)	24 (82.8)
Ann Arbor staging of tumor at study entry, n (%)				
Stage I	20 (6.5)	11 (7.3)	5 (7.6)	2 (6.9)
Stage II	37 (12.1)	14 (9.3)	8 (12.1)	3 (10.3)
Stage III	86 (28.0)	31 (20.5)	12 (18.2)	3 (10.3)
Stage IV	160 (52.1)	91 (60.3)	41 (62.1)	21 (72.4)
Missing	4 (1.3)	4 (2.6)	0	0
Time from initial diagnosis to randomization (months)				
n	307	151	66	29
Median	62.75	72.44	54.53	72.37
ECOG PS, n (%)				
0 – Fully active	182 (59.3)	95 (62.9)	41 (62.1)	17 (58.6)
1 – Restricted active	113 (36.8)	55 (36.4)	23 (34.8)	12 (41.4)
2 – Ambulatory and capable of all self-care	12 (3.9)	1 (0.7)	2 (3.0)	0
No. of lines of prior systemic anti-cancer therapies, n (%)				
n	307 (100.0)	151 (100.0)	66 (100.0)	29 (100.0)
1	150 (48.9)	71 (47.0)	35 (53.0)	19 (65.5)
2	75 (24.4)	40 (26.5)	19 (28.8)	6 (20.7)
3	38 (12.4)	23 (15.2)	8 (12.1)	3 (10.3)
≥4	44 (14.3)	17 (11.3)	4 (6.1)	1 (3.4)

ECOG = Eastern Cooperative Oncology Group; FAS = Full analysis set; FL = Follicular lymphoma; G = Grade; IgM = Immunoglobulin M; iNHL = Indolent non-Hodgkin's lymphoma; Max = Maximum; Min = Minimum; N = Total number of patients (100%); MZL = Marginal zone lymphoma; n = Number of patients with event; PI3Ki = Phosphatidylinositol 3-kinase inhibitor; PS = Performance status; StD = Standard deviation;

a: Most recent histology based on local assessment.

Numbers analysed

Table 8–3 Analysis sets (all randomized)

Analysis set Primary reasons for exclusion from analysis set	Copanlisib/ rituximab N=307 n (%)	Placebo/ rituximab N=151 n (%)
FAS	**307 (100.0)**	**151 (100.0)**
Excluded from FAS	0	0
SAF [a]	**304 (99.0)**	**149 (98.7)**
Excluded from SAF	3 (1.0)	2 (1.3)
Patient never received any study drug	3 (1.0)	2 (1.3)

FAS = Full analyses set; N = Total number of patients (100%); n = Number of patients with event; SAF = Safety analysis set

a: Three patients were randomized to the placebo/rituximab arm but received at least one dose of copanlisib by mistake. These patients were included in the copanlisib/rituximab arm in the analysis of safety variables. Therefore, the safety analysis included 307 patients for copanlisib/rituximab and 146 patients for placebo/rituximab.

Outcomes and estimation

Primary endpoint: PFS

A statistically significant treatment effect and clinically relevant difference in favour of Copa/R in the entire iNHL population was shown with a median PFS time of 21.5 months (95% CI: [17.8, 33.0]) compared with 13.8 months (95% CI: [10.2, 17.5]) in the Pbo/R arm with an HR of 0.520 (95% CI: [0.393, 0.688]; one-sided p=0.000002). The Kaplan-Meier curves continued to run separated, demonstrating longer PFS times for the Copa/R arm than for the Pbo/R arm (Fig. 9-1/CSR).

The pre-specified PFS analyses in the four histological subpopulations (FL, MZL, SLL, and LPL/WM) were consistent with the primary analysis results. A median PFS time of 22.1 months (95% CI: [13.8, NE]) in the Copa/R arm compared with 11.5 months (95% CI: [5.6, 16.3]) in the Pbo/R arm with a HR of 0.475 (95% CI: [0.245, 0.923]; p=0.012291) was observed for the MZL population (Table 9–1/CSR and Fig. 9-2/CSR).

The primary efficacy variable, PFS, is assessed in the iNHL population, while the indication sought is MZL population. Given the rarity of the condition, this is understandable, but increases the uncertainty of the efficacy assessment in MZL patients.

Table 9–1 PFS in the total iNHL study population and histological subpopulations – Independent central review (FAS)

	Total iNHL [a] N=458		FL [b] N=275		MZL [b] N=95		SLL [b] N=50		LPL/WM [b] N=38	
	Copanlisib/ rituximab N=307	Placebo/ rituximab N=151	Copanlisib/ rituximab N=184	Placebo/ rituximab N=91	Copanlisib/ rituximab N=66	Placebo/ rituximab N=29	Copanlisib/ rituximab N=35	Placebo/ rituximab N=15	Copanlisib/ rituximab N=22	Placebo/ rituximab N=16
Number (%) of patients										
With event	118 (38.4%)	87 (57.6%)	69 (37.5%)	52 (57.1%)	22 (33.3%)	15 (51.7%)	20 (57.1%)	12 (80.0%)	7 (31.8%)	8 (50.0%)
Censored	189 (61.6%)	64 (42.4%)	115 (62.5%)	39 (42.9%)	44 (66.7%)	14 (48.3%)	15 (42.9%)	3 (20.0%)	15 (68.2%)	8 (50.0%)
PFS (months)										
Median	**21.5**	**13.8**	**22.2**	**18.7**	**22.1**	**11.5**	**14.2**	**5.7**	**33.4**	**16.6**
[95% CI]	**[17.8, 33.0]**	**[10.2, 17.5]**	**[17.8, 33.1]**	**[10.2, 21.1]**	**[13.8, A]**	**[5.6, 16.3]**	**[10.9, 20.5]**	**[3.5, 11.0]**	**[15.5, A]**	**[4.4, 27.4]**
HR [95% CI]	**0.520 [0.393, 0.688]**		**0.580 [0.404, 0.833]**		**0.475 [0.245, 0.923]**		**0.243 [0.111, 0.530]**		**0.443 [0.160, 1.231]**	
One-sided p-value from log-rank test	0.000002		0.001401		0.012291		0.000064		0.054056	

CI = Confidence interval; FAS = Full analysis set; FL = Follicular lymphoma; HR = Hazard ratio; iNHL = Indolent non-Hodgkin's lymphoma; LPL = Lymphoplasmacytoid lymphoma; MZL = Marginal zone lymphoma; N = Total number of patients (100%); PFS = Progression-free survival; SLL = Small lymphocytic lymphoma; WM = Waldenström macroglobulinemia

a: PFS was evaluated with the stratified log-rank test based on stratification factors iNHL histology and entry criterion used for randomization. HR and 95% CI were based on Cox Regression Model, stratified by iNHL histology and entry criterion used for randomization.

b: PFS was evaluated with the unstratified log-rank test. Histology is based on the information entered in the eCRF for randomization. HR and 95% CI were based on unstratified Cox Regression Model.

Notes:

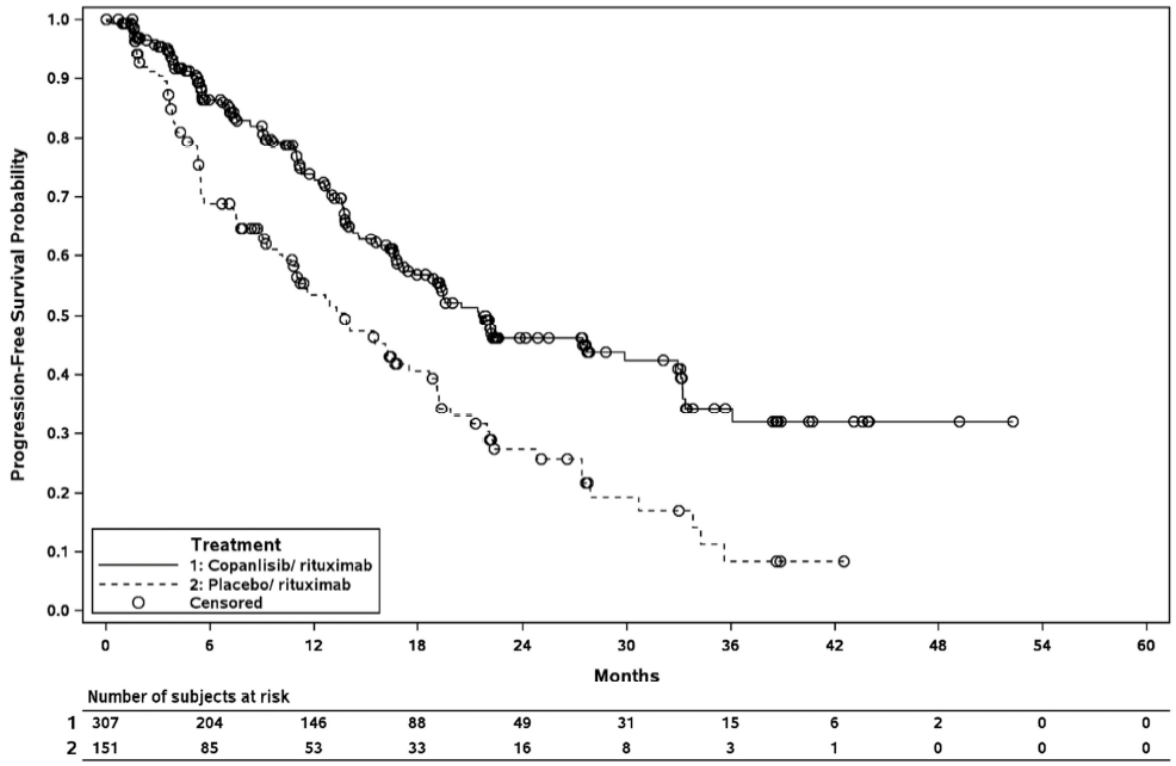
A: Value could not be estimated due to censored data.

Patients evaluated by Owen criteria (Owen et al. 2013) may include investigator assessments in the absence of independent central review.

Median, percentile, and other 95% CIs computed using Kaplan-Meier estimates.

An HR <1 indicates superiority of copanlisib/rituximab over placebo/rituximab.

Figure 9–1 Kaplan-Meier curve of PFS in the total iNHL study population – Independent central review (FAS)



FAS = Full analysis set; FL = Follicular lymphoma; iNHL = Indolent non-Hodgkin's lymphoma; MZL = Marginal zone lymphoma; PFS = Progression-free survival

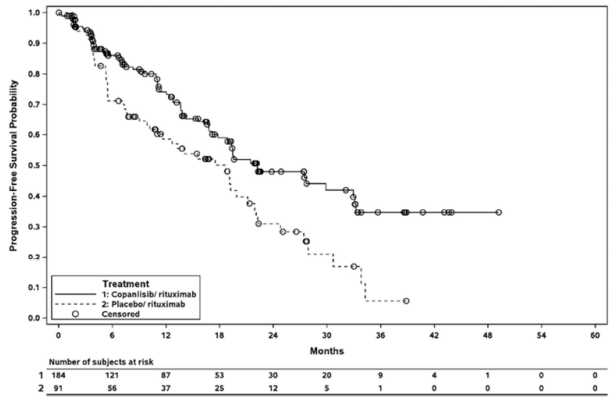
Notes:

At-risk patient counts were calculated at the start of the time point.

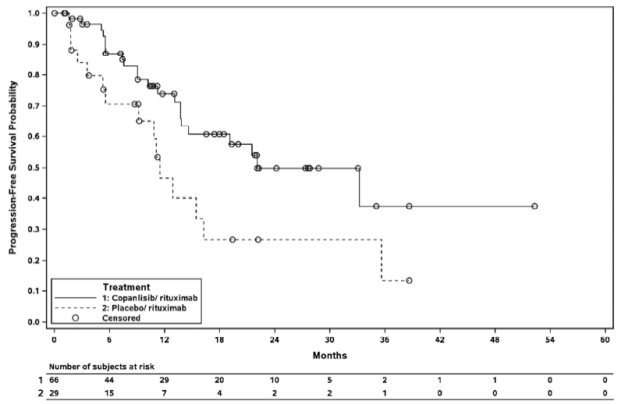
Patients evaluated by Owen criteria (Owen et al. 2013) may include investigator assessments in absence of independent central review.

Figure 9–2 Kaplan-Meier curves of PFS in the histological subpopulations – Independent central review (FAS)

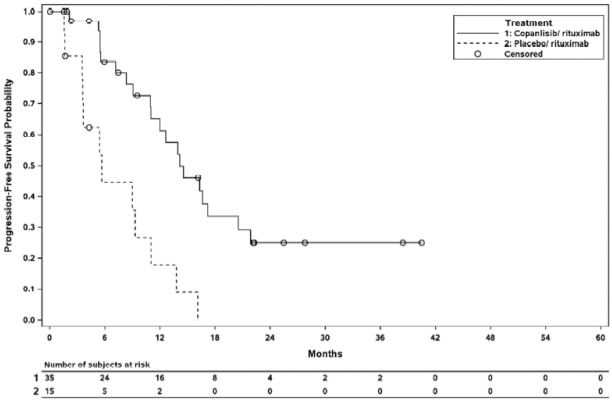
iNHL histology: FL



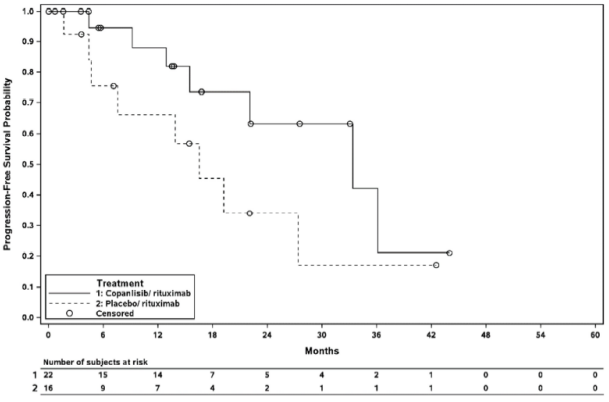
iNHL histology: MZL



iNHL histology: SLL



iNHL histology: LPL/WM



FAS = Full analysis set; FL = Follicular lymphoma; iNHL = Indolent non-Hodgkin's lymphoma; LPL = Lymphoplasmacytoid lymphoma; MZL = Marginal zone lymphoma; PFS = Progression-free survival; SLL = Small lymphocytic lymphoma; WM = Waldenström macroglobulinemia
At-risk patient counts were calculated at the start of the time point.
Patients evaluated by Owen criteria (Owen et al. 2013) may include investigator assessments in the absence of independent central review.
Source: Figure 14.2.5.1/1

No single stratification factor was driving the efficacy results, but PFS benefit seems lower in patients with bulky disease, with an HR of 0.905 (95% CI: [0.463,1.770]; one-sided p=0.385490). The applicant is requested to discuss B/R for this population.

Due to the small number of patients with prior PI3K inhibitor no conclusion regarding efficacy in this group could be made.

The results of the investigator-assessed PFS that included both radiological and clinical progression were in line with the primary analysis, with a similar number of PFS events (ICR; 206 events, INV; 211 events) and nearly identical median PFS times [ICR; 21.5 vs 13.8 months, INV; 22.0 months vs 13.8 months (Copa/R vs Pbo/R)].

Progression-free survival for binary stratification factors

Table 9–4 PFS by randomization stratification factors in the total iNHL study population – Independent central review (FAS)

		PFS (months)				
		N (total)	Copanlisib/ rituximab	Placebo/ rituximab	HR	One-sided p-value
	N / n		250 / 96	124 / 73		
Progression-free and treatment-free interval of ≥12 months after the last rituximab-containing treatment		374	22.1 [19.3, 33.1]	15.4 [11.0, 19.1]	**0.518 [0.382, 0.703]**	0.000008
	N / n		57 / 22	27 / 14		
Unwilling/unfit to receive chemotherapy		84	17.2 [11.3, A]	9.2 [5.5, A]	**0.556 [0.281, 1.101]**	0.043572
Presence of bulky disease						
	N / n		54 / 26	25 / 13		
Yes		79	14.2 [11.0, 17.2]	16.1 [3.8, 34.3]	**0.905 [0.463, 1.770]**	0.385490
	N / n		253 / 92	126 / 74		
No		379	27.5 [19.4, 33.2]	13.3 [10.2, 17.5]	**0.463 [0.340, 0.630]**	<.000001

CI = Confidence interval; FAS = Full analysis set; HR = Hazard ratio; iNHL = Indolent non-Hodgkin's lymphoma; N = Total number of patients (100%); n = number of patients with event; PFS = Progression-free survival

Notes:
A: Value could not be estimated due to censored data.
Patients evaluated by Owen criteria (Owen et al. 2013) may include investigator assessments in absence of independent central review.
PFS was evaluated with the unstratified log-rank test.
Median, percentile, and other 95% CIs computed using Kaplan-Meier estimates.
HR and 95% CI are based on the unstratified Cox Regression Model.
An HR <1 indicates superiority of copanlisib/rituximab over placebo/rituximab.

The HR for the "Unfit or Unwilling to receive chemotherapy with a progression-free and treatment-free interval of ≥6 months after completion of the last rituximab-containing treatment" (Unfit/Unwilling) seems to be somewhat higher than the HR for the "Progression-free and treatment-free interval of ≥12 months after the last rituximab-containing treatment" group. The Unfit/Unwilling group could potentially be a quite heterogenous group. Notwithstanding the limited sample size, the apparent smaller difference in treatment effect between Copa/R vs Pbo/R for this stratum could be an indication that the Unfit group experiences lower efficacy and worse safety compared to the Unwilling population. If this is the case, this has to be made clear in the SPC, section 5.1, so that the prescribing physician can take this into account. The Unwilling patients were not included in the CHMP advice (see OC in Introduction). In Table 8-5/CSR 60 patients are listed in the Copa/R arm and 30 patients in the Pbo/R arm (FAS), whereas in the results section (FAS) the corresponding numbers are 57 and 27 -please clarify. The applicant is requested to present the efficacy results (PFS, ORR, and CRR) for the Unfit (all patients fitting this description even though they may also have been Unwilling) and Unwilling separately (for both the iNHL and MZL populations) and present a short overview of safety in these two populations as well as a short discussion regarding B/R based on these data to justify that the indication is appropriate also for patients defined as Unfit. If the limited patient number in the MZL population precludes a meaningful analysis in the Unfit and Unwilling subpopulations, a Swimmer Plot of patient responses in the MZL population may be presented instead, with Unfit/Unwilling patients clearly indicated.

The results of the sensitivity analyses were generally concordant with those presented in the primary analysis for PFS:

Table 9–6 Summary of the sensitivity analyses of PFS in the total iNHL study population by independent central review (FAS)

		Copanlisib/ Rituximab N / n	Placebo/ Rituximab N / n	Hazard ratio [95% CI]	One-sided p-value from log-rank test
Analysis 1 [a]	PFS evaluated with stratified log-rank test with all four stratification factors at randomization	307 / 118	151 / 87	0.513 [0.386, 0.682]	0.000001

CI = Confidence interval; FAS = Full analysis set; HR = Hazard ratio; iNHL = Indolent non-Hodgkin's lymphoma; N = Total number of patients (100%); n = number of patients with event; PFS = Progression-free survival;
a: PFS was evaluated with the stratified log-rank test based on stratification factors used for randomization: iNHL histology, entry criterion, presence of bulky disease, and previous treatment with PI3Ki.
Notes:
Patients evaluated by Owen criteria (Owen et al. 2013) may include investigator assessments in the absence of independent central review.
Median, percentile, and other 95% CIs computed using Kaplan-Meier estimates.
An HR <1 indicates superiority of copanlisib/rituximab over placebo/rituximab.

Despite the small number of patients and events, the PFS results in the MZL subpopulations (Table 9-18/CSR) were generally consistent with the entire iNHL population.

Table 9–18 Subgroup analysis of PFS in the MZL subpopulations – Independent central review (FAS)

	Copanlisib/ rituximab N=66				Placebo/ rituximab N=29				HR	
Variable Subgroup	n	n with events	n censored	median	n	n with events	n censored	median	**Estimate [95% CI]**	**One-sided p-value from log-rank test**
MZL	66	22	44	22.1	29	15	14	11.5	**0.475** [0.245, 0.923]	0.012291
Extranodal	24	6	18	A	11	7	4	10.8	**0.334** [0.111, 1.010]	0.021046
Nodal	25	10	15	21.5	12	7	5	11.5	**0.483** [0.183, 1.276]	0.066728
Splenic	17	6	11	33.2	6	1	5	16.3	**1.455** [0.168, 12.622]	0.633964

CI = Confidence interval; FAS = Full analysis set; HR = Hazard ratio; MZL = Marginal zone lymphoma; N = Total number of patients (100%); n = Number of patients with event; PFS = Progression-free survival
Notes:
PFS was evaluated with the unstratified log-rank test.
A: Value could not be estimated due to censored data.
Median, percentile, and other 95% CIs computed using Kaplan-Meier estimates.
HR and 95% CI were based on unstratified Cox Regression Model.
An HR <1 indicates superiority of copanlisib/rituximab over placebo/rituximab.

PFS results were generally consistent across demographic and baseline disease characteristics (Fig. 9-9/CSR).

Figure 9–9 Forest plots of PFS subgroup analyses – Independent central review (FAS)

PFS by stratification factors

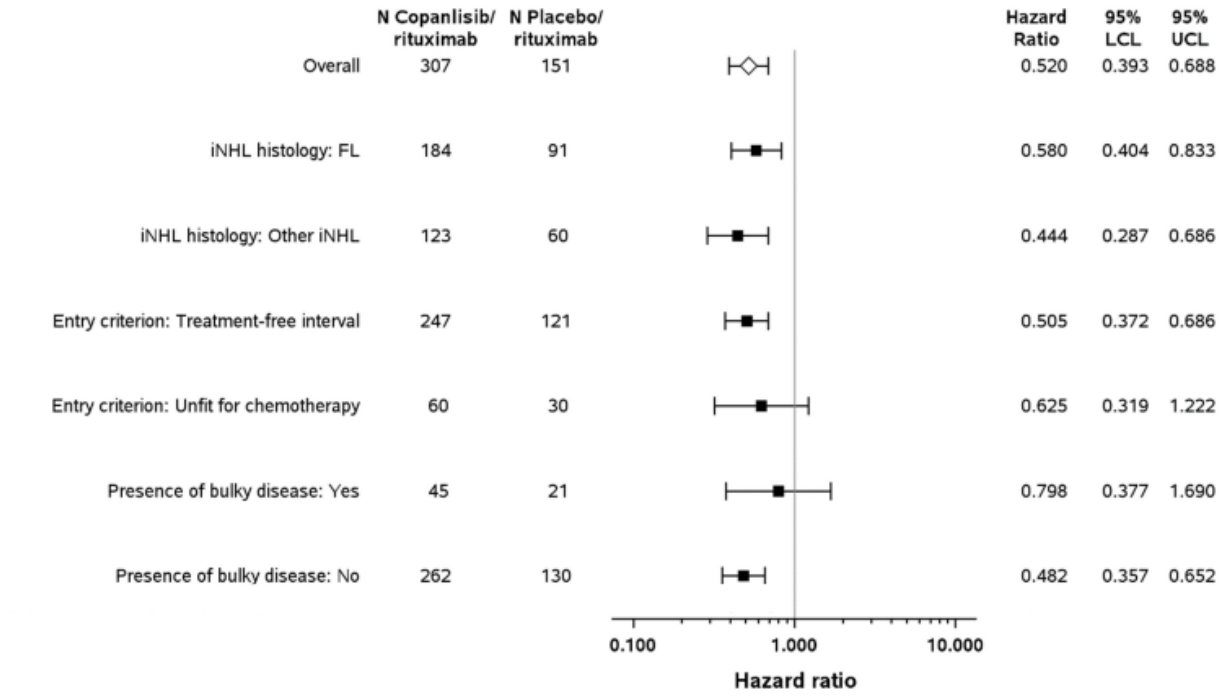
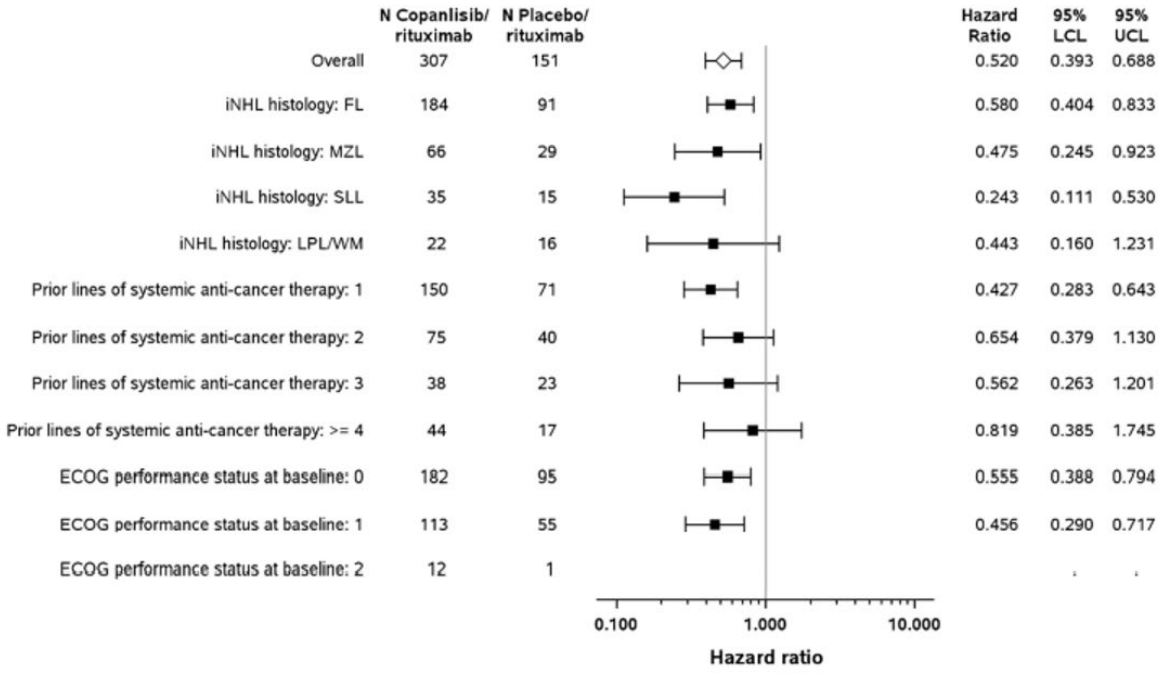
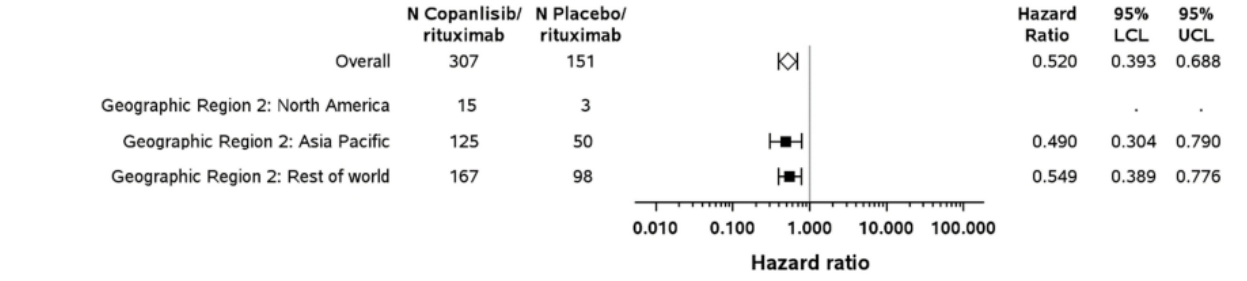


Figure 9–9 Forest plots of PFS subgroup analyses – Independent central review (FAS)

PFS by baseline cancer characteristics



PFS by demographics



By subgroup analysis, the effect in patients <65 years old appears superior to that in those >65 years old, where the upper CI for the HR was above one. The applicant should provide the equivalent information for MZL, and include this information in the SmPC if relevant.

Secondary efficacy variables

Objective response rate (ORR) and Complete response rate (CRR):

Copa/R treatment showed a significantly higher ORR than Pbo/R treatment (80.8% vs. 47.7%) in the entire iNHL study population (ICR assessed). CRR was also higher in the Copa/R arm than in the Pbo/R arm (33.9% vs. 14.6%, respectively). The difference in ORR was indicating a statistically significant positive treatment effect for copanlisib in combination with rituximab.

ORR and CRR were higher in the Copa/R arm than in the Pbo/R arm across the MZL subpopulations; (75.8% vs. 41.4% and 39.4% vs. 10.3%, respectively).

Table 9–7 Tumor response in the total iNHL study population and histological subpopulations – Independent central review by Cheson 2014 criteria/Owen criteria (FAS)

	Total iNHL N=458		FL N=275		MZL N=95		SLL N=50		LPL/WM N=38	
	Copanlisib/ rituximab N=307 n (%) [95% CI]	Placebo/ rituximab N=151 n (%) [95% CI]	Copanlisib/ rituximab N=184 n (%) [95% CI]	Placebo/ rituximab N=91 n (%) [95% CI]	Copanlisib/ rituximab N=66 n (%) [95% CI]	Placebo/ rituximab N=29 n (%) [95% CI]	Copanlisib/ rituximab N=35 n (%) [95% CI]	Placebo/ rituximab N=15 n (%) [95% CI]	Copanlisib/ rituximab N=22 n (%) [95% CI]	Placebo/ rituximab N=16 n (%) [95% CI]
Best response										
CR	104 (33.9) [28.6, 39.5]	22 (14.6) [9.4, 21.2]	68 (37.0) [30.0, 44.4]	19 (20.9) [13.1, 30.7]	26 (39.4) [27.6, 52.2]	3 (10.3) [2.2, 27.4]	6 (17.1) [6.6, 33.6]	0	4 (18.2) [5.2, 40.3]	0
VGPR [a]	2 (0.7) [0.1, 2.3]	2 (1.3) [0.2, 4.7]	N/A	N/A	N/A	N/A	N/A	N/A	2 (9.1) [1.1, 29.2]	2 (12.5) [1.6, 38.3]
PR	137 (44.6) [39.0, 50.4]	44 (29.1) [22.0, 37.1]	88 (47.8) [40.4, 55.3]	30 (33.0) [23.5, 43.6]	24 (36.4) [24.9, 49.1]	9 (31.0) [15.3, 50.8]	21 (60.0) [42.1, 76.1]	2 (13.3) [1.7, 40.5]	4 (18.2) [5.2, 40.3]	3 (18.8) [4.0, 45.6]
MR [a]	5 (1.6) [0.5, 3.8]	4 (2.6) [0.7, 6.6]	N/A	N/A	N/A	N/A	N/A	N/A	5 (22.7) [7.8, 45.4]	4 (25.0) [7.3, 52.4]
SD	35 (11.4) [8.1, 15.5]	56 (37.1) [29.4, 45.3]	15 (8.2) [4.6, 13.1]	32 (35.2) [25.4, 45.9]	8 (12.1) [5.4, 22.5]	10 (34.5) [17.9, 54.3]	7 (20.0) [8.4, 36.9]	10 (66.7) [38.4, 88.2]	5 (22.7) [7.8, 45.4]	4 (25.0) [7.3, 52.4]
PD	6 (2.0) [0.7, 4.2]	12 (7.9) [4.2, 13.5]	5 (2.7) [0.9, 6.2]	5 (5.5) [1.8, 12.4]	1 (1.5) [0.0, 8.2]	4 (13.8) [3.9, 31.7]	0	2 (13.3) [1.7, 40.5]	0	1 (6.3) [0.2, 30.2]
uSD [b]	1 (0.3) [0.0, 1.8]	2 (1.3) [0.2, 4.7]	1 (0.5) [0.0, 3.0]	0	0	0	0	1 (6.7) [0.2, 31.9]	0	1 (6.3) [0.2, 30.2]
NE [c]	3 (1.0) [0.2, 2.8]	4 (2.6) [0.7, 6.6]	0	2 (2.2) [0.3, 7.7]	2 (3.0) [0.4, 10.5]	2 (6.9) [0.8, 22.8]	1 (2.9) [0.1, 14.9]	0	0	0
NA [d]	14 (4.6) [2.5, 7.5]	5 (3.3) [1.1, 7.6]	7 (3.8) [1.5, 7.7]	3 (3.3) [0.7, 9.3]	5 (7.6) [2.5, 16.8]	1 (3.4) [0.1, 17.8]	0	0	2 (9.1) [1.1, 29.2]	1 (6.3) [0.2, 30.2]
ORR [e]	**248 (80.8)** [75.9, 85.0]	**72 (47.7)** [39.5, 56.0]	**156 (84.8)** [78.8, 89.6]	**49 (53.8)** [43.1, 64.4]	**50 (75.8)** [63.6, 85.5]	**12 (41.4)** [23.5,61.1]	**27 (77.1)** [59.9, 89.6]	**2 (13.3)** [1.7, 40.5]	**15 (68.2)** [45.1, 86.1]	**9 (56.3)** [29.9, 80.2]
One-sided p-value	<.000001 [g]		<.000001 [h]		0.000596 [f,]		0.000014 [h]		0.225774 [h]	

Table 9–7 Tumor response in the total iNHL study population and histological subpopulations – Independent central review by Cheson 2014 criteria/Owen criteria (FAS)

CI = Confidence interval; CMH = Cochran-Mantel-Haenszel; CR = Complete response; FAS = Full analysis set; FL = Follicular lymphoma; iNHL = Indolent non-Hodgkin's lymphoma; LPL = Lymphoplasmacytoid lymphoma; MR = Minor response; MZL = Marginal zone lymphoma; N = Total number of patients (100%); n = Number of patients with event; NA = Not available; N/A = Not applicable; NE = Not evaluable; ORR = Objective response rate; PD = Progressive disease; PR = Partial response; SD = Stable disease; SLL = Small lymphocytic lymphoma; uSD = Unconfirmed early stable disease; VGPR = Very good partial response; WM = Waldenström macroglobulinemia

a: VGPR and MR include only WM patients.
b: uSD is defined as SD on or before Study Day 48 relative to the first study drug dose date.
c: Not evaluable: Patients who had only post-baseline tumor assessment(s) that could not be assessed by investigator/independent assessor.
d: Not available: Patients who had no post-baseline response assessment.
e: Patients with CR, VGPR, PR, or MR.
f: Difference = copanlisib/rituximab − placebo/rituximab; For total population, CMH-weighted difference is displayed.
g: P-value from CMH test stratified by iNHL histology and entry criterion based on stratification information used for randomization.
h: P-values are from chi-square test.Notes:
Number (percentages) and 95% CI for percentages of patients. Percentages based on Total number of patients. 95% CI by exact binomial calculation.
Patients evaluated by Owen criteria (Owen et al. 2013) may include investigator assessments in absence of independent central review.

Duration of response (DOR)

Table 9–9 DOR in the total iNHL study population and MZL subpopulation – Independent central review (FAS)

	Total iNHL [a] N=458		MZL [b] N=95	
	Copanlisib/ rituximab N=307	Placebo/ rituximab N=151	Copanlisib/ rituximab N=66	Placebo/ rituximab N=29
Number (%) of patients				
Responders	248	72	50	12
DOR (months)				
Median	**20.4**	**17.3**	**25.4**	**9.3**
[95% CI]	**[17.0, 30.8]**	**[11.8, 25.3]**	**[12.1, A]**	**[7.4, A]**

CI = Confidence interval; FAS = Full analysis set; DOR = Duration of response; FL = Follicular lymphoma; iNHL = Indolent non-Hodgkin's lymphoma; MZL = Marginal zone lymphoma; N = Total number of patients (100%);
a: DOR was evaluated with the stratified log-rank test based on stratification factors iNHL histology and entry
b: DOR was evaluated with the unstratified log-rank test.
Notes:
Only patients with response in FAS were included in the analysis.
Patients evaluated by Owen criteria (Owen et al. 2013) may include investigator assessments in the absence
A: Value could not be estimated due to censored data.
Median, percentile, and other 95% CIs computed using Kaplan-Meier estimates.

Results for the histological subpopulations (FL, MZL, SLL, and LPL/WM) were consistent with the main analysis of DOR in iNHL patients. There were few patients available for subgroup analysis in the MZL population particularly in the Pbo/R arm (Table 9-9/CSR).

Local assessment and ICR-based assessment of efficacy appear to diverge for several secondary endpoints, including DOR and CRR. In the FAS of the iNHL, median DOR by ICR was 20.4mo (Copa/R) vs 17.3mo (Pbo/R). This discrepancy between local and central assessment increases the uncertainty surrounding these data. The applicant is asked to discuss possible reasons for the discrepancy. The Rapporteur may consider including a table showing local assessment of efficacy, in particular DOR and CRR.

Time to progression (TTP):

Table 9–11 TTP in the total iNHL study population and MZL subpopulation – Independent central review (FAS)

	Total iNHL[a] N=458		MZL[b] N=95	
	Copanlisib/ rituximab N=307	Placebo/ rituximab N=151	Copanlisib/ rituximab N=66	Placebo/ rituximab N=29
TTP (month)				
Median	**22.3 [19.4,33.2]**	**13.8 [10.8,18.7]**	**33.2 [13.7,A]**	**11.5 [5.6,16.3]**
[95% CI]				
HR [95% CI]	**0.476 [0.357, 0.635]**		**0.458 [0.234, 0.895]**	
One-sided p-value from log-rank test	<.000001		0.009531	

CI = Confidence interval; FAS = Full analysis set; HR = Hazard ratio; iNHL = Indolent non-Hodgkin's lymphoma; MZL = Marginal zone lymphoma; N = Total number of patients (100%); TTP = Time to progression
a: TTP was evaluated with the stratified log-rank test based on stratification factors iNHL histology and entry criterion used for randomization.
HR and 95% CI was based on Cox Regression Model, stratified by iNHL histology and entry criterion used for randomization.
b: TTP was evaluated with the unstratified log-rank test. HR ratio and 95% CI are based on unstratified Cox Regression Model.
Notes:
Patients evaluated by Owen criteria (Owen et al. 2013) may include investigator assessments in the absence of independent central review.
A: Value could not be estimated due to censored data.
Median, percentile, and other 95% CIs computed using Kaplan-Meier estimates.
An HR <1 indicates superiority of copanlisib/rituximab over placebo/rituximab.

Overall survival (OS):

Data is premature and an update of OS is requested. Furthermore, the planned follow-up analysis of OS one year after primary completion is requested, when available, together with updated efficacy data on PFS and ORR/CR.

Table 9–12 OS in the total iNHL study population and MZL subpopulation (FAS)

	iNHL [a] N=458		MZL [b] N=95	
	Copanlisib/ rituximab N=307	Placebo/ rituximab N=151	Copanlisib/ rituximab N=66	Placebo/ rituximab N=29
Number (%) of patients				
With event	43 (14.0%)	20 (13.2%)	11 (16.7%)	4 (13.8%)
Censored	264 (86.0%)	131 (86.8%)	55 (83.3%)	25 (86.2%)
OS (months)				
Median [95% CI]	**57.4 [A,A]**	**A [A,A]**	**A [A,A]**	**A [36.4,A]**
OS rate at				
24 months	0.858	0.908	0.843	0.907
[95% CI]	[0.814,0.902]	[0.856,0.961]	[0.742,0.944]	[0.782,1.000]
HR [95% CI]	**1.070 [0.628,1.821]**		**0.966 [0.307,3.043]**	
One-sided p-value from log-rank test	0.597747		0.476494	

CI = Confidence interval; FAS = Full analysis set; HR = Hazard ratio; iNHL = Indolent non-Hodgkin's lymphoma; MZL = Marginal zone lymphoma; N = Total number of patients (100%); OS = Overall survival;
a: OS was evaluated with the stratified log-rank test based on stratification factors iNHL histology and entry criterion used for randomization.
HR and 95% CI were based on Cox Regression Model, stratified by iNHL histology and entry criterion used for randomization.
b: OS is evaluated with the unstratified log-rank test. HR and 95% CI are based on unstratified Cox Regression Model.
Notes:
A: Value could not be estimated due to censored data.
Median, percentile, and other 95% CIs computed using Kaplan-Meier estimates.
An HR <1 indicates superiority of copanlisib/rituximab over placebo/rituximab.
Source: Table 14.2.2.1/16 and Table 14.2.5.1/13

DRS-P deterioration and improvement:

Copa/R did not show superiority compared with Pbo/R for time to DRS-P deterioration. Therefore, the null hypothesis could not be rejected for time to DRS-P deterioration and was not formally tested for time to DRS-P improvement.

Ancillary analyses

MZL was a subgroup of the iNHL population and the population was further divided into among others two subpopulations: The "Progression-free and treatment-free interval of ≥12 months after the last rituximab-containing treatment" group and the "Unfit or Unwilling to receive chemotherapy with a progression-free and treatment-free interval of ≥6 months after the last rituximab-containing treatment" group. With all these subgroups all subgroups considered relevant have been included and discussed in the presentation of the primary endpoint.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application.

Table XXX. Summary of efficacy for trial 17067 (CHRONOS-3)

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			
Study identifier	EudraCT number: 2013-003893-29; NCT02367040		
Design	Phase III, randomised (2:1), double-blind, placebo-controlled, multi-centre, ongoing		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Not applicable; event-driven Not applicable Not applicable
Hypothesis	Superiority		
Treatments groups	Copanlisib/ rituximab (Copa/R)		Copanlisib was administered intravenously on Days 1, 8, and 15 of each 28-day cycle before rituximab treatment until disease progression. Rituximab: 375 mg/m^2 body surface weekly during Cycle 1 on Days 1, 8, 15, and 22, and then on Day 1 of Cycles 3, 5, 7, and 9 (eight infusions). (307 iNHL of which 66 had MZL)
	Placebo/ rituximab (Pbo/R)		Placebo (Pbo): Administered as copanlisib. Rituximab; Administered as in the Copa/R-arm. (151 iNHL of which 29 had MZL)
Endpoints and definitions	Primary endpoint	Progression-free survival (**PFS**)	Time (in days) from randomisation to progressive disease (PD) or death from any cause (if no progression was documented), whichever occurred earlier. The primary PFS analysis was based on central review (IRC).
	Secondary efficacy endpoint	Objective response rate (**ORR**)	The proportion of patients who had a best response rating over the whole duration of the study (i.e., until time of analysis of PFS) of complete response (CR) or partial response (PR) according to the Cheson 2014 criteria 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. Part of the hierarchical testing strategy implemented to control the type I error due to multiple endpoints.
	Secondary efficacy endpoint	Complete response rate (**CRR**)	The proportion of patients who had a best response rating over the whole duration of the study (i.e., until the time of analysis of PFS) of CR according to the Cheson 2014 criteria and for patients with WM a response rating of CR according to the Owen criteria.
	Secondary efficacy endpoint	Time to de-terioration & improvement in **DRS-P**	Time (in days) from randomisation to DRS-P deterioration or improvement of at least three points using the FlymSI-18 questionnaire.
Database lock	31 AUG 2020		

Results and Analysis

Based on the database cut-off date (31 AUG 2020) used for the primary efficacy analysis, the study met its primary endpoint, as superiority of Copa/R over Pbo/R treatment was demonstrated for PFS based on independent central review (ICR) in the iNHL patients.

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat: 458 iNHL patients. The primary analysis was planned when at least 190 centrally evaluated PFS events were observed in the study and was performed when 205 patients were included.		
Descriptive statistics and estimate variability [iNHL[1] and **MZL[2] subgroup (in bold)**]	Treatment group	Copanlisib/ rituximab	Placebo/ rituximab
	Number of subjects; **66**	307 **29**	151
	PFS median, months [95% CI] **[13.8, A]**	21.5 [17.8, 33.0] **22.1**	13.8 [10.2, 17.5] **11.5** **[5.6, 16.3]**
	ORR, n, (%) [95% CI] **[63.6, 85.5]**	248 (80.8) [75.9, 85.0] **50 (75.8)**	72 (47.7) [39.5, 56.0] **12 (41.4)** **[23.5,61.1]**
	CRR, n, (%) [95% CI] **[27.6, 52.2]**	104 (33.9) [28.6, 39.5] **26 (39.4)**	22 (14.6) [9.4, 21.2] **3 (10.3)** **[2.2, 27.4]**
Effect estimates per comparison [iNHL and **MZL subgroup (in bold)**]	Primary endpoint: PFS	Comparison groups	Copa/R vs. Pbo/R
		Hazard ratio[1] [95% CI] One-sided P-value[3] **Hazard ratio[2]** **[95% CI]** **One-sided P-value[3]**	0.520 [0.393, 0.688] 0.000002 **0.475** **[0.245, 0.923]** **0.012291**
	Secondary endpoint: ORR	Comparison groups	Copa/R vs. Pbo/R
		Difference[4] [95% CI] One-sided P-value[5] **Difference[4]** **[95% CI]** **One-sided P-value[6]**	
	Secondary endpoint: CRR	Comparison groups	Copa/R vs. Pbo/R
		Difference[4] [95% CI] One-sided P-value[5] **Difference[4]** **[95% CI]** **One-sided P-value[6]**	

A: CMH = Cochran-Mantel-Haenszel
[1]: PFS was evaluated with the stratified log-rank test based on stratification factors iNHL histology and entry criterion used for randomization. HR and 95% CI were based on Cox Regression Model, stratified by iNHL histology and entry criterion.
[2]: PFS was evaluated with the unstratified log-rank test. Histology is based on the information entered in the eCRF for randomization. HR and 95% CI were based on unstratified Cox Regression Model.
[3]: One-sided p-value from log rank test
[4]: Difference = copanlisib/rituximab – placebo/rituximab; for the total population CMH-weighted difference is displayed
[5]: P-values from CMH test stratified by iNHL histology and entry criterion based on stratification information used for randomisation.
[6]: P-values are from chi-square test.

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

Clinical studies in special populations

The applicant is requested to fill in the table below for study 17067.

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials			
Non Controlled trials			

Study 16349 Part B (CHRONOS-1) – monotherapy:

Study 16349 Part B is an ongoing, open-label, uncontrolled, single-arm Phase 2 study to evaluate efficacy and safety of copanlisib as a single agent in patients with B-cell iNHL, relapsed or refractory after at least two prior lines of therapy.

Methods

- ***Study Participants***

Main inclusion criteria

- Male or female > 18 years and histologically confirmed diagnosis of indolent B-cell NHL, with histological subtype of: FL grade 1-2-3a, MZL (splenic, nodal, or extra-nodal), SLL with absolute lymphocyte count < 5 x 109/L at study entry and LPL/WM.
- Relapsed or refractory after ≥ 2 prior lines of therapy. Patients must have received rituximab and alkylating agents.

- Patients must have at least one not previously irradiated bi-dimensionally measurable lesion according to the recommendations of the Revised Response Criteria for Malignant Lymphoma (Cheson 2007).
- Patients with LPL/WM must have measurable disease, defined as presence of IgM level of ≥ 2 times the ULN OR > 10% of lymphoplasmacytic cells in bone marrow.
- ECOG performance status ≤ 2 and life expectancy of at least 3 months.
- Adequate bone marrow, liver and renal function:

  o 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)

  o ALT/AST ≤ 2.5 x ULN (≤ 5 x ULN for patients with lymphomatous liver involvement of their cancer)

  o Serum creatinine ≤ 1.5 x the ULN, GFR ≥ 30 ml/min/1.73 m^2 according to the MDRD

  o Platelet count ≥ 75,000 /mm^3, Hb ≥ 9 g/dL, ANC ≥ 1,500/mm^3.

Left ventricular ejection fraction (LVEF) ≥ lower limit of normal for the institution.

Main exclusion criteria (for further details, please see exclusion criteria for study 17067)

- FL grade 3b or transformed disease or CLL. Previous or concurrent cancer that is distinct in primary site or histology from indolent B-cell NHL within 5 years prior to treatment start EXCEPT for curatively treated cervical cancer in situ, non-melanoma skin cancer and superficial bladder tumours.
- Congestive heart failure > NYHA class 2, unstable and new-onset (within 3 months) angina. Myocardial infarction less than 6 months before start of test drug. Uncontrolled hypertension (blood pressure ≥ 150/90 mmHg despite optimal medical management). Cardiac arrhythmias requiring anti-arrhythmic therapy (beta blockers or digoxin are permitted).
- Known hypersensitivity to any of the test drugs, test drug classes, or excipients in the formulation.
- Proteinuria of CTCAE grade 3 or higher (urine protein:creatinine ratio > 3.5 on a random urine sample.
- Prior treatment with PI3K inhibitors, other investigational drugs within 28 days prior to treatment start.
- Ongoing immunosuppressive therapy, radiotherapy or immuno/chemotherapy within 4 weeks prior to treatment start. Radioimmunotherapy or autologous transplant within 3 months prior to treatment start. Prior allogeneic bone marrow - or organ transplant.
- Systemic corticosteroid therapy (ongoing). Previous corticosteroids therapy must be stopped at least 7 days prior to first study drug administration. Topical or inhaled corticosteroids are allowed.

Treatments

Copanlisib (BAY 80-6946) was administered IV over approximately 1 h) on Days 1, 8 and 15 of each 28-day treatment cycle. The dose was 0.8 mg/kg for 12 patients and 60 mg fixed dose for 130 patients. In the Clinical Study Protocol (CSP) Amendment 4, copanlisib dosing was changed from body

weight-based to a fixed dose. Guidance for dose modifications and treatment of toxicities is provided in Section 16.1.1, CSP, Sections 6.4.1 and 6.4.2.

Objectives

The primary objective was to evaluate the efficacy and safety of copanlisib in patients with indolent B-cell NHL relapsed after, or refractory to widely used approved therapies in standard practice.

The secondary objectives were to evaluate the pharmacokinetics of copanlisib, biomarkers and quality of life.

Outcomes/endpoints

The primary endpoint ORR was defined as the proportion of patients who had a best response rating of complete response (CR) or partial response (PR). Determination of objective tumour response was performed by using the blinded assessments of the Independent Review Committee including evaluation of radiological and clinical data.

The key secondary efficacy endpoints were:

- **Duration of response (DoR)**, defined as the time (in days) from the date of the first observed tumour response of CR or PR until progression or death, whichever occurred earlier.
- **Progression free survival (PFS)**, defined as the time (in days) from the date of first administration of study treatment to first disease progression or death due to any cause.
- **Overall survival (OS)**, defined as the time (in days) from the date of first administration of study treatment to death due to any cause.
- **Quality of life**, the change from baseline until week 16 in FACT-Lym Lymphoma subscale (FACT-Lym LymS) and FACT-Lym total score.

Randomisation and blinding (masking)

No randomisation or blinding was performed considering the single arm trial design. The main efficacy analysis will be done by the blinded assessments of an Independent Review Committee (according to the Revised Response Criteria for Malignant Lymphoma, Cheson 2007).

Statistical methods

The Full analysis set (FAS) was defined as all patients assigned to study treatment (recruited into Part B).

The Per protocol set (PPS) was defined as all patients recruited into Part B with study drug administration that are evaluable for ORR and that have no major protocol deviation affecting the primary efficacy variable. At least one evaluable post baseline tumour assessment in independent assessment should be available in order to consider the patient evaluable.

The primary and secondary efficacy variables will be analysed in the FAS and PPS. All other efficacy variables will be analysed in FAS. The primary analysis set for the efficacy variables is the FAS. Patients who signed the informed consent but were not assigned to treatment will be considered as screening failures.

The main efficacy analyses will be done by using the central blinded review tumour response assessments, but in addition some analyses will also be done by using the investigator tumour response assessments.

Efficacy analysis – The primary endpoint is ORR. The Null hypothesis is "True probability p of ORR does not exceed p0," p being the true probability of response under therapy with copanlisib and p0 being the chosen true probability of response that needs to be exceeded for the outcome to be regarded as acceptable, based on historic control, where p0 is set to 0.40.

The secondary endpoints, DoR, PFS, OS and QoL are considered of descriptive value, due to the single-arm setting

Multiplicity control - A hierarchical strategy was implemented to control the type I error across the multiple secondary endpoints.

Sample size – The sample size calculations indicate that 120 subjects would be sufficient to show with 99 % power that ORR is larger than 40%, under an assumed true ORR in the study population of 60%. Several changes were made to the original study design while the study was ongoing which affected the sample size calculations. This is of concern since it is not possible to ensure that decisions were not informed using the available data from the current study, which would affect the type I error. The most important change is the modification of the threshold of ORR response from 60 % to 40 %. Since the clinical relevance of the observed ORR can be evaluated regardless of the threshold implemented in the sample size calculations, this issue will not be pursued.

Interim analysis - No interim analysis was planned. The analysis for Part A and Part B were done separately. The primary analysis for ORR was conducted on the data collected up to 16 weeks after the last patient eligible for FAS will have started treatment. The results are presented for the primary analysis (first cut-off date 22 Jun 2016) and were updated with the data collected up to 20 Feb 2018.

Results

Participant flow

A total of 143/213 patients completed screening and assigned to treatment between 4 November 2013 (first subject first visit) and 22 June 2016 (last subject last visit). The small sample size of patients with MZL together with the fact, that more than half of them discontinued the study, does not allow the evaluation of the treatment's benefit/risk, and no firm conclusion can therefore be drawn on the dataset in the MZL population.

Conduct of the study

The original protocol was approved 5 July 2012. There were 8 protocol amendments. Key changes to the protocol and SAP pertain to the population of interest, in– and exclusion criteria, the change of the body weight-based dose to a fixed dose, the quality of endpoints and a change of the statistical test null hypothesis and the primary analysis set. Most major deviations were related to procedure (15 out of a total of 143 patients), among the 23 MZL patients, 11 patients had major protocol deviations, i.e., the PP analysis included only 12 patients. Eleven patients did not meet the in-/exclusion criteria, but entered treatment, these patients must be accounted for.

Baseline data

Median age was 63 years, for MZL 65.2% were 65 or older. Males and females are equally represented for all subtypes, except from MZL, where 65.2% were females, most patients were Caucasian (~ 85%). Regarding performance status, the baseline PS status was 0 in 56.3% of the patients and 40.1% had PS 1, although more patients in PS 1 are expected in the target population. NYHA classification was not classifiable in the majority of patients, 93.0%, which is of concern.

Follicular lymphoma (FL) was the most common histologic subtype, reported in 104 patients (73.2%), of which 86 were centrally confirmed (Table 8-8). An additional 3 patients were centrally revised from

MZL to FL, thus the total number of centrally confirmed FL patients was 89 (62.7%). The MZL was centrally confirmed in 13 patients (9.2%), of these, the subtype could not be specified. This adds to the concern, that there are too few patients with MZL in this study to make an assessment. The MZL population is thus very small. Very few numbers of patients with SLL and LPL/LWM were included. One patient was excluded since the diagnosis was centrally confirmed as being DLBCL.

Table 8–8 FL grades and MZL subtypes at baseline – investigator pathology (FAS)

	Investigator pathology n (%)
FL	
N	**104**
Grade 1	22 (21.2)
Grade 2	52 (50.0)
Grade 1 or 2	74 (71.2)
Grade 3a	27 (26.0)
Missing	3 (2.9)
Not graded	NA
MZL	
N	**23**
MALT lymphoma	4 (17.4)
Nodal MZL	15 (65.2)
Splenic MZL	4 (17.4)
Missing	0
Not otherwise specified	NA

FL = Follicular lymphoma; MZL = Marginal zone (b-cell) lymphoma; FAS = Full analysis set; n = Number of patients with event; N = Total number of patients (100%); NA = Not available; MALT = Mucosa-associated lymphoid tissue
Note: Percentages are calculated including missing values.
Source: Table 14.1.2/3 and Table 14.1.2/4

Table 8–9 Summary of baseline cancer characteristics (FAS)

Baseline cancer characteristic	FL n (%)	MZL n (%)	iNHL[a] n (%)	Total[b] n (%)
Baseline tumor size[c] (cm)				
N[d]	104	20	138	139
Mean ± SD	4.73 ± 2.73	5.41 ± 4.88	4.86 ± 3.19	4.87 ± 3.18
Median	4.20	3.55	4.00	4.00
Min, Max	1.1, 15.8	1.6, 20.0	1.1, 20.0	1.1, 20.0
Longest diameter of baseline lesion				
N	104 (100.0)	23 (100.0)	141 (100.0)	142 (100.0)
Missing	0	3 (13.0)	3 (2.1)	3 (2.1)
All lesions < 7 cm	89 (85.6)	16 (69.6)	116 (82.3)	117 (82.4)
At least one lesion ≥ 7 cm	15 (14.4)	4 (17.4)	22 (15.6)	22 (15.5)
Ann Arbor stage of tumor				
N	104 (100.0)	23 (100.0)	141 (100.0)	142 (100.0)
I	3 (2.9)	0	3 (2.1)	3 (2.1)
II	22 (21.2)	3 (13.0)	25 (17.7)	25 (17.6)
III	29 (27.9)	2 (8.7)	32 (22.7)	32 (22.5)
IV	50 (48.1)	18 (78.3)	81 (57.4)	82 (57.7)
Presence of B symptoms[e]				
N	104 (100.0)	23 (100.0)	141 (100.0)	142 (100.0)
Yes	13 (12.5)	2 (8.7)	21 (14.9)	22 (15.5)
No	89 (85.6)	19 (82.6)	115 (81.6)	115 (81.0)
Missing	2 (1.9)	2 (8.7)	5 (3.5)	5 (3.5)
Time from initial diagnosis to first study treatment (months)				
N[d]	86	20	115	116
Mean ± SD	84.6 ± 65.6	89.6 ± 93.4	82.6 ± 69.7	81.9 ± 69.7
Median	69.5	67.6	65.0	64.8
Min, Max	9, 407	20, 443	9, 443	8, 443
Time since first progression to first study treatment (months)				
N[d]	81	15	103	104
Mean ± SD	52.0 ± 47.9	72.5 ± 91.6	53.2 ± 55.9	52.8 ± 55.9
Median	34.2	50.1	36.4	36.2
Min, Max	3, 234	6, 383	3, 383	2, 383
Time from most recent progression to first study treatment (weeks)				
N[d]	93	18	120	121
Mean ± SD	12.0 ± 14.1	20.2 ± 17.2	13.1 ± 14.6	13.0 ± 14.6
Median	8.0	14.1	8.3	8.3
Min, Max	1, 73	5, 65	1, 73	1, 73
FACT-Lym LymS score[f]				
N[d]	98	20	132	132
Mean ± SD	47.44 ± 8.47	39.95 ± 8.96	45.27 ± 9.55	45.27 ± 9.55
Median	48.00	38.50	46.50	46.50
Min, Max	7.0, 60.0	21.0, 53.0	7.0, 60.0	7.0, 60.0

Table 8–9 Summary of baseline cancer characteristics (FAS)

Baseline cancer characteristic	FL n (%)	MZL n (%)	iNHL[a] n (%)	Total[b] n (%)
FACT-Lym total score[f]				
N[d]	98	20	132	132
Mean ± SD	131.78 ± 20.83	116.59 ± 20.62	126.59 ± 22.96	126.59 ± 22.96
Median	133.00	116.17	127.50	127.50
Min, Max	42.2, 166.0	80.2, 153.0	42.2, 166.0	42.2, 166.0
EQ-5D status index[f, g]				
N[d]	98	20	132	133
Mean ± SD	0.82 ± 0.20	0.68 ± 0.25	0.78 ± 0.21	0.78 ± 0.21
Median	0.85	0.69	0.80	0.80
Min, Max	-0.2, 1.0	0.2, 1.0	-0.2, 1.0	-0.2, 1.0
EQ-5D status VAS[f]				
N[d]	97	20	131	132
Mean ± SD	74.68 ± 17.07	71.70 ± 15.11	72.73 ± 16.95	72.62 ± 16.93
Median	76.00	70.50	70.00	70.00
Min, Max	30.0, 100.0	40.0, 100.0	30.0, 100.0	30.0, 100.0

FAS = Full analysis set; FL = Follicular lymphoma; MZL = Marginal zone lymphoma; iNHL = Indolent Non-Hodgkin's lymphoma; n = Number of patients with event; N = Total number of patients (100%); FACT-Lym = Functional Assessment of Cancer Therapy – Lymphoma; LymS = Lymphoma subscale; SD = Standard deviation; Min = Minimum; Max = Maximum; EQ-5D = EuroQol five dimensions questionnaire; VAS = Visual analogue scale; DLBCL = Diffuse large B-cell lymphoma

Note: Percentages are calculated including missing values.

a: iNHL: FL grade 1-2-3a, MZL, SLL and LPL/WM.

b: Total includes patients with iNHL and 1 patient who had DLBCL (further details in Section 8.5). Data for the DLBCL patient can be found in Table 14.1.2/3.

c: Longest diameter (maximum of all target lesions).

d: Data not available for all 142 patients.

e: B symptoms: fever above 38 °C, night sweats, and weight loss of more than 10% of body mass in the previous 6 months.

f. FACT-Lym and EQ-5D VAS data are missing for 10 patients and EQ-5D status index data for 9 patients at baseline. For 5 patients each, these questionnaires were completed later than 30 minutes after the start of the first infusion and were therefore not considered as baseline values (see Section 16.2.5/2 and Section 16.2.8.2).

g: EQ-5D status index values were rounded manually.

Source: Table 14.1.2/3

Overall the study population was heavily pre-treated and is considered representative of the target population. All patients had received prior anti-cancer therapy, mostly a combination of chemotherapy and immunotherapy (90.1%), followed by chemotherapy alone (47.9%) and immunotherapy alone (33.8%). They had all received rituximab and alkylating agents, and the median number of previous therapy lines was 3.0 (range 2-9).

Table 8–13 Prior systemic anti-cancer therapy (FAS)

	FL N = 104 n (%)	MZL N = 23 n (%)	iNHL[a] N = 141 n (%)	Total[b] N = 142 n (%)
Type of therapy				
Any type	104 (100.0)	23 (100.0)	141 (100.0)	142 (100.0)
Chemotherapy/ immunotherapy	93 (89.4)	20 (87.0)	127 (90.1)	128 (90.1)
Chemotherapy	43 (41.3)	18 (78.3)	68 (48.2)	68 (47.9)
Immunotherapy	38 (36.5)	9 (39.1)	48 (34.0)	48 (33.8)
High dose chemotherapy and autologous transplant	18 (17.3)	1 (4.3)	19 (13.5)	19 (13.4)
Radioimmunotherapy	13 (12.5)	0	13 (9.2)	13 (9.2)
Non-conventional	1 (1.0)	0	2 (1.4)	2 (1.4)
Number of prior therapy lines				
Median	3.0	3.0	3.0	3.0
Min, Max	2, 8	2, 9	2, 9	2, 9
Number of prior therapies				
< 4	72 (69.2)	18 (78.3)	101 (71.6)	102 (71.8)
≥ 4	32 (30.8)	5 (21.7)	40 (28.4)	40 (28.2)
Number of prior treatment regimens (any intent)				
2	35 (33.7)	10 (43.5)	49 (34.8)	50 (35.2)
3	37 (35.6)	8 (34.8)	52 (36.9)	52 (36.6)
4	15 (14.4)	2 (8.7)	18 (12.8)	18 (12.7)
5	8 (7.7)	2 (8.7)	12 (8.5)	12 (8.5)
6	3 (2.9)	0	3 (2.1)	3 (2.1)
7	5 (4.8)	0	5 (3.5)	5 (3.5)
8	1 (1.0)	0	1 (0.7)	1 (0.7)
9	0	1 (4.3)	1 (0.7)	1 (0.7)
Time since last systemic therapy until PD (months)				
N	93	22	129	130
Mean ± SD	15.16 ± 19.23	20.80 ± 19.02	15.85 ± 19.45	15.73 ± 19.42
Median	8.54	15.93	10.15	10.02
Min, Max	0.0, 108.2	0.7, 57.5	0.0, 108.2	0.0, 108.2
Time since last systemic therapy until PD > 6 months				
Total (N)	104	23	141	142
n (%)	47 (45.2)	13 (56.5)	66 (46.8)	66 (46.5)
Relapsed (N)	39	12	56	56
n (%)	39 (100.0)	12 (100.0)	56 (100.0)	56 (100.0)
Refractory[c] (N)	65	11	85	86
n (%)	8 (12.3)	1 (9.1)	10 (11.8)	10 (11.6)

FAS = Full analysis set; FL = Follicular lymphoma; MZL = Marginal zone lymphoma; iNHL = Indolent Non-Hodgkin's lymphoma; N = Total number of patients (100%); n = Number of patients with event; Min = Minimum; Max = Maximum; PD = Progressive disease; SD = Standard deviation; DLBCL = Diffuse large B-cell lymphoma

Note: This table may not include all investigational compounds.

a: iNHL: FL grade 1-2-3a, MZL, SLL and LPL/WM.

b: Total includes patients with iNHL and 1 patient who had DLBCL (further details in Section 8.5). Data for the DLBCL patient can be found in Table 14.1.5/3, Table 14.1.5/8, Table 14.1.5/10, Table 14.1.5/11 and Table 14.1.5/12.

c: Patients with "unknown" best response are considered as refractory.

The majority of the MZL patients (18/23) had received either 2 or 3 prior treatment regimens, and 43.5% of the MZL patients were refractory to their last rituximab regimen.

Numbers analysed

A total of 142 patients were treated in the study and included in the FAS. The PPS consisted of 113 patients, comprising all patients with study drug administration that were evaluable for tumour response and had no major protocol deviation affecting the primary efficacy variable.

Outcomes and estimation

Primary endpoint: ORR

The primary analyses of ORR were performed in 2016. Follow-up analyses were performed in 2018.

The ORR was based on all patients up to 16 weeks after the last patient eligible for the FAS had started treatment. The ORR for the study population was 59.15% (95% CI: 50.60; 67.32), 84 patients achieved CR or PR, 17 patients experienced a CR (11.97%) and 67 patients had a PR (47.18%) No difference in ORR was reported between the investigator and the central pathology review.

The small sample size of patients with MZL does not allow the evaluation of the treatment's benefit/risk, and no firm conclusion can be drawn on the dataset in the 2L+ MZL population The secondary endpoints, median DOR, FACT-Lym LymS and FACTLym total score, were all immature.

Table 9–1 Tumor response – independent review (FAS)

	Total	
	N = 142 n (%)	**[95% CI]**
Best response		
CR	17 (11.97)	[7.13;18.48]
PR	67 (47.18)	[38.76;55.73]
SD	42 (29.58)	[22.22;37.81]
PD	3 (2.11)	[0.44;6.05]
uSD[a]	1 (0.70)	[0.02;3.86]
NE[b]	1 (0.70)	[0.02;3.86]
NA[c]	11 (7.75)	[3.93;13.44]
ORR		
Yes	**84 (59.15)**	[50.60;67.32]
No	47 (33.10)	[25.44;41.48]
NA[c]	11 (7.75)	[3.93;13.44]
DCR		
Yes	122 (85.92)	[79.09;91.18]
No	9 (6.34)	[2.94;11.69]
uSD or late best response of PR/SD[d]	5	
PD/NE[b]	4	
NA[c]	11 (7.75)	[3.93;13.44]

FAS = Full analysis set; N = Total number of patients (100%); n = Number of patients with event; CI = Confidence interval; CR = Complete response; PR = Partial response; SD = Stable disease; PD = Progressive disease; uSD = Unconfirmed early SD; NE = Not evaluable; NA = Not available; ORR = Objective response rate; DCR = Disease control rate

a: uSD: Assessment of SD earlier than 7 weeks after start of study treatment, with no radiologic assessment of SD, PR or CR at later cycles.

b: NE: Patients who had only post-baseline tumor assessment(s) that could not be assessed by Independent Review Committee oncologist.

c: NA: Patients who had no post-baseline tumor assessment and who discontinued due to a drug-related toxicity, death or progression by clinical judgment before disease was re-evaluated.

d: uSD or best response of PR/SD later than 35 days after last dose of study treatment.

Ancillary analyses

Not applicable

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table Summary of efficacy for study 16349 Part B (CHRONOS-1)

Title: Open-label, uncontrolled Phase II trial of copanlisib in patients with relapsed, indolent or aggressive Non-Hodgkin's lymphomas. Part B: indolent patients only			
Study identifier	EudraCT number: 2012-002602-52, ClinicalTrials.gov Identifier: NCT01660451		
Design	Single arm Phase II, multi-centre, open-label, uncontrolled relapsed or refractory B-cell indolent NHL.		
	Duration of main phase: Duration of run-in phase: Duration of extension phase:		04 NOV 2013 (FPFV) 22 JUN 2016 (database cut-off date, primary analysis) 20 FEB 2018 (database cut-off date, follow-up analysis) not applicable not applicable
Hypothesis	Exploratory		
Treatment groups	Copanlisib		Copanlisib 60 mg fixed intravenous (IV) dose (N=130) or 0.8 mg/kg (IV) (N=12). Dose was administered on Days 1, 8, and 15 of each 28-day treatment cycle.
Endpoints and definitions	**Primary:** Objective response rate	ORR	The proportion of patients who had CR or PR, according to the Cheson 2007 criteria.
	Secondary:	DOR	Time (in days) from first observed

	Duration of response		CR or PR (whichever was noted earlier) to first subsequent PD, first adverse event associated with PD or death, whichever occurred first.
	Secondary: Progression-free survival	PFS	Time from the date of first administration of study treatment to first PD or death due to any cause.
	Secondary: Overall survival	OS	Time from the date of first administration of study treatment to death due to any cause.

Results and analysis

Analysis description		**Primary analysis** 22 JUN 2016 (database cut-off date)			**Follow-up analysis** 20 FEB 2018 (database cut-off date)		
Analysis population and time point description		FAS	FL	MZL	FAS	FL	MZL
Descriptive statistics and estimate variability	Treatment group	Copanlisib					
	Number of subjects	142	104	23	142	104	23
	ORR (%) [95% CI] [a]	59.15 [50.60,67.32]	58.65 [48.58,68.23]	69.57 [47.08,86.79]	60.56 [52.02,68.65]	58.65 [48.58,68.23]	78.26 [56.30,92.54]
	DOR Median (months) [95% CI] [b]	22.6 [7.4, 22.6]	12.2 [6.9, 22.6]	A [3.3, A]	14.1 [8.3, 22.3]	12.2 [7.6, 22.3]	17.4 [8.3, A]
	PFS Median (months) [95% CI] [b]	11.2 [8.1, 24.2]	11.2 [7.8, 24.2]	A [A, A]	12.5 [9.0, 18.4]	11.2 [8.1, 17.6]	24.1 [18.4, A]
	OS Median (months) [95% CI] [b]	A [A, A]	A [A, A]	A [A, A]	42.6 [36.5, A]	38.3 [28.5, A]	A [A, A]

CI = Confidence interval; CR = Complete response; DOR = Duration of response; FACT-Lym = Functional Assessment of Cancer Therapy – Lymphoma; FAS = Full analysis set; FL = Follicular lymphoma; FPFV = First patient first visit; HRQoL = Health-related quality of life; LymS = Lymphoma subscale; MZL = Marginal zone lymphoma; n = Number of patients with event; NHL = Non-Hodgkin's lymphoma; ORR = Objective response rate; OS = Overall survival; PFS = Progression-free survival; PI3K = Phosphatidylinositol 3-kinase; PR = Partial response; StD = Standard deviation

A: Value could not be estimated due to censored data.

a: 95% CI by exact Clopper-Pearson calculation. Denominator for rates (%) and 95% CIs based on patient population evaluable for response.

b: Median, percentile, and other 95% CIs computed using Kaplan-Meier estimates.

c: Change from baseline to Week 16.

Source:

Primary analysis: Module 5.3.5.2, Report PH-38670, conversion tables, Tables 14.2/1 to 14.2/9 and Tables 14.2/13 to 14.2/18

Follow-up analysis: Module 5.3.5.2, Report PH-40438, Tables 14.1.1/4 and conversion tables, Tables 14.2/1 to 14.2/9 and Tables 14.2/13 to 14.2/18, and Table 16.4.1.1/4.

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

Clinical studies in special populations

Not applicable

Supportive study(ies)

Not applicable

3.3.5. Discussion on clinical efficacy

Design and conduct of clinical studies

Two indications in MZL are sought based on study 17067 (CHRONOS-3) and study 16349 Part B (CHRONOS-1):

- Aliqopa in combination with rituximab (anti-CD20 antibody) is indicated for the treatment of adult patients with previously treated marginal zone lymphoma. *(Combination therapy)*
- Aliqopa is indicated as monotherapy for the treatment of adult patients with marginal zone lymphoma who have received at least two prior therapies. (*Monotherapy)*

Study 17067 (CHRONOS-3) is a randomised (2:1), double-blind, placebo-controlled, two-arm Phase 3 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.

The applicant is seeking an indication for the MZL subgroup only (66/307 in the Copa/R arm vs 29/151 in the Pbo/R arm).

The study enrolled patients with rituximab-sensitive relapsed iNHL who were deemed suitable for rituximab monotherapy and had received one or more prior lines of therapy (≥2nd line). Two distinctive populations were included:

- Patients who had a progression-free and treatment-free interval of ≥12 months after completion of the last rituximab-containing treatment

OR

- Patients 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.

The choice of comparator to the Copa/R treatment is endorsed, but the Unfit/Unwilling population is considered problematic: the population could potentially be heterogenous. The Unwilling population was not included in the CHMP advice and justification for this mixing of two different populations has been questioned. An OC regarding the appropriateness of including the Unfit (as defined in the protocol) in the indication has been raised, as the results for this subgroup were not assessed separately.

The primary and secondary endpoints are considered relevant and clinically meaningful in the proposed patient population.

The study was double-blinded and measures were in place to minimise potential unblinding. This is acceptable.

Study 16349 is an open-label, uncontrolled, parallel group (i.e., including an indolent as well as an aggressive NHL cohort) study to evaluate efficacy and safety of copanlisib as a single agent in patients with indolent or aggressive NHL who have progressed after standard therapy. Part B of this study, which includes patients with indolent NHL, is the pivotal part for providing data to support copanlisib monotherapy.

In the **study 16349 Part B** (CHRONOS-1), the applicant is seeking an indication for the subgroup MZL only, as single agent copanlisib for patients relapsed or refractory after at least two prior lines of therapy, they had all received prior rituximab and alkylating agents. The study is a single arm trial, although the CHMP suggested a comparative arm of at least physician's best choice. The applicant is asked to justify the single arm regimen.

The study design was changed during the course of the study by several amendments, based on new evidence observed in other studies with copanlisib. Among others, the dose was changed from weight-based dose to flat dose. Changes were also made while the study was ongoing, which affected the sample size calculations. This is of concern, since it is not possible to ensure that decisions were not informed using the available data from the current study, which would affect the type I error. The most important change with regard to the sample size calculation is the modification of the threshold of ORR response from 60 % to 40 %. It is however considered that the clinical relevance of the ORR can be evaluated regardless of the threshold implemented in the sample size calculations.

The ORR is considered a clinical meaningful primary endpoint in a single-arm non-comparative trial, but the secondary endpoints as PFS, OS and QoL, have serious drawbacks in a single-arm study setting. These endpoints are therefore considered to provide only descriptive information.

Efficacy data and additional analyses

In the **study 17067**, a statistically significant treatment effect and clinically relevant difference in favour of Copa/R in the entire iNHL population was shown with a median PFS time of 21.5 months (95% CI: [17.8, 33.0]) compared with 13.8 months (95% CI: [10.2, 17.5]) in the Pbo/R arm with an HR of 0.520 (95% CI: [0.393, 0.688]; one-sided p=0.000002). The Kaplan-Meier curves continued to run separated, demonstrating longer PFS times for the Copa/R arm than for the Pbo/R arm.

The pre-specified PFS analyses in the four histological subpopulations (FL, MZL, SLL, and LPL/WM) were consistent with the primary analysis results with a HR of 0.475 (95% CI: [0.245, 0.923]; p=0.012291) for the MZL population.

No single stratification factor was driving the efficacy results, but PFS benefit seems lower in patients with bulky disease, with an HR of 0.905 (95% CI: [0.463,1.770]; one-sided p=0.385490) (Table 9-4/CSR and Fig. 9-9). Due to the small number of patients with prior PI3K inhibitor, no conclusion regarding efficacy in this group could be made. The HR for the "Unfit or Unwilling to receive chemotherapy with a progression-free and treatment-free interval of ≥6 months after the last rituximab-containing treatment" (Unfit/Unwilling) seems to be somewhat higher than the HR for the "Progression-free and treatment-free interval of ≥12 months after the last rituximab-containing treatment" group. The Unfit/Unwilling group could potentially be a quite heterogenous group. Notwithstanding the limited sample size, the apparent smaller difference in treatment effect between Copa/R vs Pbo/R for this stratum could be an indication that the Unfit group experiences lower efficacy and worse safety compared to the Unwilling population. If this is the case, this has to be made clear in the SPC, section 5.1, so that the prescribing physician can take this into account. The Unwilling patients were not included in the CHMP advice. Justification for "mixing" the two populations (Unfit and

Unwilling) has been requested. The applicant has also been requested to present the efficacy results (PFS, ORR, and CRR) for the Unfit (all patients fitting this description even though they may also have been Unwilling) and Unwilling separately (for both the iNHL and MZL populations) and to present a short overview of safety in these two populations as well as a short discussion regarding B/R based on these data to justify that the indication is appropriate also for the patients defined as Unfit.

Data for the secondary endpoints ORR and CRR supports the primary endpoint: Copa/R treatment showed a significantly higher ORR than Pbo/R treatment (80.8% vs. 47.7%) in the entire iNHL study population (ICR assessed). CRR was also higher in the Copa/R arm than in the Pbo/R arm (33.9% vs. 14.6%, respectively). The difference in ORR was 32.99 (95% CI: [23.95; 42.03]; one-sided p<.000001), indicating a statistically significant positive treatment effect for copanlisib in combination with rituximab. ORR and CRR were higher in the Copa/R arm than in the Pbo/R arm across the MZL subpopulations (75.8% vs. 41.4% and 39.4% vs. 10.3%, respectively). For MZL patients having received ≥2 prior treatments the ORR was 61.3% (19/31) in the Copa/R arm and 50% (5/10) in the Pbo/R arm and the corresponding CRR 29% (9/31) and 0, showing clear efficacy also in patients having received more than one prior systemic treatment. It is agreed that the difference in the ORR and CRR showed a clinically meaningful positive treatment effect of copanlisib in combination with rituximab.

A number of uncertainties remain regarding the efficacy results described above. In particular, local and ICR-based assessment of efficacy diverged for several secondary endpoints, including DOR and CRR. In the FAS of the iNHL, median DOR by ICR was 20.4mo (Copa/R) vs 17.3mo (Pbo/R), while by investigator assessment, it was 20.4mo in Copa/R vs 22.3mo in Pbo/R. CRR in the MZL population assessed locally was 33.3% (Copa/R) vs. 17.2% (Pbo/R), while by ICR it was 39.4% (Copa/R) vs 10.3% (Pbo/R). This discrepancy between local and central assessment increases the uncertainty surrounding these data and an OC has been raised. In addition, it appears diagnosis is by local laboratory and it is unclear if it was confirmed centrally. In light of the significant difference in MZL diagnosis by ICR and by local investigator in CHRONOS-1, this presents a significant uncertainty. OS data is not mature and the applicant is asked to submit updated OS, PFS and DOR data. Furthermore, there were a large number of protocol deviations in CHRONOS-3, most of which are classified as important (269 important protocol deviations in 458 patients) and did not lead to exclusion from the study. This included 53 instances where inclusion/exclusion criteria were not met but the patient entered treatment. The classification of protocol deviations is not clear and the applicant is requested to discuss the classification used for deviations (important, major, minor), as well as criteria for what constituted a deviation necessitating exclusion of data. Furthermore, there is some indication that the baseline disease status of patients may differ between the arms which, needs to be discussed.

In the **study 16349 Part B**, a total of 142 patients were included, the most common histologic subtype was FL, reported in 104 patients (73.2%), 23 had MZL and very few numbers of patients with SLL and LPL/LWM were included (8 and 7 respectively). Eleven patients who entered treatment, did not meet the in-/exclusion criteria, The applicant should provide narratives for these patients. Overall, 21% of the patients were considered to have a major protocol deviation, and thus, were excluded from the PP analysis. Among the 23 MZL patients, 11 patients had major protocol deviations, i.e. the PP analysis included only 12 patients.

A total of 23 patients with MZL entered treatment. Most discontinuations were due to AEs not associated with PD and withdrawal by subject. The main efficacy analysis used central blinded tumour response assessment, which is agreed. The MZL was exploratorily centrally confirmed in 13 patients (9.2%), 2 (15.4%) of these, had MALT lymphoma and nodal MZL and for 9 (69.2%) the subtype could not be specified.

The ORR for the whole study population was 59.15% (95% CI: 50.60; 67.32), 84 patients achieved CR or PR, 17 patients experienced a CR (11.97% in the FAS) and 67 patients had a PR (47.18%). In the MZL patients diagnosed by local pathology, 16 of 23 patients achieved CR or PR (ORR 69.57%, 95% CI: [47.08, 86.79]). The overall concordance between independent review and investigator assessment of response in the FAS was 63%. There is also low concordance between investigator and independent review in terms of determining complete response. In the MZL subgroup, there were 3 CRs as assessed by independent review, while investigator did not observe any CRs in the MZL patients.

The indication is based on a single-arm trial in iNHL, where MZL patients constitute a small subgroup (n=23, local pathology). Although an impressive ORR is observed for the MZL subgroup (78% in the 2018 follow-up), the number of patients (n=23) is considered inadequate for evaluation of copanlisib as monotherapy, with more than half of the patients discontinued from the study for other causes than PD. Furthermore, the robustness of the trial, beyond lack of a control group, is questioned. Only 13 patients were considered to have MZL when determined by central pathology. The number of major protocol deviations (>20%) further weakens the robustness of the study, with 11/23 patients in the MZL group registered within this category.

Although it is clear from both CHRONOS-1 and CHRONOS-3 that copanlisib has activity in MZL, the efficacy estimate obtained in CHRONOS-1 does not seem robust, especially in the small MZL subgroup. Discussion of the weaknesses of CHRONOS-1 and deliberation regarding the uncertainties in the effect size of copanlisib as monotherapy in MZL should be provided.

3.3.6. Conclusions on clinical efficacy

Study 17067 (CHRONOS-3) demonstrated a superior effect of Copa/R vs. rituximab monotherapy in relapsed, rituximab-sensitive iNHL patients having received at least one prior rituximab-containing therapy. For the MZL subpopulation, for which the indication is sought, the results were consistent with the overall iNHL population, and the PFS results were supported by clinically meaningful ORR and CRR responses. Some uncertainties remain regarding the efficacy results in CHRONOS-3, including several OCs, precluding a firm conclusion on efficacy in the indication sought.

With Study 16349 Part B being a single arm trial with a small subgroup of MZL patients, together with the fact that more than half of these patients discontinued the study, no firm conclusion can be drawn on the effect of copanlisib monotherapy in the 2L+ relapsed-refractory MZL population.

3.3.7. Clinical safety

The applicant has characterised the safety profile of copanlisib both in combination with rituximab and as monotherapy in iNHL. A more detailed description of safety data in FL and MZL has been provided. For the copanlisib combination therapy, safety data in additional histological subtypes of iNHL – SLL and LPL/WM – stemming from the same phase 3 CHRONOS-3 study as the FL and MZL data, has been provided. The presentation of the data is agreed.

For the monotherapy indication the major emphasis is on Pool 1, as the patients best resemble those in the proposed indication.

Table 1–2 Overview of clinical studies contributing to the safety evaluation of copanlisib in combination therapy and monotherapy

Study no. (NCT / EudraCT no.) Region (No. of countries, No. of centers) Study status	Design Copanlisib dose and schedule	Study population	No. of treated patients (database cut-off date)	Main outcomes References
Phase 3 combination study in iNHL				
17067 – CHRONOS-3 (NCT02367040, EudraCT: 2013-003893-29) Asia, Australia, Europe, New Zealand, North America (Mexico and the US), Russia, South Africa, and South America (37 countries, 186 study centers) Primary completion	*A Phase III, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of copanlisib in combination with rituximab in patients with relapsed iNHL – CHRONOS-3*			
	Randomized (2:1), double-blind, placebo-controlled (copanlisib/rituximab vs. placebo/rituximab), two-arm Combination therapy: Copanlisib 60 mg (or placebo) IV Days 1, 8, and 15 of a 28-day treatment cycle Rituximab 375 mg/m^2 IV Weekly during Cycle 1, and on Day 1 of Cycles 3, 5, 7, and 9	Patients with relapsed iNHL after one or more prior lines of therapy	Copanlisib: 307 Placebo: 146 (as analyzed in safety analysis set) (database cut-off: 31 AUG 2020)	Efficacy, safety, tolerability Module 5.3.5.1, Report PH-41310
Phase 2 studies in NHL				
16349 Part B – CHRONOS-1 (NCT01660451, EudraCT: 2012-002602-52) US, Canada, Europe, Asia Pacific, Russia, Israel, Australia, New Zealand (24 countries, 81 study centers) Primary completion	*Open-label, uncontrolled Phase II trial of intravenous PI3K inhibitor BAY 80-6946 in patients with relapsed, indolent or aggressive NHL (Part B: indolent patients only)*			
	Open-label, uncontrolled, single-arm Monotherapy: 60 mg IV [a] Days 1, 8, and 15 of a 28-day treatment cycle	Patients with relapsed or refractory iNHL after at least two prior lines of therapy	142 (database cut-off: 20 FEB 2020)	Efficacy, safety Module 5.3.5.2, Report PH-38670 Module 5.3.5.2, Report PH-40438
16349 Part A (NCT01660451, EudraCT: 2012-002602-52) US, Canada, Europe (10 countries, 41 study centers) Completed	*Open-label, uncontrolled Phase II trial of intravenous PI3K inhibitor BAY 80-6946 in patients with relapsed, indolent or aggressive NHL*			
	Open-label, uncontrolled, parallel group Monotherapy: 0.8 mg/kg IV Days 1, 8, and 15 of a 28-day treatment cycle	Patients with relapsed or refractory iNHL, aNHL, or CLL after at least two prior lines of therapy	84 (LPLV: 13 AUG 2018)	Efficacy, safety Module 5.3.5.2, Report PH-37856 Module 5.3.5.2, Report PH-38458 Module 5.3.5.2, Report PH-38661 Module 5.3.5.2, Report PH-40792
17119 (NCT02391116, EudraCT: 2014-004848-36) Europe, Asia Pacific, Canada, Australia (10 countries, 32 study centers) Completed	*An open-label, single-arm Phase II study in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) to evaluate efficacy and safety of treatment with single agent copanlisib and the impact of biomarkers thereupon*			
	Open-label, uncontrolled, exploratory, single-arm Monotherapy: 60 mg IV Days 1, 8, and 15 of a 28-day treatment cycle	Patients with relapsed or refractory DLBCL after at least one prior line of therapy	67 (LPLV: 18 JAN 2018)	Efficacy, biomarkers, safety, tolerability Module 5.3.5.2, Report PH-39013 Module 5.3.5.2, Report PH-39339 Module 5.3.5.2, Report PH-40163
17120 [b] (NCT02455297) US (one study center) Completed (study terminated)	*A single-arm, open-label Phase IIa study to evaluate the efficacy and safety of copanlisib monotherapy in patients with relapsed or refractory mantle cell lymphoma (MCL) who failed ibrutinib treatment or were unable to tolerate ibrutinib*			
	Open-label, uncontrolled, exploratory, single-arm Monotherapy: 60 mg IV Days 1, 8, and 15 of a 28-day treatment cycle	Patients with relapsed or refractory MCL previously treated with ibrutinib	2 (LPLV: 13 APR 2016)	Efficacy, safety, tolerability Module 5.3.5.4, Report PH-39324
Phase 1b/2 study in iNHL				
17792 (NCT02342665) Japan (13 study centers) Primary completion	*Open-label, uncontrolled, single-arm, Phase Ib/II study of intravenous copanlisib in Japanese patients with indolent B-cell Non-Hodgkin's Lymphomas relapsed after or refractory to standard therapy*			
	Open-label, uncontrolled, single-arm Monotherapy: 45 or 60 mg IV Days 1, 8, and 15 of a 28-day treatment cycle	Japanese patients with relapsed or refractory iNHL	25 (database cut-off: 20 FEB 2020)	Safety (efficacy was a further objective) Module 5.3.3.3, Report PH-39332 Module 5.3.3.3, Report PH-40185 Module 5.3.3.3 Report PH-41437 [c]

Phase 1 studies in NHL or solid tumors				
16866 (NCT03498430) China (one study center) Completed	*An open-label, Phase I study of copanlisib to evaluate the pharmacokinetics, safety, and tolerability in Chinese patients with relapsed indolent non-Hodgkin's lymphoma (iNHL)*			
	Open-label, uncontrolled, non-randomized, single-arm Monotherapy: 60 mg IV Days 1, 8, and 15 of a 28-day treatment cycle	Chinese patients with relapsed iNHL	13 (database cut-off: 06 AUG 2019 for the primary completion)	Safety, tolerability, PK, efficacy Module 5.3.3.3, Report PH-40801 Module 5.3.3.3, Report PH-41608 [d]
12871 (NCT00962611) US (three study centers) Completed	*An open-label Phase I dose-escalation study to evaluate the safety, tolerability, pharmacokinetics, maximum tolerated dose, and biomarker response after intravenous administration of weekly BAY 80-6946 to patients with advanced cancer*			
	Open-label, uncontrolled Monotherapy: Dose-escalation cohorts 0.1–1.2 mg/kg IV MTD expansion cohort 0.8 mg/kg IV Diabetic cohort 0.4 mg/kg IV Days 1, 8, and 15 of a 28-day treatment cycle	Dose-escalation cohort: Patients with advanced ST Expansion cohorts: Patients with NHL or ST Diabetic cohort: Patients with ST	57 (LPLV: 23 FEB 2016)	MTD, safety, tolerability, PK, biomarkers, pharmacodynamics, efficacy Module 5.3.3.2, Report PH-37433 (amended as of 15 NOV 2016)
16790 (NCT02155582, EudraCT: 2013-004746-42) Europe (three countries, 10 study centers) Completed	*A Phase I pharmacodynamic study of copanlisib (BAY 80-6946) as monotherapy in patients with non-Hodgkin's lymphomas and solid tumors*			
	Open-label, uncontrolled Monotherapy: Non-diabetic patients 0.4 or 0.8 mg/kg IV Diabetic patients: 45 mg or 60 mg IV Days 1, 8, and 15 of a 28-day treatment cycle	Patients with iNHL, aNHL, or ST (diabetic patients included)	63 (LPLV: 04 OCT 2016)	Pharmacodynamics, safety, tolerability, efficacy Module 5.3.3.2, Report PH-38915 Module 5.3.3.2, Report PH-39827
16270 (NCT02253420) US and Canada (two countries, five study centers) Completed	*An open-label, non-randomized, Phase I study to evaluate the effect of (a) itraconazole or rifampin on the pharmacokinetics of a single intravenous dose of copanlisib and (b) copanlisib on cardiovascular safety in subjects with advanced solid tumors and non-Hodgkin's lymphoma*			
	Open-label, non-randomized, uncontrolled Arm A: 12 mg, 60 mg (Part 1) or 60 mg (Part 2) copanlisib IV Days 1, 8, and 15 of a 28-day treatment cycle Itraconazole CYP3A4 inhibition Arm B: 60 mg copanlisib IV Days 1, 8, and 15 of a 28-day treatment cycle Rifampin CYP3A4 induction and QT/QTc assessment study	Patients with advanced ST or NHL	Arm A: 26 (LPLV: 21 AUG 2017) Arm B: 25 (LPLV: 13 AUG 2019)	Arm A: Effect of itraconazole on copanlisib PK Arm B: Effect of rifampin on copanlisib PK, cardiovascular safety Arm A: Module 5.3.3.4, Report PH-39051 Arm B: Module 5.3.3.4, Report PH-39642 Module 5.3.3.4, Report PH-39626 Module 5.3.3.4, Report PH-41079 Arm A and B: Module 5.3.3.4 Report PH-40176
15205 (NCT01404390) Japan (one study center) Completed	*An open-label, single center, Phase I study of PI3K inhibitor BAY 80-6946 to evaluate the safety, tolerability, and pharmacokinetics in Japanese patients with advanced or refractory solid tumors*			
	Open-label, uncontrolled, non-randomized Monotherapy: 0.4 or 0.8 mg/kg IV Days 1, 8, and 15 of a 28-day treatment cycle	Japanese patients with advanced or refractory ST	10 (LPLV: 12 JUL 2012)	Safety, tolerability, PK, efficacy Module 5.3.3.2, Report PH-36918
		Exposed to copanlisib:		
		Copanlisib in combination with rituximab	**307**	
		Copanlisib monotherapy	**514**	
		TOTAL (copanlisib in combination with rituximab or copanlisib monotherapy)	**821**	

aNHL = Aggressive non-Hodgkin's lymphoma; CLL = Chronic lymphocytic leukemia; CSR = Clinical Study Report; CYP3A4 = Cytochrome P450 family 3 subfamily A member 4; DLBCL = Diffuse large B-cell lymphoma; EudraCT = European Clinical Trials Database; iNHL = Indolent non-Hodgkin's lymphoma; IV = Intravenous; LPLV = Last patient last visit; MCL = Mantle cell lymphoma; MTD = Maximum tolerated dose; NCT = National Clinical Trial; NHL = Non-Hodgkin's lymphoma; No = Number; PI3K = Phosphatidylinositol 3-kinase; PK = Pharmacokinetics; QoL = Quality of life; QT = QT interval in an electrocardiogram; QTc = QT interval corrected for heart rate; ST = Solid tumor(s); US = United States (of America)

a: Twelve patients were enrolled and assigned to a 0.8 mg/kg dose before Protocol Amendment 4 introducing the 60 mg dose became effective.

b: Study 17120 was prematurely terminated due to low recruitment rate.

c: After the conduct of the integrated safety analysis, source data verification was completed for study 17792 until the database cut-off date of 20 FEB 2020 and a CSR including the full data was prepared (Module 5.3.3.3, Report PH-41437).

d: After the conduct of the integrated safety analysis, a CSR addendum of the three ongoing patients was prepared (LPLV: 02 JUN 2020) (Module 5.3.3.3, Report PH-41608).

Table 1–3 Copanlisib monotherapy – Integrated analysis: description of the pools

Pool 1 iNHL	• iNHL patients: FL, MZL, LPL/WM, and SLL
Pool 1b FL	• FL patients only
Pool 1c MZL	• MZL patients only
Pool 2 NHL/CLL	• NHL (FL, MZL, LPL/WM, SLL, and aNHL) and CLL patients
Pool 3 NHL/CLL/ST	• NHL (FL, MZL, LPL/WM, SLL, and aNHL), CLL, and ST patients

aNHL = Aggressive non-Hodgkin's lymphoma; CLL = Chronic lymphocytic leukemia; FL = Follicular lymphoma; iNHL = Indolent non-Hodgkin's lymphoma; LPL = Lymphoplasmacytoid lymphoma; MZL = Marginal zone lymphoma; NHL = Non-Hodgkin's lymphoma; SLL = Small lymphocytic lymphoma; ST = Solid tumor(s); WM = Waldenström macroglobulinemia

Patient exposure

The applicant has presented the safety evaluations for study 17067 comparing copanlisib plus rituximab (Copa/R) to placebo plus rituximab (Pbo/R) separately from the integrated analysis as this is a combination treatment as opposed to the monotherapy treatment in the integrated analysis. This approach is agreed.

Study 17067 (CHRONOS-3); combination treatment:

Exposure:

In the total iNHL study population, the overall median time of copanlisib treatment (including drug holidays and drug interruptions or delays) was 8.31 months in the Copa/R arm and 10.78 months in the Pbo/R arm. Despite this, the mean duration of treatment was comparable between the two treatment arms: 11.99 (StD 11.46) vs. 12.72 (StD 9.89) months in the Copa/R and Pbo/R arms, respectively. Accordingly, the median percentage of the planned dose of copanlisib or placebo received was slightly lower in the Copa/R arm (95.2%) than in the Pbo/R arm (100.0%).

In the total iNHL study population, the overall median time of rituximab treatment was the same in both treatment arms (7.59 months) and the median percentage of the planned dose of rituximab received was 100.0% in both treatment arms.

Demographics and baseline characteristics:

The median age was above 60 years (Copa/R: 63.0 years, Pbo/R: 62.5 years) in the iNHL population and 66.0 years and 63.0 years, respectively, in the MZL population. Given that the median age of the various types of MZL at diagnosis is 65-70 years, and the median number of prior treatments in the study was two, this population is younger than the real-world MZL population.

In the total iNHL study population as well as in the FL and MZL subpopulations demographics and baseline characteristics (including disease characteristics) were generally comparable between the Copa/R and Pbo/R arms. The minor differences detected generally favoured the Pbo/R-arm.

Table 1.3A–2 Demographics and baseline characteristics in the total iNHL population and histological subpopulations in study 17067 (SAF)

	Total iNHL N=453		MZL N=94	
	Copa/R N=307	Pbo/R N=146	Copa/R N=65	Pbo/R N=29
Gender, n (%)				
Male	154 (50.2)	82 (56.2)	33 (50.8)	12 (41.4)
Female	153 (49.8)	64 (43.8)	32 (49.2)	17 (58.6)
Age (years)				
Median	63.0	62.5	66.0	63.0
Min, Max	28, 91	34, 85	37, 91	46, 76
Age category (years), n (%)				
<65	166 (54.1)	85 (58.2)	29 (44.6)	17 (58.6)
≥65	141 (45.9)	61 (41.8)	36 (55.4)	12 (41.4)
Geographic Region 2, n (%) [b]				
North America	15 (4.9)	3 (2.1)	3 (4.6)	1 (3.4)
Asia Pacific	123 (40.1)	49 (33.6)	20 (30.8)	7 (24.1)
Rest of the world	169 (55.0)	94 (64.4)	42 (64.6)	21 (72.4)
History of hypertension, n (%)				
Yes	113 (36.8)	51 (34.9)	35 (53.8)	11 (37.9)
History of diabetes, n (%)				
Yes	45 (14.7)	21 (14.4)	13 (20.0)	2 (6.9)

Copa = Copanlisib; iNHL = Indolent non-Hodgkin's lymphoma; Max = Maximum; Min = Minimum; MZL = Marginal zone lymphoma; N = Total number of patients (100%); n = Number of patients with event; Pbo = Placebo; R = Rituximab; SAF = Safety analysis set; StD = Standard deviation; US = United States (of America);

b: Geographic Region 2 (used for sensitivity analysis of PFS and subgroup analysis of selected efficacy endpoints only):
North America includes Canada and the US (however; no patients were enrolled in Canada);
Asia Pacific includes China, Japan, South Korea, Taiwan (Province of China), Hong Kong, Malaysia, Singapore, Thailand, Vietnam, and Philippines;
Rest of the world includes Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Chile, Colombia, France, Germany, Greece, Hungary, Ireland, Italy, Lithuania, Mexico, New Zealand, Poland, Portugal, Romania, Russian Federation, Slovakia, South Africa, Spain, Turkey, and Ukraine (Module 5.3.5.1, Report PH-41310, Table 14.1.1/1).

Source: Module 5.3.5.1, Report PH-41310, Table 14.1.2/2, Table 14.1.2/4

The use of prior systemic anti-cancer therapies was similar between the two treatment arms with the most common prior systemic anti-cancer therapies being (Copa/R arm vs. Pbo/R arm): rituximab (), cyclophosphamide and vincristine. The results were generally comparable in the MZL population although patients with prior immunotherapy were more frequent in the Copa/R arm compared to the Pbo/R arm but the number of patients is small.

Table 1.3A–3 Baseline cancer characteristics in the total iNHL population and MZL histological subpopulation in study 17067 (SAF)

	Total iNHL N=453		MZL N=94	
	Copa/R N=307	Pbo/R N=146	Copa/R N=65	Pbo/R N=29
Most recent histology of lymphoma [a], n (%)				
FL	184 (59.9)	87 (59.6)	-	-
Grade:				
Grade 1	57 (18.6)	27 (18.5)	-	-
Grade 2	87 (28.3)	40 (27.4)	-	-
Grade 3a	40 (13.0)	20 (13.7)	-	-
MZL	65 (21.2)	29 (19.9)	65 (100.0)	29 (100.0)
Subtype:				
Extranodal	23 (7.5)	11 (7.5)	23 (35.4)	11 (37.9)
Nodal	25 (8.1)	12 (8.2)	25 (38.5)	12 (41.4)
Splenic	17 (5.5)	6 (4.1)	17 (26.2)	6 (20.7)
SLL	36 (11.7)	14 (9.6)	-	-
LPL/WM	22 (7.2)	16 (11.0)	-	-
Progression-free and treatment-free interval of at least 12 months after completion of the last rituximab-containing treatment, n (%)	247 (80.5)	116 (79.5)	48 (73.8)	22 (75.9)
Unfit or unwilling to receive chemotherapy, n (%)	60 (19.5)	30 (20.5)	17 (26.2)	7 (24.1)
Ann Arbor stage of tumor at study entry, n (%)				
Stage I	19 (6.2)	11 (7.5)	5 (7.7)	2 (6.9)
Stage II	37 (12.1)	13 (8.9)	8 (12.3)	3 (10.3)
Stage III	86 (28.0)	31 (21.2)	12 (18.5)	3 (10.3)
Stage IV	161 (52.4)	87 (59.6)	40 (61.5)	21 (72.4)
Missing	4 (1.3)	4 (2.7)	0	0
Presence of bulky disease, n (%)				
Yes	45 (14.7)	21 (14.4)	8 (12.3)	5 (17.2)
No	262 (85.3)	125 (85.6)	57 (87.7)	24 (82.8)
ECOG PS, n (%)				
0 – Fully active	182 (59.3)	91 (62.3)	41 (63.1)	17 (58.6)
1 – Restricted active	113 (36.8)	54 (37.0)	22 (33.8)	12 (41.4)
2 – Ambulatory and capable of all self-care	12 (3.9)	1 (0.7)	2 (3.1)	0

Copa = Copanlisib; ECOG = Eastern Cooperative Oncology Group; FL = Follicular lymphoma; G = Grade; IgM = Immunoglobulin M; iNHL = Indolent non-Hodgkin's lymphoma; MZL = Marginal zone lymphoma; N = Total number of patients (100%); n = Number of patients with event; Pbo = Placebo; PS = Performance status; R = Rituximab; SAF = Safety analysis set

a: Most recent histology based on local assessment.

Source: Module 5.3.5.1, Report PH-41310, Table 14.1.2/4 and Table 14.1.2/8

Table 1.3A–6 Overview of prior systemic anti-cancer therapies in the total iNHL population and histological subpopulations in study 17067 (FAS)

	Total iNHL N=453		MZL N=94	
	Copa/R N=307	Pbo/R N=146	Copa/R N=65	Pbo/R N=29
Lines of prior systemic anti-cancer therapy, n (%)				
1	150 (48.9)	71 (47.0)	35 (53.0)	19 (65.5)
2	75 (24.4)	40 (26.5)	19 (28.8)	6 (20.7)
3	38 (12.4)	23 (15.2)	8 (12.1)	3 (10.3)
≥4	44 (14.3)	17 (11.3)	4 (6.1)	1 (3.4)
Time since the last systemic anti-cancer therapy (months)				
Median	25.07	25.26	24.84	31.44

Copa = Copanlisib; FAS = Full analysis set; iNHL = Indolent non-Hodgkin's lymphoma; MZL = Marginal zone lymphoma; N = Total number of patients (100%); n = Number of patients with event; Pbo = PlaceboR = Rituximab

The size of the safety database at 6 months is 187 patients, at 12 months 114 patients and at 24 months 45 patients. Long term safety is thus limited, and has been raised to include "Long term safety" as Missing information in the RMP Summary of safety concerns.

Integrated analysis (ISS); Copanlisib monotherapy:

The monotherapy safety population was analysed using different pools.

Pool 1 is considered the main pool for adverse events evaluation as this pool contained the iNHL patients, including 29 MZL patients and 161 FL patients. Pool 2 added CLL and some aggressive NHL patients to Pool 1 and Pool 3 added solid tumour (ST) patients to Pool 2.

Of the 207 patients in Pool 1 the dose of copanlisib was either 60 mg IV or 0.8 mg/kg (max 65 mg IV) D. 1, 8, and 15 of a 28-day cycle (3 patients received 45 mg IV).

The overall median time of copanlisib treatment (including drug holidays and drug interruptions or delays) was 5.52 months in Pool 1, and similar in FL Pool 1b (5.36 months), and MZL Pool 1c (5.32 months).

In the iNHL Pool 1 the median age of patients was 63.0 years. The number of prior systemic anti-cancer therapy ranged from 1-13; no median is given but 5 (2.4%) had 1, 63 (30.4%) had 2, 68 (32.9%) had 3, and 34 (16.4%) had 4 prior systemic treatments.

Table 1.2B–1 Extent of exposure to copanlisib in the integrated analysis (SAF)

	Pool 1 iNHL N=207	Pool 1b FL N=161	Pool 1c MZL N=29	Pool 2 NHL/CLL N=377
Overall time under treatment [a] (months [b])				
Mean (StD)	10.03 (12.24)	10.28 (12.66)	10.32 (12.89)	7.25 (10.63)
Median	5.52	5.36	5.32	3.45
Min, Max	0.2, 64.5	0.2, 56.3	0.2, 64.5	0.2, 64.5
Number of cycles [c]				
Mean (StD)	10.90 (13.31)	11.17 (13.76)	11.22 (14.02)	7.88 (11.56)
Median	6.00	5.82	5.79	3.75
Min, Max	0.3, 70.1	0.3, 61.3	0.3, 70.1	0.3, 70.1
Number of infusions				
Mean (StD)	31.09 (37.57)	31.84 (39.08)	31.79 (38.32)	22.71 (32.66)
Median	18.00	17.00	18.00	11.00
Min, Max	1.0, 191.0	1.0, 180.0	1.0, 191.0	1.0, 196.0
Actual dose per administration (mg)				
Mean (StD)	56.42 (6.46)	56.14 (6.76)	56.92 (6.07)	54.85 (9.25)
Median	60.00	60.00	60.00	60.00
Min, Max	30.7, 65.0	30.7, 65.0	39.4, 65.0	19.0, 65.3

CLL = Chronic lymphocytic leukemia; FL = Follicular lymphoma; iNHL = Indolent non-Hodgkin's lymphoma; Max = Maximum, Min = Minimum; MZL = Marginal zone lymphoma; N = Total number of patients (100%); NHL = Non-Hodgkin's lymphoma; SAF = Safety analysis set; StD = Standard deviation; ST = Solid tumors
a: Including drug interruptions or delays, and drug holidays.
b: ([Day of last dose minus day of first dose]+7)/30.4375.
c: One cycle = 28 days.

At the time of the above data, only 18 patients in the iNHL Pool 1 have been exposed for copanlisib monotherapy for ≥ 12 months. The long-term safety data is thus quite limited. As of the data cut-off, 10 of the 207 participants (4.85%) in iNHL (pool 1), including 1 of the 29 participants (3.4%) in the MZL Population, were continuing to receive copanlisib. It is therefore not expected that significant updated safety data for copanlisib monotherapy will be available.

The lack of long-term safety data is a concern, and the potential for cumulative or late onset ADRs is unknown. Even if the highest incidence of AEs was seen early in the first 6 months as opposed to later on, suggesting that there is little evidence of cumulative toxicity, "Long term safety" should be included as Missing information in the RMP Summary of safety concerns.

Considering that the applied indication is for a third line or above setting, it can be speculated that the study population might be a healthier population than the one seen in clinical practice. As mentioned by the applicant, MZL patients tend to be diagnosed at advanced age and comorbidities are prevalent. On average 70-80% of MZL patients will have at least one comorbidity at diagnosis, 19% will have signs of cognitive decline (delirium, dementia) and 32% emotional problems (depression), 39% will have reduced physical capacity, and 26% and 44% will have impairments to perform basal or instrumental activities of daily living, respectively (from the proposed RMP).

Adverse events

Study 17067:

Table 10–5 Overview of TEAEs in the total iNHL study population and histological subpopulations (SAF)

	Total iNHL N=453		MZL N=94	
	Copanlisib/ rituximab N=307 n (%)	Placebo/ rituximab N=146 n (%)	Copanlisib/ rituximab N=65 n (%)	Placebo/ rituximab N=29 n (%)
Any TEAE [a]	**307 (100.0)**	**134 (91.8)**	**65 (100.0)**	**25 (86.2)**
Worst CTCAE grade:				
Grade 3	164 (53.4)	63 (43.2)	35 (53.8)	11 (37.9)
Grade 4	110 (35.8)	19 (13.0)	26 (40.0)	3 (10.3)
Grade 5 (fatal)	6 (2.0)	1 (0.7)	0	0
TESAEs	145 (47.2)	27 (18.5)	37 (56.9)	8 (27.6)
TEAEs leading to permanent copanlisib or placebo discontinuation	96 (31.3)	12 (8.2)	23 (35.4)	3 (10.3)
Any copanlisib- or placebo-related TEAE [a, c]	**293 (95.4)**	**95 (65.1)**	**60 (92.3)**	**18 (62.1)**
Worst CTCAE grade				
Grade 3	168 (54.7)	42 (28.8)	34 (52.3)	7 (24.1)
Grade 4	95 (30.9)	15 (10.3)	23 (35.4)	3 (10.3)
Grade 5 (fatal)	1 (0.3)	0	0	0
TESAEs	103 (33.6)	11 (7.5)	27 (41.5)	3 (10.3)
TEAEs leading to permanent copanlisib or placebo discontinuation	77 (25.1)	5 (3.4)	15 (23.1)	1 (3.4)

AE = Adverse event; CTCAE = Common Terminology Criteria for Adverse Events; iNHL = Indolent non-Hodgkin's lymphoma; MZL = Marginal zone lymphoma; N = Total number of patients (100%); n = Number of patients with event; SAF = Safety analysis set; StD = Standard deviation; TEAE = Treatment-emergent adverse event; TESAE = Treatment-emergent serious adverse event

a: "Any TEAE" also includes patients with grade not available for all AEs.

c: Patients could have TEAEs related to both copanlisib or placebo and rituximab.

Notes:

Number (%) of patients with the specified event that started or worsened between the start of study treatment and 30 days after the end of study treatment.

TEAEs graded using CTCAE v. 4.03.

Table contains deaths only if due to a TEAE.

ISS:

Treatment-emergent adverse events

Study 17067; combination treatment:

All patients in the Copa/R-arm and almost all patients (91.8%) in the Pbo/R-arm experienced at least one AE. The most common AEs in the Copa/R arm compared to the Pbo/R arm were: Hyperglycaemia (69.4% vs. 23.3%), hypertension (49.2% vs. 19.2%), diarrhoea (33.6% vs. 9.6%), neutrophil count decreased (33.2% vs. 23.3%), nausea (22.5% vs. 11.6%), neutropenia (20.8% vs. 16.4%), and pyrexia (20.5% vs. 7.5%). Events with a ≥15 % point higher incidence were hyperglycaemia, hypertension, and diarrhoea.

For the majority of SOCs, there were more TEAEs in the Copa/R arm than in the Pbo/R arm. In the Copa/R arm, TEAEs occurred most commonly in the SOCs of metabolism and nutrition disorders (Copa/R arm vs. Pbo/R arm; 74.9% vs. 36.3%), infections and infestations (72.6% vs. 52.1%), gastrointestinal disorders (64.5% vs. 37.7%), and investigations (63.5% vs. 44.5%). In all of these SOCs, TEAEs occurred with a ≥15 percentage point higher incidence in the Copa/R arm than in the Pbo/R arm.

The most common AEs considered to be **copanlisib-related** (occurring in ≥15% of patients) in the Copa/R arm were (Copa/R arm vs. placebo-related TEAEs in the Pbo/R arm): hyperglycaemia (67.4% vs. 22.6%), hypertension (46.9% vs. 15.8%), neutrophil count decreased (31.6% vs. 21.2%),

diarrhoea (22.5% vs. 2.1%), white blood cell count decreased (19.5% vs. 10.3%), neutropenia (18.6% vs. 13.7%), and nausea (15.6% vs. 4.1%).

The most common AEs considered to be **rituximab-related** were (Copa/R arm vs. Pbo/R arm): neutrophil count decreased (20.8% vs. 15.8%), hyperglycaemia (16.0% vs. 8.9%), white blood cell count decreased (16.0% vs. 6.8%), and hypertension (15.3% vs. 8.9%).

In the Copa/R arm the incidences of the most common AEs by preferred term (PT) were highest in the first 90 days of treatment in particular for hyperglycaemia and hypertension. No clear trend was observed for neutropenia. In the Pbo/R arm, the incidences of the most common TEAEs remained more stable over time.

ISS; monotherapy:

In Pool 1, the most common AEs were hyperglycaemia (59.9%), hypertension (39.1%), diarrhoea (37.2%), fatigue (27.5%), neutropenia and pyrexia (26.6% each), nausea (24.6%), and anaemia (20.3%); the most frequent AEs are in line with the combination study as is also the case for AEs by SOC: In iNHL Pool 1, AEs occurred most commonly in the SOCs of metabolism and nutrition disorders (72.9%), gastrointestinal disorders (68.1%), infections and infestations (65.2%), and general disorders and administration site conditions (64.3%).

For the most common AEs higher incidences were generally observed during the first 90 days of study treatment, at >360 days after the start of study treatment, or both. The applicant is requested to speculate on the possible reason for the increase in adverse events after 1 year.

Grade 3 and higher adverse events

Study 17067; combination treatment:

The majority of patients in both treatment arms experienced TEAEs with a worst CTCAE grade of 3 or 4, with higher incidences observed in the Copa/R arm than in the Pbo/R arm (Grade 3: 53.4% vs. 43.2%, respectively, and Grade 4: 35.8% vs. 13.0%, respectively).

The most common AEs with a worst grade of 3 in the copanlisib/rituximab arm were (Copa/R arm vs. Pbo/R arm): hyperglycaemia (48.2% vs. 8.2%), hypertension (39.7% vs. 8.9%), neutrophil count decreased (11.1% vs. 6.8%), neutropenia (6.8% vs. 6.2%), and white blood cell count decreased (6.5% vs. 3.4%) (Table 10-8). The AEs occurring with a ≥15 percentage point higher incidence in the Copa/R arm than in the Pbo/R arm were hyperglycaemia and hypertension.

The most common TEAEs with a worst grade of 4 in the Copa/R arm vs. Pbo/R arm were: neutrophil count decreased (11.7% vs. 6.8%), neutropenia (8.8% vs. 6.2%), and hyperglycaemia (8.1% vs. 0%) (Table 10-9).

Table 10–8 Incidence of worst Grade 3 TEAEs in the total iNHL study population and histological subpopulations (SAF)

	Total iNHL N=453		MZL N=94	
MedDRA PT (v. 23.0)	Copanlisib/ rituximab N=307 n (%)	Placebo/ rituximab N=146 n (%)	Copanlisib/ rituximab N=65 n (%)	Placebo/ rituximab N=29 n (%)
Hyperglycaemia	148 (48.2)	12 (8.2)	30 (46.2)	3 (10.3)
Hypertension	122 (39.7)	13 (8.9)	29 (44.6)	3 (10.3)
Neutrophil count decreased	34 (11.1)	10 (6.8)	5 (7.7)	1 (3.4)
Neutropenia	21 (6.8)	9 (6.2)	4 (6.2)	2 (6.9)
White blood cell count decreased	20 (6.5)	5 (3.4)	3 (4.6)	1 (3.4)
Diarrhoea	15 (4.9)	0	1 (1.5)	0
Pneumonia	15 (4.9)	4 (2.7)	3 (4.6)	2 (6.9)
Lymphocyte count decreased	14 (4.6)	4 (2.7)	4 (6.2)	2 (6.9)
Anaemia	13 (4.2)	4 (2.7)	4 (6.2)	0
Lipase increased	8 (2.6)	3 (2.1)	3 (4.6)	0
Blood creatine phosphokinase increased	7 (2.3)	1 (0.7)	2 (3.1)	0
Mucosal inflammation	6 (2.0)	0	2 (3.1)	0
Pneumonitis	6 (2.0)	1 (0.7)	3 (4.6)	1 (3.4)

CTCAE = Common Terminology Criteria for Adverse Events; iNHL = Indolent non-Hodgkin's lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; MZL = Marginal zone lymphoma; N = Total number of patients (100%); n = Number of patients with event; SAF = Safety analysis set; PT = Preferred term; TEAE = Treatment-emergent adverse event;

Notes:

Number (%) of patients with the specified event that started or worsened between the start of study treatment and 30 days after the end of study treatment.

TEAEs graded using CTCAE v. 4.03.

Table 10–9 Incidence of worst Grade 4 TEAEs in the total iNHL study population and histological subpopulations (SAF)

	Total iNHL N=453		MZL N=94	
MedDRA PT (v. 23.0)	Copanlisib/ rituximab N=307 n (%)	Placebo/ rituximab N=146 n (%)	Copanlisib/ rituximab N=65 n (%)	Placebo/ rituximab N=29 n (%)
In ≥1% of patients in either treatment arm of the total iNHL study population:				
Neutrophil count decreased	36 (11.7)	10 (6.8)	7 (10.8)	0
Neutropenia	27 (8.8)	9 (6.2)	8 (12.3)	2 (6.9)
Hyperglycaemia	25 (8.1)	0	5 (7.7)	0
White blood cell count decreased	4 (1.3)	0	1 (1.5)	0
Amylase increased	3 (1.0)	0	0	0
Lymphocyte count decreased	3 (1.0)	0	2 (3.1)	0
Platelet count decreased	3 (1.0)	1 (0.7)	0	0
Pneumonia	3 (1.0)	0	0	0

CTCAE = Common Terminology Criteria for Adverse Events; iNHL = Indolent non-Hodgkin's lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; MZL = Marginal zone lymphoma; N = Total number of patients (100%); n = Number of patients with event; SAF = Safety analysis set; PT = Preferred term; TEAE = Treatment-emergent adverse event;

Notes:

Number (%) of patients with the specified event that started or worsened between the start of study treatment and 30 days after the end of study treatment.

TEAEs graded using CTCAE v. 4.03.

ISS; monotherapy:

The most common AEs with a worst grade of 3 in Pool 1 were hyperglycaemia (35.3%), hypertension (28.5%), neutropenia (9.2%), pneumonia (8.7%), white blood cell count decreased (7.7%), diarrhoea (6.3%), and anaemia (5.8%).

The most common AEs with a worst grade of 4 in iNHL Pool 1 were neutropenia (11.6%), neutrophil count decreased (5.3%), and hyperglycaemia (4.8%).

The applicant is requested to present the most common (≥2%) grade 3-4 Adverse events by SOC for study 17067 and the ISS.

Copanlisib-related AEs with a worst grade of 3 or 4 occurred more commonly in the copanlisib/rituximab arm (85.7%) of the CHRONOS-3 study than in the placebo/rituximab arm (39.0%). The most common related-AEs were: (Copa/R arm vs. Pbo/R arm): hyperglycaemia (67.4% vs. 22.6%), hypertension (46.9% vs. 15.8%), neutrophil count decreased (31.6% vs. 21.2%), diarrhoea (22.5% vs. 2.1%), white blood cell count decreased (19.5% vs. 10.3%), neutropenia (18.6% vs. 13.7%), and nausea (15.6% vs. 4.1%).

The most common AEs considered copanlisib-related were in line with the all grade AEs as well as those observed in the ISS.

Rituximab-related AEs with a worst grade of 3 occurring in ≥5% of patients in the Copa/R arm were (Copa/R arm vs. Pbo/R arm): hypertension (11.4% vs. 1.4%), hyperglycaemia (9.8% vs. 3.4%), neutrophil count decreased (6.2% vs. 4.1%), and white blood cell count decreased (5.2% vs. 2.1%).

Rituximab-related AEs with a worst grade of 4 occurring in ≥1% of patients in the Copa/R arm were (Copa/R arm vs. Pbo/R arm): neutrophil count decreased (7.5% vs. 4.8%), neutropenia (2.9% vs. 3.4%), hyperglycaemia (2.0% vs. 0%), and white blood cell count decreased (1.3% vs. 0%).

Adverse Events of Interest

Infusion-related adverse events

Study 17067:

Infusion-related AEs occurred more frequently in the Pbo/R arm (15.1%) than in the Copa/R arm (7.2%).

ISS:

No data could be found for the monotherapy studies; please present data regarding infusion-related adverse events from the ISS.Non-infectious pneumonitis (NIP)

In the total iNHL study population of study 17067, there was a higher percentage of patients with NIP in the Copa/R arm than in the Pbo/R arm The events were considered related to copanlisib or placebo in most patients with NIP. For the majority of patients with NIP in the Copa/R arm, the events resolved following discontinuation of study treatment. Corresponding incidences were seen in the ISS for overall AEs, Grade 3-4 AEs and SAEs.

Infections

Study 17067; combination therapy:

In the total iNHL study population, AEs in the SOC of infections and infestations occurred more commonly in the copanlisib/rituximab arm (72.6%) than in the placebo/rituximab arm (52.1%). The median exposure in the two arms were 8.31 months in the Copa/R arm and 10.78 months in the Pbo/R arm.

In the total iNHL study population, respiratory tract infection events (HLGT and HLTs for respiratory tract infections) occurred in 55.4% of patients in the copanlisib/rituximab arm and in 42.5% of patients in the placebo/rituximab arm.

The incidences for the MZL-population were of the same magnitude as the entire iNHL population.

Table 10–30 TEAEs in the SOC of infections and infestations in the total iNHL study population and histological subpopulations (SAF)

	Total iNHL N=453		MZL N=94	
	Copanlisib/ rituximab N=307 n (%)	Placebo/ rituximab N=146 n (%)	Copanlisib/ rituximab N=65 n (%)	Placebo/ rituximab N=29 n (%)
Upper respiratory tract infection	56 (18.2)	24 (16.4)	10 (15.4)	7 (24.1)
Pneumonia	42 (13.7)	14 (9.6)	7 (10.8)	4 (13.8)
Urinary tract infection	33 (10.7)	11 (7.5)	8 (12.3)	1 (3.4)
Nasopharyngitis	27 (8.8)	7 (4.8)	6 (9.2)	1 (3.4)
Bronchitis	18 (5.9)	8 (5.5)	3 (4.6)	3 (10.3)
Oral herpes	17 (5.5)	4 (2.7)	5 (7.7)	1 (3.4)
Influenza	8 (2.6)	9 (6.2)	2 (3.1)	2 (6.9)

CTCAE = Common Terminology Criteria for Adverse Events; iNHL = Indolent non-Hodgkin's lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; MZL = Marginal zone lymphoma; N = Total number of patients (100%); n = Number of patients with event; SAF = Safety analysis set; SOC = System organ class; PT = Preferred term; TEAE = Treatment-emergent adverse event;

Notes:

Number (%) of patients with the specified event that started or worsened between the start of study treatment and 30 days after the end of study treatment.

TEAEs graded using CTCAE v. 4.03.

There were more opportunistic infections in the Copa/R arm compared to the Pbo/R arm. A question regarding CMV prophylaxis has been raised (see Deaths section).

ISS; monotherapy:

Adverse events in the SOC of infections and infestations occurred in 65.2% of patients in iNHL Pool 1. Most infections and infestations occurred in patients with FL as the incidences in the other analysis pools were lower. The incidence in Pool 1 was of the same magnitude as in the combination therapy study keeping in mind, that the median exposure was lower in the ISS, Pool 1 (5.5 months), but also that the number of prior therapies was higher.

Respiratory tract infection events (HLGT and HLTs for respiratory tract infections) occurred in 48.3% of patients in Pool 1.

Neutropenia

Study 17067; combination therapy:

Neutropenia events (MLG neutropenia) occurred more commonly in the Copa/R arm than in the Pbo/R arm in the all iNHL population. The corresponding Grade 3-4 events were with similar incidence in the MZL population in the Copa/R arm (the number of patients at risk was small in the Pbo/R arm). A table showing the use of g-csf in the two arms including subpopulations is requested.

ISS; monotherapy:

In Pool 1 (iNHL) the incidence of neutropenia (MLG) was 41.1% with a Grade 3-4 incidence of 29.9%.

Immunosuppression

The incidences reflect the events of neutropenia in both safety groups (combination and monotherapy) as this was the main event in the immunosuppression MLG.

Study 17067; combination therapy:

In the total iNHL study population, events in the MedDRA grouping immunosuppression occurred in a higher percentage of patients in the copanlisib/rituximab arm than in the placebo/rituximab arm. The corresponding Grade 3-4 events were 41.0% vs. 24.7% with similar incidence in the MZL population of 43.1% in the Copa/R arm (the number of patients at risk was small in the Pbo/R arm).

ISS; monotherapy:

In Pool 1 the incidence of immunosuppression was 47.8% with a Grade 3-4 incidence of 34.8%.

Thrombocytopenia

Study 17067; combination therapy:

Thrombocytopenia (MLG neutropenia) occurred more commonly in the Copa/R arm than in the Pbo/R arm in the all iNHL population. The corresponding Grade 3-4 events were 3.3% vs. 2.8%.

ISS; monotherapy:

In Pool 1 the incidence of thrombocytopenia (MLG) was 26.6% with a Grade 3-4 incidence of 7.3%. The number of prior therapies were higher in the ISS monotherapy group compared to the combination therapy group.

Hyperglycaemia

Hyperglycaemia is considered to be related to the mechanism of action of copanlisib by inhibiting the PI3K-α-isoform, which is critical in glucose homeostasis (Engelman 2009, Foukas et al. 2006, Luo et al. 2006) and is implicated in insulin metabolism.

Study 17067; combination therapy:

The mean glucose values after copanlisib or placebo infusion were higher in the Copa/R arm than in the Pbo/R arm (Table 10-37/CSR). On C1D1, at 2 h after the end of copanlisib infusion, the mean glucose values increased from pre-dose by 96.22 mg/dL in the Copa/R arm (n=235, fasting patients with assessments), but in the Pbo/R arm (n=113; fasting patients with assessments), the mean values increased less, by 19.35 mg/dL, at 2 h after the end of placebo infusion. Afterwards, the mean glucose values increased further; at the end of rituximab infusion, the mean glucose values increased from pre-dose by 131.21 mg/dL in the Copa/R arm (n=263, fasting patients with assessments) and by 40.44 mg/dL in the Pbo/R arm (n=132; fasting patients with assessments).

Overall, the mean HbA1c values increased over the course of study treatment in the Copa/R arm. A similar increase was not observed in the Pbo/R arm.

There was an increase in the mean HbA1c values from baseline to EoT. At the end of treatment visit, 38.8% of patients in the Copa/R arm vs. 14.6% of patients in the Pbo/R arm had shifted from the normal to prediabetic HbA1c category, and 13.6% of patients in the Copa/R vs. 2.1% of patients in the Pbo/R arm had shifted from the normal to diabetic HbA1c category (Table 10-40/CSR). Follow-up data > 90 days after EoT is too sparse to evaluate the outcome of these events. Correspondingly, in the integrated analysis (see below) 16.8% shifted from normal to diabetic category in the iNHL Pool 1. The

applicant should present updated follow-up data and comment on the course and outcome of these events.

In the total iNHL study population, AEs in the MLG for hyperglycaemia occurred in the of patients in the Copa/R arm. In the Pbo/R arm, hyperglycaemia events were less common, occurring in of patients. The corresponding Grade 3-4 events were 57.0% vs 8.2%. The incidence in the MZL population was of similar magnitude. The incidences of hyperglycaemia were highest during the first 90 days of study treatment.

The incidence of AEs was increased in patients with a history of diabetes (n=45) compared with patients without such history (82.2% vs. 69.1%). The corresponding incidences of SAEs were 17.8% and 5.0%, and for permanent discontinuation of copanlisib, 8.9% and 1.5%.

In the Copa/R arm, more than half of the patients with hyperglycaemia events (136/218 patients, 62.4%) received antihyperglycaemic medication (50% of the patients needed insulin, 39% needed other glucose lowering medication) Of these patients, 34/218 (15.6%) had a history of diabetes and 102/218 (46.8%) had no history of diabetes.

In the total iNHL study population, approximately half of the patients (47.6%) in the copanlisib/ rituximab arm received antihyperglycaemic medication during the course of the study. In the Copa/R arm 12.1% of patients received antihyperglycaemic medication before the start of study treatment. In the Pbo/R arm, 20.5% of patients received antihyperglycaemic medication during the study and 16.6% had received antihyperglycaemic medication before the start of study treatment.

Table 10–43 Patients with TEAEs in the MLG for hyperglycemia requiring post-baseline antihyperglycemic medication in the total iNHL study population (SAF)

	Copanlisib/rituximab N=218 [a] n (%)	Placebo/rituximab N=36 [a] n (%)
Number of patients requiring at least one post-baseline		
Insulin therapy	**109 (50.0)**	**3 (8.3)**
Blood glucose lowering medication, excluding insulins	**85 (39.0)**	**5 (13.9)**

ATC = Anatomical therapeutic chemical; iNHL = Indolent non-Hodgkin's lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; MLG = MedDRA labeling grouping; N = Total number of patients (100%); n = Number of patients with event; SAF = Safety analysis set; TEAE = Treatment-emergent adverse event; WHO-DD = World Health Organization Drug Dictionary

a: Number of patients with TEAEs in the MLG for hyperglycemia.

Notes:

Hyperglycemia events were identified using an MLG hyperglycemia.

Medications with a start date on or after the start date of the first TEAEs in the MLG for hyperglycemia were included.

Antihyperglycemic medication included: WHO-DD (v.2020mar) ATC subclass "drugs used in diabetes", excluding "other drugs used in diabetes"

ISS; monotherapy:

In Pool 1 (iNHL) the incidence of hyperglycaemia (MLG) was 62.3% with a Grade 3-4 incidence of 41.5% (Table 2B-28/SCS). In iNHL Pool 1, more than half of the patients with hyperglycaemia events

(79/129 patients, 61.2%) received antihyperglycaemic medication. Of these patients, 19/129 (14.7%) had a history of diabetes and 60/129 (46.5%) had no history of diabetes.

Hyperglycaemia is clearly a major adverse event for copanlisib. In the SPC section 4.4 an instruction for when to measure glucose and which action(s) to take should be clearly specified (preferably in tabulated form).

Hypertension

Study 17067; combination therapy:

Higher mean BP values were observed after copanlisib infusion in the Copa/R arm than after placebo infusion in the Pbo/R arm

Most patients in both treatment arms had abnormal systolic and/or diastolic post-infusion BP values at any visit, but 125 (41.1%) in the Copa/R arm compared to 20 (13.8%) in the Pbo/R arm had Grade 3 (no grade 4) hypertension

In the total iNHL study population, arterial hypertension (MLG hypertension) events occurred more commonly in the Copa/R arm (51.1%) than in the Pbo/R arm (19.9%). The corresponding Grade 3 events (no Grade 4 or 5 events) were 41.0% vs 9.6%.

The frequencies of hypertension were highest during the first 90 days of study treatment in both treatment arms.

In the Copa/R arm, the majority of patients with hypertension events (113/157 patients, 72.0%) received antihypertensive treatment. Of these patients, 34.4% had a history of hypertension and 37.6% had no history of hypertension. The anti-hypertensive medication used is presented where it can be seen, that while baseline medication was comparable between the two arms, treatment with in particular calcium channel blockers and agents affecting the renin-angiotensin system increased markedly in the Copa/R arm during treatment.

Table 10–48 Patients with TEAEs in the MLG for arterial hypertension requiring post-baseline antihypertensive treatment in the total iNHL study population (SAF)

	Copanlisib/rituximab N=157 [a] n (%)	Placebo/rituximab N=29 [a] n (%)
Number of patients requiring at least one post-baseline antihypertensive treatment	**113 (72.0)**	**13 (44.8)**

ATC = Anatomical therapeutic chemical; iNHL = Indolent non-Hodgkin's lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; MLG = MedDRA labeling grouping; N = Total number of patients (100%); n = Number of patients with event; SAF = Safety analysis set; TEAE = Treatment-emergent adverse event; WHO-DD = World Health Organization Drug Dictionary

a: Number of patients with TEAEs in the MLG for arterial hypertension.

Notes:

Arterial hypertension events were identified using an MLG hypertension.

Medications with a start date on or after the start date of the first TEAE in the MLG for arterial hypertension were included.

Antihypertensive treatment included: WHO-DD (v.2020mar) ATC subclasses "antihypertensives", "diuretics", "beta blocking agents", "calcium channel blockers", and "agents acting on the renin-angiotensin. system".

ISS; monotherapy:

In Pool 1 (iNHL) the incidence of hypertension (MLG) was 39.1% with a Grade 3 incidence (no Grade 4 or 5 events) of 28.5%. There was a clear increase across all pools in the use of anti-hypertensive mediation after study start, as shown for the combination therapy study.

Hypertension is clearly a major adverse event for copanlisib.

Pancreatitis

Based on the low incidence of pancreatitis noted in the clinical studies, it is considered unlikely that copanlisib is associated with pancreatitis.

Myocardial ischemia

No evidence was found for an increased risk of myocardial ischemia.

Gastrointestinal disorders

Study 17067; combination therapy:

Gastrointestinal disorders (SOC) occurred in 64.5% of patients in the Copa/R arm and 37.7% of patients in the Pbo/R arm. The most common GI AEs were diarrhoea (33.6% vs. 9.6%), nausea (22.5% vs. 11.6%), vomiting (14.7% vs. 3.4%), stomatitis (12.7% vs. 2.7%), constipation (9.8% vs. 8.2%), and mouth ulceration (6.2% vs. 2.7%). The majority of patients had events with a worst grade of ≤ 2. AEs with a worst grade of 3 occurred in 10.1% of patients in the Copa/R arm and in 0.7% of patients in the Pbo/R arm. The most common AE with a worst grade of 3 in patients receiving Copa/R was diarrhoea (4.9%). In the Copa/R arm, AEs with a worst grade of 4 occurred in one patient (0.3%) (enteritis) and Grade 5 AEs also occurred in one patient (0.3 %) (enterocolitis). No patients in the Pbo/R arm had Grade 4 or 5 GI TEAEs.

SAEs occurred in 3.3% of patients in the Copa/R arm and in none of the patients in the Pbo/R arm. Colitis, diarrhoea, and enteritis were the most common SAEs in patients receiving Copa/R, all reported with an incidence of 0.7.

ISS; monotherapy:

AEs in the SOC of gastrointestinal disorders occurred in 68.1% of the patients in iNHL pool 1. The most common AEs in iNHL Pool 1 were diarrhoea (37.2%), nausea (24.6%), stomatitis (14.5%), and constipation and vomiting (13.5% each). The majority of patients had events with a worst grade of ≤ 2. The most common AE with a worst grade of 3 was diarrhoea, occurring in 6.3% of the iNHL patients. The AEs with a worst grade of 4 were colitis and gastrointestinal haemorrhage in one patient (0.5%) each in iNHL Pool 1. No grade 5 AEs occurred in iNHL pool 1.

The incidence of SAEs was 5.3% in the iNHL Pool 1. The most common SAE was diarrhoea with incidence 1.9% in iNHL Pool 1.

Serious cases of diarrhoea and colitis are well-known for oral PI3K-inhibitors. As copanlisib is administered intermittently and avoid gastric passage by iv administration, the applicant claims that this is a lesser problem for this product.

The frequency of serious cases of diarrhoea was 0,7% for combination therapy and 1.9% (iNHL Pool 1) for monotherapy.

For combination therapy four cases (1.3%) of colitis have been reported in the Copa/R arm (Pbo/R 0). Two of them were serious and considered to be copanlisib-related. In addition, one serious case of colitis microscopic (considered copanlisib-related) was reported. One fatal case of enterocolitis

was also reported that was considered not related to copanlisib. This case is described in more detail in the section on Deaths (considered possibly related to CMV-infection by the Rapporteur). Four cases of colitis (0.8%) were also reported for copanlisib used in monotherapy (Pool 3). Three of them were serious, considered to be copanlisib-related. It should also be noted that diarrhoea and colitis may occur several months after treatment initiation for oral PI3K-inhibitors. The SmPC of Copiktra (duvelisib) states that the median time to onset was 4 months and that 75% of cases occurred within 8 months. It should be remembered that the median exposure time was 5.52 months for copanlisib monotherapy and 8.31 months for combination therapy. In conclusion, serious cases of diarrhoea and colitis that were considered to be related to copanlisib, have been reported. The applicant should describe all serious cases of diarrhoea and colitis reported for copanlisib in more detail and include a warning against these AEs in section 4.4. of the SmPC. For the same reason, the applicant should include "serious diarrhoea" as an important identified risk and "serious colitis" as an important potential risk in the RMP to gain more information on these AEs.

Cutaneous disorders

In section 4.8 of the proposed SmPC rash is listed as a very common ADR for copanlisib used alone or in combination with rituximab. Rash of grade 3 is stated to be a common event. For monotherapy grade 4 events are listed with frequency uncommon. No grade 4 events have been reported for combination therapy. In a footnote it is stated that exfoliative skin reactions have been reported.

The applicant does not discuss cutaneous reactions in the SCS. The FDA monograph for Aliqopa (approved as monotherapy for relapsed follicular lymphoma) warns against serious cutaneous reactions (frequency of serious AEs is stated to be 0.9%). Serious cutaneous reactions have been associated with oral PI3K-inhbitors, including SJS, TEN and DRESS. It should also be noted that serious cutaneous reactions including SJS and TEN, are listed for rituximab (frequency very rare). The applicant should discuss the frequency and seriousness of cutaneous events reported for copanlisib given alone or in combination with rituximab, and discuss whether a warning should be included in section 4.4 of the SmPC**.**

Comparison between copanlisib combination therapy and monotherapy

When comparing the results between the two treatments, the following points need to be considered: In study 17067, patients treated with Copa/R had received at least one line of prior treatment (≥2L) and included approximately half of the patients that had received at least two prior therapies, while in the integrated analysis of copanlisib monotherapy, almost all patients had received at least two prior therapies (≥3L). In addition, the median exposure to copanlisib was different in the two settings: 8.31 months and 5.52 months, respectively.

A similar safety profile was seen for the most common TEAEs reported in the iNHL patients treated with the Copa/R combination vs. copanlisib monotherapy. The higher incidences of the events in the combination treatment are possibly due to the effect of rituximab or associated premedication (steroids, if used) or due to the differences in the patient population and/or treatment duration.

Other observations related to safety

<u>Electrocardiogram</u>

Summary statistics are available for the integrated analysis and study 17067.

In the iNHL Pool 1 (integrated analysis), the mean changes from baseline for ECG interval measurements of QTcB and QTcF at different visits ranged from −1.5 to 20.8 ms and 0.2 to 15.2 ms,

respectively. The results are not discussed by the applicant. There is no information on possible outliers. In addition, information on time point for recording ECG post-infusion and reason why this timepoint was chosen, is not stated. The applicant should provide a discussion.

Further it is unclear whether the number of clinically significant ECG findings (not only QT findings) increases during treatment with copanlisib. The applicant should also provide summarised information on which clinically significant ECG-findings were reported.

Similar ECG-recordings have been performed for study 17067, and results should be discussed by the applicant.

Echocardiogram and MUGA Scan

Data from echocardiogram and MUGA are available for study 17067 and for the integrated analysis, but is not discussed properly by the applicant. It is unclear whether the number of clinically significant echocardiogram and/or MUGA findings increased during treatment with copanlisib (mono- and combination treatment). The applicant should also provide summarised information on which clinically significant echocardiogram/MUGA-findings were seen.

Serious adverse events and deaths

Deaths

Study 17067; combination therapy:

Seven patients (2.3%) in the Copa/R arm and one patient (0.7%) in the Pbo/R arm died during study treatment or within 30 days after the last dose of study treatment. The most common cause of death during this period in the Copa/R arm was AE not associated with clinical disease progression (six patients, 2.0%), which was also the cause of death in the Pbo/R arm (one patient, 0.7%)

Table 2A–8 Overview of all deaths in the total iNHL population in study 17067 (SAF)

Number of patients who died Primary cause of death	Copa/R N=307 n (%)	Pbo/R N=146 n (%)
All deaths	**43 (14.0)**	**20 (13.7)**
During study treatment or within 30 days after last dose of study treatment	**7 (2.3)**	**1 (0.7)**
AE not associated with clinical disease progression	6 (2.0)	1 (0.7)
PD	1 (0.3)	0
Unknown	0	0
Other	0	0

AE = Adverse event; Copa = Copanlisib; COVID-19 = Coronavirus disease 2019; iNHL = Indolent non-Hodgkin's lymphoma; N = Total number of patients (100%); n = Number of patients with event; Pbo = Placebo; PD = Progressive disease; R = Rituximab; SAF = Safety analysis set

Table 2A–9 Summary of deaths during study treatment or within 30 days after permanent discontinuation of study treatment in the total iNHL population in study 17067 (SAF)

Patient ID	Age (years)/ sex/ race	Histology	Relative days to start/stop of study treatment	Primary cause of death	MedDRA PT v. 23.0	Related to study drug
Copa/R						
		FL	11/3	AE not associated with clinical disease progression	Death [a]	No
		SLL	495/5	AE not associated with clinical disease progression	Acute myocardial infarction	No
		FL	54/19	AE not associated with clinical disease progression	Enterocolitis	No
		SLL	65/5	AE not associated with clinical disease progression	Pneumonia	No
		SLL	431/10	AE not associated with clinical disease progression	Dislocation of vertebra	No
		FL	295/29	AE not associated with clinical disease progression	Pneumonitis	Related to copanlisib and rituximab
			295/29	AE not associated with clinical disease progression	Respiratory failure	Related to copanlisib and rituximab
		FL	82/19	Progressive disease		
Pbo/R						
		LPL/WM	144/17	AE not associated with clinical disease progression	Pneumonia bacterial	No

A = Asian; AE = Adverse event; B = Black or African American; Copa = Copanlisib; CIOMS = Council for International Organizations of Medical Sciences; F = Female; FL = Follicular lymphoma; ID = Identification; iNHL = Indolent non-Hodgkin's lymphoma; LPL = Lymphoplasmacytoid lymphoma; M= Male; MedDRA = Medical Dictionary for Regulatory Activities; Pbo = Placebo; PT = Preferred term; R = Rituximab; SAF = Safety analysis set; SLL = Small lymphocytic lymphoma; W = White; WM = Waldenström macroglobulinemia

a: Reported term "Death unknown"

Deaths during study treatment or within 30 days after permanent discontinuation of study treatment for individual patients were presented including the relatedness or not to treatment.

Furthermore, the applicant should describe the use of medication for CMV infection whether used as prophylaxis or treatment in study 17067 and whether regular CMV-testing should be recommended in the SPC.

ISS; monotherapy:

There were six deaths in Pool 1 three of which were considered related to copanlisib.

Serious adverse events

Study 17067; combination therapy:

The incidence of SAE was higher in the Copa/R arm (47.2%) compared to the Pbo/R arm (18.5%) and Grade 3-4 SAEs were seen in 39.7% and 13.7%, respectively. The SAEs occurring in ≥2% of patients in the copanlisib/rituximab arm were (Copa/R arm vs. Pbo/R): hyperglycaemia (6.8% vs. 0%),

pneumonia (5.5% vs. 3.4%), pneumonitis (4.9% vs. 0%), and *Pneumocystis jirovecii* pneumonia (2.6% vs. 0%).

Table 2A–11 Incidence of TESAEs in the total iNHL population and histological subpopulations in study 17067 (SAF)

	Total iNHL N=453		MZL N=94	
	Copa/R N=307 n (%)	Pbo/R N=146 n (%)	Copa/R N=65 n (%)	Pbo/R N=29 n (%)
Any TESAE	**145 (47.2)**	**27 (18.5)**	**37 (56.9)**	**8 (27.6)**
Grade 3	82 (26.7)	19 (13.0)	22 (33.8)	6 (20.7)
Grade 4	40 (13.0)	1 (0.7)	11 (16.9)	1 (3.4)
TESAEs (any grade) by MedDRA PT (v. 23.0)				
Hyperglycaemia	21 (6.8)	0	5 (7.7)	0
Pneumonia	17 (5.5)	5 (3.4)	2 (3.1)	2 (6.9)
Pneumonitis	15 (4.9)	0	5 (7.7)	0

Copa = Copanlisib; CTCAE = Common Terminology Criteria for Adverse Events; iNHL = Indolent non-Hodgkin's lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; MZL = Marginal zone lymphoma; N = Total number of patients (100%); n = Number of patients with event; Pbo = Placebo; PT = Preferred term; R = Rituximab; SAF = Safety analysis set; TESAE = Treatment-emergent serious adverse event

Notes: Number (%) of patients with the specified event that started or worsened between the start of study treatment and 30 days after the end of study treatment.
TEAEs graded using CTCAE v. 4.03.

Source: Module 5.3.5.1, Report PH-41310, Table 14.3.1.1/7 and Table 14.3.1.1/8

Looking at the MZL-subpopulation, the incidence of SAEs is higher in this population than in the total iNHL-population, both for the active arm, as well as for the placebo-arm (MZL: 56.9%, 27.6%, total iNHL: 47.2% and 18.5% in active and placebo-arm, respectively). The applicant should discuss reasons behind the higher incidence of SAEs seen in the MZL-subpopulation compared to the total iNHL-population

ISS; monotherapy:

SAEs occurring in ≥2% of patients in iNHL Pool 1 were pneumonia (11.1%), pneumonitis and pyrexia (5.3%, each), hyperglycaemia (4.3%), and interstitial lung disease (2.4%).

Table 2B–10 Incidence of TESAEs in the integrated analysis (SAF)

	Pool 1 iNHL N=207 n (%)	Pool 1b FL N=161 n (%)	Pool 1c MZL N=29 n (%)	Pool 2 NHL/CLL N=377 n (%)
Any TESAE	**107 (51.7)**	**83 (51.6)**	**15 (51.7)**	**213 (56.5)**
Worst CTCAE grade:				
Grade 1	2 (1.0)	1 (0.6)	1 (3.4)	3 (0.8)
Grade 2	11 (5.3)	5 (3.1)	4 (13.8)	18 (4.8)
Grade 3	70 (33.8)	55 (34.2)	9 (31.0)	122 (32.4)
Grade 4	18 (8.7)	16 (9.9)	1 (3.4)	31 (8.2)
Grade 5 (fatal)	6 (2.9)	6 (3.7)	0	39 (10.3)
TESAEs (any grade) by MedDRA PT (v. 23.0)				
Pneumonia	23 (11.1)	19 (11.8)	4 (13.8)	31 (8.2)

CLL = Chronic lymphocytic leukemia; CTCAE = Common Terminology Criteria for Adverse Events; FL = Follicular lymphoma; iNHL = Indolent non-Hodgkin's lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; MZL = Marginal zone lymphoma; N = Total number of patients (100%); n = Number of patients with event; NHL = Non-Hodgkin's lymphoma; PT = Preferred term; SAF = Safety analysis set; TESAE = Treatment-emergent serious adverse event

Notes: Number (%) of patients with the specified event that started or worsened between the start of copanlisib treatment and 35 days after the end of copanlisib treatment.
TEAEs graded using CTCAE v. 4/4.03

Laboratory findings

Study 17067; combination therapy:

In the Copa/R arm, the most common laboratory abnormality was hyperglycaemia, which was observed in 296/307 patients with assessments (96.4%). The majority of patients (193/307 patients, 62.9%) had hyperglycaemia grade 3. Hyperglycaemia grade 4 was observed in 14/307 patients (4.6%).

The most common haematological and chemistry laboratory abnormalities (all grades) observed in ≥50% of patients with assessments in the Copa/R arm after the start of treatment were (in decreasing order): hyperglycaemia, lymphocyte count decreased, neutrophil count decreased, white blood cell decreased, anaemia, platelet count decreased, and hypertriglyceridemia.

No evidence was found for an increased risk of renal impairment in either treatment arm but patients with severe and end-stage renal disease were not included in the study. The SPC states that the pharmacokinetics in patients with end-stage renal disease are unknown.

Copanlisib is predominantly eliminated by the liver. Therefore, patients with hepatic impairment may experience increased copanlisib exposure. Dose recommendations for patients with hepatic impairment are based on population pharmacokinetic analysis and a dedicated pharmacokinetic study evaluating a single IV dose of 12 mg copanlisib, but proposed dose regimens in patients with moderate and severe hepatic impairment are currently not considered adequately justified. An OC has been raised in the pharmacology section whether the results of the latter study can be transferred to the recommended dose of 60 mg. No patients with severe hepatic impairment were included in study 17067.

ISS; monotherapy:

In iNHL Pool 1, the most common laboratory abnormality was hyperglycaemia, which was observed in 200/207 patients with assessments (96.6%). The majority of patients (46.9%) had grade 3 and 4.3% had grade 4 hyperglycaemia.

The most common haematological and general chemistry laboratory abnormalities with a worst grade of 3 in iNHL Pool 1 were (in decreasing order of incidence): hyperglycaemia, lymphocyte count decreased, and hyperuricemia.

In iNHL Pool 1, there were 3/206 patients with assessments (1.5%) with severely impaired renal function during the studies as measured with eGFR. Two of these patients had moderate renal impairment at baseline and one had normal renal function.

The overall incidence of hepatobiliary disorders was relatively low: in the range of 3.7–6.9% across the analysis pools, with <1% of patients having events considered related to copanlisib. There were no cases of drug-induced liver injury (DILI). All laboratory values of AST/ALT >3 x the ULN and total bilirubin >2 x ULN, or AST/ALT >20 and >10 x ULN were due to progression/complication of the underlying malignancy, according to the applicant. Links to the narratives with the previously mentioned elevated tests are requested.

Safety in special populations

The applicant is requested to fill in the table regarding incidences of various adverse event subgroups according to age: One for the combination therapy study and one for the ISS.

MedDRA Terms	Age <65 number (percentage)	Age 65-74 number (percentage)	Age 75-84 number (percentage)	Age 85+ number (percentage)
Total AEs				
Serious AEs – Total				
- Fatal				
- Hospitalization/prolong existing hospitalization				
- Life-threatening				
- Disability/incapacity				
- Other (medically significant)				
AE leading to drop-out				
Psychiatric disorders				
Nervous system disorders				
Accidents and injuries				
Cardiac disorders				
Vascular disorders				
Cerebrovascular disorders				
Infections and infestations				
Anticholinergic syndrome				
Quality of life decreased				
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures				
<other AE appearing more frequently in older patients>				

There were no meaningful differences in the safety profiles with respect to TEAE incidences between genders within either treatment arm.

Immunological events

Not applicable.

Safety related to drug-drug interactions and other interactions

See pharmacology section.

Discontinuation due to AEs

Study 17067; combination therapy:

Adverse events leading to permanent discontinuation of copanlisib treatment occurred more commonly in the Copa/R arm (31.3%) than AEs leading to permanent discontinuation of placebo in the Pbo/R arm (8.2%) (Table 2A-14/SCS).

In the Copa/R arm, pneumonitis was the most common AE leading to permanent discontinuation of copanlisib, occurring in 19 patients (6.2% vs. 0% in the Pbo/R arm) followed by hyperglycaemia (2.6% vs. 0%, respectively). All other individual AEs leading to permanent discontinuation of copanlisib or placebo occurred in <2% of patients in both treatment arms. It could be argued that interstitial lung disease is the result of pneumonitis, so adding this brings the AE of pneumonitis/interstitial lung disease leading to discontinuation up to 7.5%. When the Standardized MedDRA Query (SMQ) "Interstitial lung disease" with narrow search (i.e., Category 2A) was used, the incidence in the iNHL population was 9.8%; see section re. Adverse events of interest; Non-infectious pneumonitis (NIP). Pneumonitis is listed as Very common in the SPC, section 4.8, ADR table, which is satisfactory.

Table 2A–14 Incidence of TEAEs leading to permanent copanlisib or placebo discontinuation in the total iNHL population in study 17067 (SAF)

	Total iNHL N=453	
	Copa/R N=307 n (%)	Pbo/R N=146 n (%)
Any TEAE leading to permanent copanlisib or placebo discontinuation	**96 (31.3)**	**12 (8.2)**
TEAEs (any grade) occurring in >1 patient in either treatment arm of the total iNHL study population by MedDRA PT (v. 23.0)		
Pneumonitis	19 (6.2)	0
Hyperglycaemia	8 (2.6)	0
Interstitial lung disease	4 (1.3)	0
Pneumocystis jirovecii pneumonia	4 (1.3)	0
Pneumonia	4 (1.3)	1 (0.7)
Amylase increased	3 (1.0)	0
Bronchitis	3 (1.0)	0
Hyponatraemia	3 (1.0)	0
Lipase increased	3 (1.0)	0
Alanine aminotransferase increased	2 (0.7)	0
Aspartate aminotransferase increased	2 (0.7)	0
Cough	2 (0.7)	0
Hepatitis B DNA increased	2 (0.7)	0
Hypertension	2 (0.7)	1 (0.7)
Mucosal inflammation	2 (0.7)	0
Pruritus	2 (0.7)	0
Respiratory failure	2 (0.7)	0
Weight decreased	2 (0.7)	0
Blood creatine phosphokinase increased	0	2 (1.4)
Dyspnoea	0	2 (1.4)

Copa = Copanlisib; CTCAE = Common Terminology Criteria for Adverse Events; DNA = Deoxyribonucleic acid; iNHL = Indolent non-Hodgkin's lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; MZL = Marginal zone lymphoma; N = Total number of patients (100%); n = Number of patients with event; Pbo = Placebo; PT = Preferred term; R = Rituximab; SAF = Safety analysis set; TEAE = Treatment-emergent adverse event

Notes: Number (%) of patients with the specified event that started or worsened between the start of study treatment and 30 days after the end of study treatment.
TEAEs graded using CTCAE v. 4.03.

Source: Module 5.3.5.1, Report PH-41310, Table 14.3.1.3/1

AEs leading to permanent discontinuation of rituximab treatment occurred in a higher percentage of patients in the Copa/R arm (20.8%) than in the Pbo/R arm (3.4%). These AEs were considered copanlisib- or placebo-related in 16.6% and 2.1% of patients, respectively and rituximab-related in 10.1% and 2.1% of patients, respectively. The AEs leading to permanent discontinuation of rituximab treatment occurring in ≥2% of patients in the Copa/R arm were pneumonitis (4.2% in the Copa/R arm vs. 0% in the Pbo/R arm) and hyperglycaemia (2.3% vs. 0%, respectively).

The most common AEs leading to copanlisib interruption in the Copa/R arm and placebo interruption in the Pbo/R arm were neutrophil count decreased (14.0% vs. 9.6%, respectively) and neutropenia (10.1% vs. and 7.5%, respectively).

The TEAEs leading to dose reduction occurring in ≥2% of patients in the Copa/R arm were (vs. Pbo/R arm): hypertension (7.8% vs. 0%), hyperglycaemia (6.8% vs. 0%), neutrophil count decreased (3.3% vs. 3.4%), and neutropenia (2.3% vs. 2.1%).

Generally, the AEs leading to discontinuation, dose interruption and dose reduction are in line with the known AEs.

Table 2A–16 Incidence of TEAEs leading to dose reduction of copanlisib or placebo in the total iNHL population in study 17067 (SAF)

	Copa/R N=307 n (%)	Pbo/R N=146 n (%)
TEAEs (any grade) by MedDRA PT (v. 23.0)		
Hypertension	24 (7.8)	0
Hyperglycaemia	21 (6.8)	0

Copa = Copanlisib; CTCAE = Common Terminology Criteria for Adverse Events; iNHL = Indolent non-Hodgkin's lymphoma; MedDRA = Medical Dictionary for Regulatory Activities; N = Total number of patients (100%); n = Number of patients with event; Pbo = Placebo; PT = Preferred term; R = Rituximab; SAF = Safety analysis set; TEAE = Treatment-emergent adverse event

Notes: Number (%) of patients with the specified event that started or worsened between the start of study treatment and 30 days after the end of study treatment.
TEAEs graded using CTCAE v. 4.03.

ISS; monotherapy:

The percentage of adverse events leading to permanent discontinuation of copanlisib treatment was comparable with what was seen for combination therapy (32.4% in the iNHL pool 1).

The AEs that led to permanent discontinuation of copanlisib in ≥2% of patients in iNHL Pool 1 were pneumonia (3.4%), pneumonitis (2.9%), and neutropenia (2.4%).

Post marketing experience

Copanlisib had received a marketing approval in the US (SEP 2017) and Taiwan (OCT 2019). In the US the approved indication is relapsed follicular lymphoma. There were in total 60 post-marketing spontaneous cases reporting 142 events. 32 cases were serious. Common adverse events (other than in off-label use) were consistent with the known safety profile of copanlisib observed in monotherapy clinical studies; hypertension, hyperglycaemia, diarrhoea, pneumonia, neutropenia, and paresthesia and for SAEs; hypertension, hyperglycaemia, pneumonia, and neutropenia.

There were four cases with fatal outcome. Of these, one case was considered possibly related to copanlisib by the reporter and the company.

Table 6–3 Post-marketing death cases

Case ID / Country / Source / Age / Gender	Reported term	MedDRA PT (seriousness) [a]	Additional information
US/ spontaneous/	Progression	Disease progression (s)*	Patient progressed, opted for hospice, and passed away 10 days later.
US/ spontaneous/	Cardiac arrest; Pain	Cardiac arrest (s)*; Pain (n)	Patient with known atrial fibrillation received copanlisib and left the infusion center in stable condition. Two hours later he clutched, complained of pain, and became unresponsive. He was found to have asystole by EMS, was resuscitated but had anoxic brain injury. Cardiac testing revealed significant triple vessel CAD, including 80% ulcerated RCA. Further care was withdrawn (family decision), and the patient died the following day.
US/ spontaneous/	Severe diarrhea (resulting in acute colitis throughout the entire bowel)/Pseudomembranous colitis; Refractory lactic acidosis; Hypotension; Thrombocytopenia; Fever; Early bruising; Lower extremity and scrotal edema	Pseudomembranous colitis (s)*; Colitis (s)*; Diarrhoea (s)*; Lactic acidosis (s)*; Hypotension (s)*; Thrombocytopenia (s); Pyrexia (n); Contusion (n); Oedema peripheral (n); Scrotal oedema (n);	Two months after starting copanlisib, the patient experienced thrombocytopenia and easy bruising. During the 3rd month, his treatment was held due to diarrhea (last dose on 19 OCT 2018), and 2 weeks later he was hospitalized (03 NOV 2018) due to persistent diarrhea. Stool studies were negative for parasites, Shigella, Salmonella, and Campylobacter. Testing for the *Clostridium difficile* toxin gene was interpreted as negative (presumptive negative for NAP1), but colonoscopy showed classic pseudomembraneous colitis. The pathology report revealed evidence of pancolitis, morphologic findings consistent with pseudomembraneous colitis, and the recommendation was to consider repeat testing for *Clostridium difficile* and RNA test for *Clostridium difficile* on a fresh specimen. In the next few days the patient's condition worsened and he developed hypotension, fever, and lactic acidosis and subsequently died on 14 NOV 2018. No autopsy was performed. The reported cause of death was hypotension, lactic acidosis, pseudomembranous colitis, and diarrhea. The reporter commented that the patient had developed severe diarrhea, which resulted in acute colitis throughout the entire bowel. Per the physician's progress note (26 OCT 2018, 1 week before hospitalization), the diarrhea may have been related to recent antibiotic use (amoxicillin) and could have been related to copanlisib as well. Company Assessment: While copanlisib may have contributed to the onset of diarrhea, the overall clinical picture is most consistent with amoxicillin-induced severe or fulminant pseudomembranous colitis.
US/ spontaneous	Pharmacist believes that the cause of death was respiratory in origin (not sure)	Respiratory disorder (s)*	Vague report. No further information available.

CAD = Coronary artery disease; EMS =Emergency medical system; ID = Identification number; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred term; RCA = Right coronary artery; RNA = Ribonucleic acid; US = United States (of America)

The reporter and company's evaluation is supported. As discussed in the section on Adverse events, the applicant should include a warning on diarrhoea and colitis in section 4.4. of the SmPC.

Post marketing data for copanlisib is available until 20.02.20. Updated data should be provided.

3.3.8. Discussion on clinical safety

Study 17067; combination therapy:

The safety population consists of 453 patients with relapsed iNHL (307 patients in the Copa/R arm and 146 in the Pbo/R arm). This included 94 patients with marginal zone lymphoma (65 in the Copa/R-arm and 29 in the Pbo/R-arm).

Overall, the safety profile of copanlisib in combination with rituximab was generally consistent between the total iNHL study population and the FL and MZL subpopulations, although the frequency of SAEs seemed to be higher in the MZL subpopulation than in the iNHL population (see below). In the total iNHL study population, the overall median time of copanlisib treatment (including drug holidays and drug interruptions or delays) was 8.31 months in the Copa/R arm and 10.78 months in the Pbo/R arm. Despite this, the mean duration of treatment was comparable between the two treatment arms: 11.99 vs. 12.72 months in the Copa/R and Pbo/R arms, respectively. Accordingly, the median percentage of the planned dose of copanlisib or placebo received was slightly lower in the Copa/R arm (95.2%) than in the Pbo/R arm (100.0%). In the total iNHL study population, the overall median time of rituximab treatment was the same in both treatment arms (7.59 months) and the median percentage of the planned dose of rituximab received was 100.0% in both treatment arms.

In the total iNHL study population as well as in the FL and MZL subpopulations demographics, baseline characteristics (including disease characteristics), and systemic anti-cancer therapies were generally

comparable between the Copa/R and Pbo/R arms. The minor differences detected generally favoured the Pbo/R-arm.

All patients in the Copa/R-arm and almost all patients (91.8%) in the Pbo/R-arm experienced at least one AE. The most common AEs in the Copa/R arm compared to the Pbo/R arm were: Hyperglycaemia (69.4% vs. 23.3%), hypertension (49.2% vs. 19.2%), diarrhoea (33.6% vs. 9.6%), neutrophil count decreased (33.2% vs. 23.3%), nausea (22.5% vs. 11.6%), neutropenia (20.8% vs. 16.4%), and pyrexia (20.5% vs. 7.5%). Events with a ≥15 % point higher incidence were hyperglycaemia, hypertension, and diarrhoea.

The most common AEs with a worst grade of 3 in the copanlisib/rituximab arm were (Copa/R arm vs. Pbo/R arm): hyperglycaemia (48.2% vs. 8.2%/ Grade 4; 8.1% vs. 0%), hypertension (39.7% vs. 8.9%), neutrophil count decreased (11.1% vs. 6.8%/ Grade 4; 11.7% vs. 6.8%), neutropenia (6.8% vs. 6.2%/ Grade 4; 8.8% vs. 6.2%), and white blood cell count decreased (6.5% vs. 3.4%)(Table 10-8). The AEs occurring with a ≥15 percentage point higher incidence in the Copa/R arm than in the Pbo/R arm were hyperglycaemia and hypertension.

Almost all patients (97.4%) in the Copa/R arm and most patients (79.5%) in the Pbo/R arm experienced AEs during the first 90 days of study treatment. Then the frequency of AEs generally decreased. This trend was especially pronounced for hyperglycaemia and hypertension.

The SAEs occurring in ≥2% of patients in the Copa/R arm vs. Pbo/R were: hyperglycaemia (6.8% vs. 0%), pneumonia (5.5% vs. 3.4%), pneumonitis (4.9% vs. 0%), and *Pneumocystis jirovecii* pneumonia (2.6% vs. 0%).

Selected adverse events of special interest:

- In the total iNHL study population of study 17067, there was a higher percentage of patients with **non-infectious pneumonitis (NIP)** in the Copa/R arm (9.8%, SAE; 7.2%) than in the Pbo/R arm (1.4%, SAE; 0). The events were considered related to copanlisib or placebo in most patients with NIP. For the majority of patients with NIP in the Copa/R arm, the events resolved following discontinuation of study treatment.
- In the total iNHL study population, AEs in the SOC of **infections** and infestations occurred more commonly in the Copa/R arm (72.6%) than in the Pbo/R arm (52.1%). There were more opportunistic infections in the Copa/R arm compared to the Pbo/R arm.
- In the total iNHL study population, neutropenia (MLG) occurred more commonly in patients receiving Copa/R (51.8%) than Pbo/R (34.9%). Most patients had events with a worst grade 3 or 4.
- In the total iNHL study population, AEs in the MLG for **hyperglycaemia** occurred in the majority (71.0%, SAE 6.8%) of patients in the Copa/R arm. In the Pbo/R arm, hyperglycaemia events were less common, occurring in 24.7% (SAE 0) of patients. Most events were of grade 3. The frequency of AEs was increased in patients with a history of diabetes (n=45) compared with patients without such history (82.2% vs. 69.1%). The corresponding frequencies of SAEs were 17.8% and 5.0%, and for permanent discontinuation of copanlisib 8.9% and 1.5%. At the end of treatment visit, 38.8% of patients in the Copa/R arm vs. 14.6% of patients in the Pbo/R arm had shifted from the normal to prediabetic HbA1c category, and 13.6% of patients in the Copa/R vs. 2.1% of patients in the Pbo/R arm had shifted from the normal to diabetic HbA1c category.

Follow-up data is too sparse to evaluate the outcome of these reactions. The applicant has been requested to present updated follow-up data and comment on the course and outcome of these events. This also applies to similar data from monotherapy.

- In the Copa/R arm, more than half of the patients with hyperglycaemia events (136/218 patients, 62.4%) received antihyperglycaemic medication. Of these patients, 34/218 (15.6%) had a history of diabetes and 102/218 (46.8%) had no history of diabetes.
- Hyperglycaemia is clearly a major adverse event for copanlisib.

- In the total iNHL study population, **arterial hypertension** (MLG hypertension) events occurred more commonly in the Copa/R arm (51.1%) than in the Pbo/R arm (19.9%). The corresponding Grade 3 events (no Grade 4 or 5 events) were 41.0% vs 9.6%. The frequency of SAEs was low (Copa/R 1.3%, Pbo 0).
  - In the Copa/R arm, the majority of patients with hypertension events (113/157 patients, 72.0%) received antihypertensive treatment. Of these patients, 34.4% had a history of hypertension and 37.6% had no history of hypertension. The anti-hypertensive medication used is presented where it can be seen, that while baseline medication was comparable between the two arms, treatment with in particular calcium channel blockers and agents affecting the renin-angiotensin system increased markedly in the Copa/R arm during treatment.
  - Hypertension is clearly a major adverse event for copanlisib.

  Serious diarrhoea and colitis have been associated with oral PI3K-inhibitors. The applicant claims that this is a less problem with copanlisib as it is administered intermittently and by the intravenous route. It avoids daily gastric passage for absorption.

  Nevertheless, serious cases of diarrhoea have been reported (frequency for combination therapy 0.7% and for monotherapy 1.9% (iNHL Pool 1)). For combination therapy four cases (1.3%) of colitis have been reported in the Copa/R arm (Pbo/R 0). Two of them were serious and considered to be copanlisib-related. In addition, one serious case of colitis microscopic (considered copanlisib-related) was reported. One fatal case of enterocolitis was also reported that was considered not related to copanlisib. This case is described in more detail in the section on Deaths (considered possibly related to CMV-infection by the Rapporteur). Four cases of colitis (0.8%) were also reported for copanlisib used in monotherapy (Pool 3). Three of them were serious and considered to be copanlisib-related. One FL patient (0.5% in iNHL Pool 1) had a non-serious enterocolitis that was considered copanlisib-related.

  It should also be noted that diarrhoea and colitis may occur several months after treatment initiation for oral PI3K-inhibitors. The SmPC of Copiktra (duvelisib) states that the median time to onset was 4 months and that 75% of cases occurred within 8 months. It should be remembered that the median exposure time was 5.52 months for copanlisib monotherapy and 8.31 months for combination therapy.

  For the same reason, the applicant has been requested to include "Serious diarrhoea" as an important identified risk and "serious colitis" as an important potential risk in the RMP to gain more information on these AEs.

  The applicant does not discuss **cutaneous AEs** of copanlisib. According to the proposed SmPC rash of grade 3 is a common AE, and cases of exfoliative skin reactions have been reported. For copanlisib monotherapy grade 4 events have also been reported. Serious cutaneous reactions have been associated with oral PI3K-inhibitors. The applicant has been requested to discuss the

frequency and seriousness of cutaneous events reported for copanlisib alone or in combination with rituximab.

No evidence was found for an increased risk of renal impairment in either treatment arm but patients with severe and end-stage renal disease were not included in the study. In the SmPC it is stated, that the pharmacokinetics in patients with end-stage renal disease is unknown.

Adverse events leading to permanent discontinuation of copanlisib treatment occurred more commonly in the Copa/R arm (31.3%) than AEs leading to permanent discontinuation of placebo in the Pbo/R arm (8.2%). In the Copa/R arm, pneumonitis was the most common AE leading to permanent discontinuation of copanlisib (6.2% vs. 0% in the Pbo/R arm) followed by hyperglycaemia (2.6% vs. 0%, respectively). The frequencies of copanlisib interruptions were Copa/R 67.4% and Pbo/R 35.6% and for dose-reductions Copa/R 26.7%, Pbo/R 6.8%. Additionally, the frequencies of AEs leading to permanent discontinuation of rituximab was Copa/R 20.8% and Pbo/R 3.4%.

Long term safety data is limited.

ISS; monotherapy:

The monotherapy safety population include in total 514 subjects organised into five pools according to the underlying malignancy (iNHL, FL, MZL, NHL/CLL and NHL/CLL/ST). Pool 1 is considered the main pool for adverse events evaluation as this pool contained the iNHL patients, including 29 MZL patients and 161 FL patients. Of the 207 patients in Pool 1 the dose of copanlisib was either 60 mg IV or 0.8 mg/kg (max 65 mg IV) D. 1, 8, and 15 of a 28-day cycle (3 patients received 45 mg IV). The overall median time of copanlisib treatment (including drug holidays and drug interruptions or delays) was 5.52 months in Pool 1, and similar in FL Pool 1b, and MZL Pool 1c.

In Pool 1, the most common AEs were hyperglycaemia (59.9%), hypertension (39.1%), diarrhoea (37.2%), fatigue (27.5%), neutropenia and pyrexia (26.6% each), nausea (24.6%), and anaemia (20.3%); the most frequent AEs are in line the combination study as is also the case for AEs by SOC.

The most common AEs with a worst grade of 3 in Pool 1 were hyperglycaemia (35.3%), hypertension (28.5%), neutropenia (9.2%), pneumonia (8.7%), white blood cell count decreased (7.7%), diarrhoea (6.3%), and anaemia (5.8%). The most common AEs with a worst grade of 4 in iNHL Pool 1 were neutropenia (11.6%), neutrophil count decreased (5.3%), and hyperglycaemia (4.8%).

SAEs occurring in ≥2% of patients in iNHL Pool 1 were pneumonia (11.1%), pneumonitis and pyrexia (5.3%, each), hyperglycaemia (4.3%), and interstitial lung disease (2.4%).

Adverse events of special interest:

- **Non-infectious pneumonitis (NIP):** In Pool 1 overall AE was 10.1% with 7.7% being categorised as an SAE; this corresponded to what was observed in the combination therapy study.
- Adverse events in the SOC of **infections** and infestations occurred in 65.2% of patients in iNHL Pool 1. The incidence in Pool 1 was of the same magnitude as in the combination therapy study keeping in mind, that the median exposure was lower in the ISS, Pool 1 (5.5 months), but also that the number of prior therapies was higher.
- In Pool 1 (iNHL) the incidence of **neutropenia** (MLG neutropenia) was 41.1% with a Grade 3-4 incidence of 29.9%; slightly lower than in the combination study, which is not unexpected given the addition of rituximab in that study.
- In Pool 1 (iNHL) the incidence of **hyperglycaemia** (MLG) was 62.3% with a Grade 3-4 incidence of 41.5% (Table 2B-28/SCS). In iNHL Pool 1, more than half of the patients with hyperglycaemia events (79/129 patients, 61.2%) received antihyperglycaemic medication. Of these patients,

19/129 (14.7%) had a history of diabetes and 60/129 (46.5%) had no history of diabetes. As for combination therapy an increase in mean Hb1Ac values from baseline to end of treatment was seen. Shifts from baseline normal to diabetic category were observed in 20/119 (16.8%) patients in iNHL Pool 1.

- In Pool 1 (iNHL) the incidence of **hypertension** (MLG) was 39.1% with a Grade 3 incidence (no Grade 4 or 5 events). There was a clear increase across all pools in the use of anti-hypertensive mediation after study start, as shown for the combination therapy study. Hypertension is clearly a major adverse event for copanlisib.
- **Gastrointestinal AEs**: As for combination therapy serious cases of diarrhoea and colitis have been reported.

The frequency of AEs leading to permanent discontinuation of copanlisib was 32.4% in the iNHL Pool 1 which is similar as for combination therapy (31.3%). The AEs that led to permanent discontinuation of copanlisib in ≥2% of patients in iNHL Pool 1 were pneumonia (3.4%), pneumonitis (2.9%), and neutropenia (2.4%). Frequencies of AEs leading to interruptions and dose reductions of copanlisib were 68.6% and 25.1% which is rather similar as for combination therapy.

Additional expert consultation

Not applicable

Assessment of paediatric data on clinical safety

Not applicable

Additional safety data needed in the context of a conditional MA under exceptional circumstances

Not applicable

3.3.9. Conclusions on clinical safety

The safety profile of Aliqopa is as it can be expected for PI3K inhibitors. In the combination study it was clearly shown, that hyperglycaemia, hypertensive events, and pneumonitis are important adverse events due to a high incidence and/or seriousness. These events were also observed in the ISS for copanlisib monotherapy. Close observation and awareness of these adverse events is crucial as well as clear guidance for their management. No major safety issues were identified.

3.4. Risk management plan

- **Populations not studied in clinical trials**

Patients with hepatic impairment

Patients with moderate and severe hepatic impairment were excluded from the majority of clinical trials with copanlisib.

Mild hepatic impairment was present in n=76 (14.8%) of the patients exposed to copanlisib in clinical trials (monotherapy pool 3 with n=514 patients) as well as in n=45 (14.7%) of patients treated with

copanlisib/rituximab in the Phase 3 study 17067. In the latter study, 2 patients with moderate hepatic impairment were treated with copanlisib/rituximab.

Study 18041 evaluated a single i.v. dose of 12 mg (0.2 times the recommended approved dose of 60 mg) of copanlisib in patients with moderate and severe hepatic impairment. Proposed dose regimens in patients with moderate and severe hepatic impairment are currently not considered adequately justified

Patients with renal impairment

Based on estimated glomerular filtration rate values, renal function was mildly impaired in 253 patients (49.2%) and moderately impaired in 78 patients (15.2%) in the monotherapy pool 3 with n=514 patients). In one patient, severely impaired renal function was seen.

In the Phase 3 combination therapy study, 45 patients (50.0%) had mild and 35 patients (11.4%) moderate renal impairment (in n=307 patients treated with copanlisib/rituximab).

Study 18041 evaluated a single i.v. dose of 12 mg (0.2 times the recommended approved dose of 60 mg) of copanlisib in patients with severely impairment renal function. No clinically relevant changes in copanlisib exposures (in terms of AUCs and C_{max}) were observed in patients with severe renal impairment compared to matched healthy controls. Based on the results of this study, dose adjustment is not considered necessary in patients with severe renal impairment.

3.4.1. Safety Specification

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Hyperglycaemia Arterial hypertension Non-infectious pneumonitis Infections Neutropenia (incl. febrile neutropenia) and lymphopenia
Important potential risks	Birth defects/pregnancy loss
Missing information	Experience in children

3.4.2. Discussion on safety specification

Experience in children as Missing information should be removed according to guidance, as the indication does not include children and a PIP has been issued.

The applicant is requested to change "Infections" to "Serious infections."

For combination therapy size of the safety database at 6 months is 187 patients, at 12 months 114 patients and at 24 months 45 patients. For monotherapy only 26 subjects have been exposed for 12 months (Pool 3). Long term safety is thus limited, and "Long-term safety" should be listed in the RMP as Missing information

Serious diarrhoea and colitis are known side effects of oral PI3K-inhibitors. The applicant claims that this is a less problem with copanlisib as it is administered intravenously and intermittently.

Nevertheless, serious cases of diarrhoea and colitis have been reported that were considered related to copanlisib (combination- and mono-therapy). The applicant should include "Serious diarrhoea" as an Important identified risk and "Serious colitis" as an Important potential risk in the RMP to gain more information on these events.

3.4.3. Conclusions on the safety specification

Having considered the data in the safety specification It is considered that the following issues should be addressed:

It is considered that the following should not be a Missing information safety concern: Experience in children.

It is considered that "Long-term safety" should be listed as Missing information.

It is considered that "Infections" should be changed to "Serious infections" (as an Important identified risk).

It is considered to include "Serious diarrhoea" as an Important identified risk.

It is considered that "Serious colitis" should be listed as an Important potential risk.

3.4.4. Pharmacovigilance plan

3.4.4.1. Routine pharmacovigilance activities

The applicant suggests a specific adverse reaction follow-up questionnaire for the important identified risk non-infectious pneumonitis to collect details including but not limited to the basis for diagnosis and risk factors. Considering the non-infectious pneumonitis is a diagnosis of exclusion, the questionnaire will enable better characterisation of the risk of non-infectious pneumonitis reported with copanlisib.

PRAC Rapporteur comment:
The PRAC Rapp considers the proposed follow-up questionnaire for the listed adverse reaction – pneumonitis – to be a superfluous activity. The questionnaire is proposed to manage an important identified risk, which is already sufficiently covered in the proposed SmPC (sections 4.2, 4.4 and 4.8). It requests/collects the information basically requested within a routine process of follow-up for spontaneous reporting (concomitant medication, laboratory findings and tests etc.). Moreover, it seems to be designed for clinical trial purposes (used terminology includes "adverse events" and study ID) rather than for a post-marketing surveillance. We are of the opinion that proposed questionnaire will not provide any new safety data on the listed adverse reaction, whilst a concern of administrative overloading of HCPs may be present. The PRAC Rapp considers routine PhV activities sufficient to cover the important identified risk of non-infectious pneumonitis.

3.4.4.2. Summary of planned additional PhV activities from RMP

Table Part III.3.1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
BAY 80-6946/19176 – A nonrandomised, open-label, multicentre, Phase 1/2 study of PI3K inhibitor copanlisib in paediatric relapsed/ refractory solid tumours or lymphoma Status: ongoing	• Phase 1 (dose escalation) part • To evaluate • Safety, MTD and/or RP2D of copanlisib in paediatric patients with a relapsed/refractory solid tumour or lymphoma • PK of copanlisib • Antitumour activity of copanlisib and to identify specific potential tumour type(s) for further development • Phase 2 (extension) part • To determine • ORR of copanlisib in relapsed/refractory neuroblastoma, rhabdomyosarcoma, or Ewing sarcoma. • DCR and PFS in relapsed/refractory osteosarcoma • PFS (in indications other than osteosarcoma), OS, and DOR • Population PK <u>For both parts:</u> • Pharmacodynamics	<u>Missing information:</u> Experience in children	FPFV LPLV (planned)	30/04 2018 21/04 2027

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	• Biomarkers of efficacy, mode-of-action related effect, and/or the pathomechanism of the disease.			

PRAC Rapporteur comment:

Although the indication of Aliqopa in children has not been approved yet, the applicant suggested to include a clinical trial phase 1/2 in children in the PhV plan. The study is a part of the Paediatric investigation plan (PIP). Considering that the studies stated in the RMP must fulfil pharmacovigilance legislation requirements, i.e. to address current safety need in approved indication and not missing safety information for an indication which is expected to be established in the future, the applicant is asked to remove the Paediatric investigation plan from the pharmacovigilance plan. If the list of safety concerns is amended based on the CHMP discussion, the PhV plan will be updated accordingly.

3.4.4.3. Overall conclusions on the PhV Plan

The PRAC Rapporteur, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product. If the list of safety concerns is amended based on the CHMP discussion, the PhV plan will be updated accordingly.

The PRAC Rapporteur also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

3.4.5. Plans for post-authorisation efficacy studies

3.4.5.1. Summary of Post authorisation efficacy development plan

Table Part IV.1: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorisation				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				

PRAC Rapporteur comment:

The applicant does not propose any post-authorisation efficacy study.

3.4.6. Risk minimisation measures

3.4.6.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Hyperglycaemia	Routine risk communication: Inclusion of hyperglycaemia in SmPC section 4.8 "Undesirable effects", section 4.4 "Special warnings and precautions for use", and section 4.2 "Posology and method of administration". Routine risk minimisation activities recommending specific clinical measures to address the risk: Guidance for glucose monitoring, management of hyperglycaemia, and dose management/discontinuation of Aliqopa in SmPC section 4.4 "Special warnings and precautions for use". Guidance for dose modification and toxicity management in section 4.2 "Posology and method of administration". Other routine risk minimisation measures beyond the Product Information: Legal status: Aliqopa is a prescription-only medicine and is administered by a healthcare professional providing an opportunity to monitor blood glucose and to identify early signs and symptoms of complications that could be precipitated by hyperglycaemia.
Arterial hypertension	Routine risk communication: Inclusion of hypertension in SmPC section 4.8 "Undesirable effects", section 4.4 "Special warnings and precautions for use", and section 4.2 "Posology and method of administration". Routine risk minimisation activities recommending specific clinical measures to address the risk: Guidance in SmPC section 4.4 "Special warnings and precautions for use" for monitoring/management of hypertension and dose management/discontinuation of Aliqopa. Guidance for dose modification and toxicity management in section 4.2 "Posology and method of administration". Other routine risk minimisation measures beyond the Product Information: Legal status: Aliqopa is a prescription-only medicine and is administered by a healthcare professional providing an opportunity to monitor blood pressure during/after

	infusion and to identify early signs and symptoms of complications associated with hypertension in at risk patients
Non-infectious pneumonitis	Routine risk communication: Inclusion of pneumonitis (including interstitial lung disease) in SmPC section 4.8 "Undesirable effects", section 4.4 "Special warnings and precautions for use", and section 4.2 "Posology and method of administration". Routine risk minimisation activities recommending specific clinical measures to address the risk: Guidance for symptom monitoring, management of non-infectious pneumonitis and on Aliqopa dose reductions/discontinuation recommendations in SmPC section 4.4 "Special warnings and precautions for use". Guidance for dose modification and toxicity management in section 4.2 "Posology and method of administration". Other routine risk minimisation measures beyond the Product Information: Legal status: Aliqopa is a prescription-only medicine and is administered by a healthcare professional providing an opportunity to identify early signs and symptoms of respiratory disorders including pneumonitis.
Infections	Routine risk communication: Inclusion of lower respiratory tract infection in SmPC section 4.8 "Undesirable effects" and infections in section 4.4 "Special warnings and precautions for Use" and in section 4.2 "Posology and method of administration". Routine risk minimisation activities recommending specific clinical measures to address the risk: Guidance for prophylaxis, symptoms monitoring and management of infections, and on Aliqopa discontinuation rules in SmPC section 4.4 "Special warnings and precautions for use". Guidance for dose modification and toxicity management in section 4.2 "Posology and method for administration" (for Grade ≥3 infections and for PJP infection of any Grade). Other routine risk minimisation measures beyond the Product Information: Legal status: Aliqopa is a prescription-only medicine and is administered by a healthcare professional providing an opportunity to identify early signs and symptoms of infections or predisposition to infections.
Neutropenia (incl. febrile neutropenia) and lymphopenia	Routine risk communication: Inclusion of neutropenia, febrile neutropenia, and lymphopenia in SmPC section 4.8 "Undesirable effects" as well as of neutropenia/febrile

	neutropenia in section 4.4 "Special warnings and precautions for use" and in section 4.2 "Posology and method of administration". Routine risk minimisation activities recommending specific clinical measures to address the risk: Guidance for symptoms monitoring and management of neutropenia (febrile and non-febrile) and on Aliqopa discontinuation rules in SmPC section 4.4 "Special warnings and precautions for use". Guidance for dose modification and toxicity management in section 4.2 "Posology and method of administration". Other routine risk minimisation measures beyond the Product Information: Legal status: Aliqopa is a prescription-only medicine and is administered by a healthcare professional providing an opportunity to identify early signs and symptoms of neutropenia and lymphopenia.
Birth defects/ pregnancy loss	Routine risk communication: Inclusion of embryo-foetal toxicity in SmPC section 4.4 "Special warnings and precautions for use" and of "Fertility, pregnancy and lactation" as section 4.6. SmPC section 5.3 "Preclinical safety data" Routine risk minimisation activities recommending specific clinical measures to address the risk: Potential for adverse effects of Aliqopa on reproduction/ development is addressed and guidance on contraception/ breast-feeding is provided in the SmPC sections 4.6 "Fertility, pregnancy and lactation" and 4.4 "Special warnings and precautions for use". Other routine risk minimisation measures beyond the Product Information: Legal status: Aliqopa is a prescription-only medicine and is administered by a healthcare professional thereby minimising the risk of exposure to copanlisib during pregnancy.
Experience in children	Routine risk communication: Information that copanlisib is not recommended for use in paediatric patients as its safety and efficacy have not been established in patients under 18 years of age in SmPC section 4.2 "Posology and method of administration" (section on paediatric population") Routine risk minimisation activities recommending specific clinical measures to address the risk: Potential for adverse effects of Aliqopa on reproduction/ development is addressed and guidance on contraception/ breast-feeding is provided in the

	SmPC sections 4.6 "Fertility, pregnancy and lactation" and 4.4 "Special warnings and precautions for use". Other routine risk minimisation measures beyond the Product Information: Legal status: Aliqopa is a prescription-only medicine and is administered by a healthcare professional thereby minimising the risk of exposure in children.

PRAC Rapporteur comment: Based on the list of safety concerns currently proposed by applicant, this is considered acceptable. If the list of safety concerns is updated based on the received comments, summary of risk minimisation measures will need to be updated accordingly.

3.4.6.2. Additional risk minimisation measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns associated with copanlisib administration.

3.4.6.3. Overall conclusions on risk minimisation measures

The PRAC Rapporteur having considered the data submitted was of the opinion that:

the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indications.

3.4.7. Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan version 1.1 could be acceptable if the applicant implements the changes to the RMP as detailed in the endorsed Rapporteur assessment report and in the list of questions.

The list of safety concerns as proposed by applicant (RMP v. 1.1):

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Hyperglycaemia Arterial hypertension Non-infectious pneumonitis Infections Neutropenia (incl. febrile neutropenia) and lymphopenia
Important potential risks	Birth defects/pregnancy loss
Missing information	Experience in children

3.5. Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The active substance is not included in the EURD list and a new entry will be required. The new EURD list entry uses the EU birth date (EBD) or international birth date (IBD) to determine the forthcoming data lock points. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP opinion. The applicant should indicate if they wish to align the PSUR cycle with the IBD.

4. Significance of paediatric studies

Not applicable

5. Benefit risk assessment

5.1. Therapeutic Context

5.1.1. Disease or condition

The claimed indications:

- Aliqopa in combination with rituximab (anti-CD20 antibody) is indicated for the treatment of adult patients with previously treated marginal zone lymphoma

  (Combination therapy)

- Aliqopa is indicated as monotherapy for the treatment of adult patients with marginal zone lymphoma who have received at least two prior therapies. (*Monotherapy)*

5.1.2. Available therapies and unmet medical need

Currently, there is no treatment specifically approved for MZL patients in the European Union (EU). The therapeutic regimens used for MZL are summarised in the European Society for Medical Oncology (ESMO) clinical practice guidelines for MZL (Zucca et al. 2020). In the absence of approved specific treatments for MZL, chemotherapy, chemoimmunotherapy (with rituximab), rituximab monotherapy, ibrutinib, and lenalidomide are being used in the EU for the treatment of MZL patients.

MZL represents approximately 5–15% of all NHLs in the Western world (Zucca et al. 2020). In 2018, over 11500 individuals were diagnosed with MZL in Europe (geographic area) and there were approximately 4800 deaths due to the disease (Ferlay et al. 2020).

The MZL classification is based on a common origin in the marginal-B-cell-compartment of the lymph nodes and spleen. The three distinct clinical entities, extranodal, splenic, and nodal MZL, have specific diagnostic criteria, different genetic features, clinical behaviour, and therapeutic implications.

MZL is characterised by the need for multiple lines of therapy due to the incurable nature of the disease (Broccoli and Zinzani 2020). Relapses are common even after successful therapy and can occur decades after treatment. More than 50% of MZL patients experience relapse within 10 years (Bertoni et al. 2020, Oh et al. 2009).

Several studies reported 5-year OS rates for MZL with a wide range depending on different factors such as age, gender, geographic location, disease stage at diagnosis and treatment received (Smith et al. 2015). In the UK, a 5-year survival rate of 61.2% was reported (Smith et al. 2015). In Germany, a 5-year survival rate of 83.8% was reported in patients, the majority of whom had received first line of

therapy (Meyer et al. 2014). A 5-year OS rate of 62% was reported for treatment-naive patients older than 60-years of age with nodal MZL (Kuper-Hommel et al. 2013). Reports for a 10-year OS rate have varied between 42% to 58% (Olszewski and Castillo 2013).

Data reporting outcomes in relapsed/refractory settings including targeted therapies is lacking as a result of the rarity of MZL, heterogeneity of MZL subtypes, low numbers of patients included in clinical trials to date and no available data from randomised-controlled clinical trials (Noy et al. 2017).

As many patients invariably relapse, additional active and well-tolerated therapies are needed since treatment with standard agents hardly ever leads to a cure in patients whose disease has relapsed. Advanced stage MZL patients who have been treated with multiple regimens experience shorter duration of response at relapse. Even though initial therapy can be very effective, there is a need for more treatment options.

5.1.3. Main clinical studies

Combination therapy (with rituximab – as second or later line therapy):

Pivotal Phase 3 study 17067 (CHRONOS-3) is an ongoing randomised, double-blind, placebo-controlled study evaluating the efficacy and safety of copanlisib in combination with rituximab in patients with relapsed B-cell iNHL. The histological subtypes included in the study were FL, MZL, SLL, and LPL/WM. The primary objective of this study was to evaluate whether copanlisib in combination with rituximab is superior to placebo in combination with rituximab in prolonging progression-free survival (PFS).

Monotherapy (after at least two prior therapies):

Pivotal Phase 2 study 16349 Part B (CHRONOS-1). Study 16349 is an open-label, uncontrolled, parallel group study to evaluate efficacy and safety of copanlisib as a single agent in patients with indolent or aggressive NHL who have progressed after standard therapy. Based on efficacy data in FL patients reported in the first human Phase 1 study 12871, study 16349 was divided into two parts: 16349 Part A evaluating the efficacy and safety of copanlisib in patients with iNHL/CLL or aggressive NHL (aNHL), and 16349 Part B evaluating the efficacy and safety of copanlisib in patients with B-cell iNHL (FL, MZL, SLL and WM/LPL). The applicant is seeking an indication for Aliqopa as monotherapy in adult patients with MZL who have received at least two prior therapies.

5.2. Favourable effects

Combination therapy

In the **study 17067**, a statistically significant treatment effect and clinically relevant difference in favour of Copa/R in the entire iNHL population was shown with a median PFS time of 21.5 months (95% CI: [17.8, 33.0]) compared with 13.8 months (95% CI: [10.2, 17.5]) in the Pbo/R arm with an HR of 0.520 (95% CI: [0.393, 0.688]; one-sided p=0.000002). The Kaplan-Meier curves continued to run separated, demonstrating longer PFS times for the Copa/R arm than for the Pbo/R arm.

The pre-specified PFS analyses in the four histological subpopulations (FL, MZL, SLL, and LPL/WM) were consistent with the primary analysis results. A median PFS time of 22.1 months (95% CI: [13.8, NE]) in the Copa/R arm compared with 11.5 months (95% CI: [5.6, 16.3]) in the Pbo/R arm with a HR of 0.475 (95% CI: [0.245, 0.923]; p=0.012291) was observed for the MZL population.

Data for the secondary endpoints ORR and CRR supports the primary endpoint: Copa/R treatment showed a significantly higher ORR than Pbo/R treatment (80.8% vs. 47.7%) in the entire iNHL study population (ICR assessed). CRR was also higher in the Copa/R arm than in the Pbo/R arm (33.9% vs.

14.6%, respectively). The difference in ORR was 32.99 (95% CI: [23.95; 42.03]; one-sided p<.000001), indicating a statistically significant positive treatment effect for copanlisib in combination with rituximab.

ORR and CRR were higher in the Copa/R arm than in the Pbo/R arm also in the MZL subpopulation; (75.8% vs. 41.4% and 39.4% vs. 10.3%, respectively). For MZL patients having received ≥2 prior treatments the ORR was 61.3% (19/31) in the Copa/R arm and 50% (5/10) in the Pbo/R arm and the corresponding CRR 29% (9/31) and 0, showing clear efficacy also in patients having received more than one prior systemic treatment. Median DOR (by ICR) in the iNHL population was 20.4 months (95% CI: [17.0, 30.8]) in Copa/R arm vs. 17.3 months (95% CI: [11.8, 25.3]) in Pbo/R arm, while in the MZL population it was 25.4 months (95% CI: [12.1, NA]) in Copa/R arm vs 9.3 months (95% CI: [7.4, NA]) in Pbo/R arm. It is agreed that the difference in the ORR, CRR and DOR showed a clinically meaningful positive treatment effect of copanlisib in combination with rituximab.

Monotherapy

For **study 16349 Part B**, the primary analyses of ORR were performed in 2016. Follow-up analyses were performed in 2018.

A total of 23 patients with MZL entered treatment, and the ORR (IRC) in these patients was **69.57%** (95% CI: [47.08, 86.79]) with cutoff in 2016. In the follow-up analysis, the ORR was **78.26%** (95% CI: [56.30, 92.54]), with 3 patients having CR as best response, compared to 2 patients in the primary analysis, all in the splenic MZL subpopulation.

The diagnosis of MZL was exploratorily centrally confirmed in 13 patients, of which 10 patients (76.9%) responded to treatment with copanlisib according to IRC; one patient achieved a CR, and 9 achieved PR (69.2%) Of the 13 patients, 2 each (15.4%) had MALT - and nodal MZL and for 9 (69.2%) the subtype could not be specified.

The ORR (IRC) for the whole study population with B-cell iNHL (FL, MZL, SLL and WM/LPL) was 59.15% (95% CI: 50.60; 67.32), 17 patients experienced a CR (11.97% in the FAS) and 67 patients had a PR (47.18%). The lower limit of the 95% CI was above the predefined threshold of 40% for the statistical analysis (p<0.0001, one-sample exact binomial test).

5.3. Uncertainties and limitations about favourable effects

Combination therapy

Population

The application is based on the results of CHRONOS-3, which is performed in iNHL patients, of which the sought indication, MZL, is a subgroup. The primary endpoint, which was met, was superiority of median PFS in the Copa/R arm vs. the Pbo/R arm, as assessed in the FAS of the iNHL population. The secondary efficacy endpoints in iNHL also support an effect of copanlisib combination therapy in this patient group. While efficacy analyses done in the MZL subpopulation of iNHL are generally in agreement with results in iNHL(n=458), the MZL subgroup is substantially smaller (n=95) and therefore results in this group are less robust and no confirmatory statistical testing was performed in this population. The patient numbers in the MZL subtypes (splenic, nodal and MALT/extranodal MZL) are very limited, thus efficacy cannot be accurately assessed and it is unclear whether patients with different MZL sub-histologies benefit from copanlisib combination therapy to the same extent.

No single stratification factor was driving the efficacy results, but PFS benefit seems lower in patients with bulky disease, with an HR of 0.905 (95% CI: [0.463,1.770]; one-sided p=0.385490). Due to the

small number of patients with prior PI3K inhibitor no conclusion regarding efficacy in this group could be made.

The HR for the "Unfit or Unwilling to receive chemotherapy (Unfit/Unwilling) seems to be somewhat closer to 1 than the HR for the "Progression-free and treatment-free interval of ≥12 months after the last rituximab-containing Treatment group. The Unfit/Unwilling group could potentially be a quite heterogenous group. Notwithstanding the limited sample size, the apparent smaller difference in treatment effect between Copa/R vs Pbo/R for this stratum could be an indication that the Unfit group experiences lower efficacy and worse safety compared to the Unwilling population. 60 patients are listed in the Copa/R arm and 30 patients in the Pbo/R arm (FAS), whereas in the results section (FAS), the corresponding numbers are 57 and 27 ; please clarify. The applicant has been requested to present the efficacy results (PFS, ORR, and CRR) for the Unfit (all patients fitting this description even though they may also have been Unwilling) and Unwilling separately (for both the iNHL and MZL populations) and present a short overview of safety in these two populations as well as a short discussion regarding B/R based on these data to justify that the indication is appropriate also for the patients defined as Unfit.

Local versus Central Assessment of Diagnosis and Response

Local assessment and ICR-based assessment of efficacy appear to diverge for several secondary endpoints, including DOR in the iNHL population and CRR in the MZL population. The discrepancy between local and central response assessment increases the uncertainty surrounding these data. In addition, it appears that diagnosis was by local laboratory assessment and it is unclear to what extent diagnosis is confirmed by central laboratory. Given the significant discrepancy between locally and centrally determined MZL diagnoses in CHRONOS-1, it is possible that this could present a significant uncertainty in CHRONOS-3 as well.

Protocol Deviations

There were a large number of protocol deviations in CHRONOS-3, most of which were classified as important (269 important protocol deviations in 458 patients) but were not excluded from the efficacy data analysis. This included 53 instances where inclusion/exclusion criteria were not met but the patient entered treatment. These protocol deviations present an uncertainty in the efficacy results.

Baseline Health status

The baseline disease status of the patients in the control and treatment arms appears to differ in a few aspects. In particular, the time from diagnosis to randomization in the MZL population was 54.54mo in the Copa/R arm and 72.37mo in the Pbo/R arm. Furthermore, the percentage of patients with Stage IV Ann Arbor score was 62.1% in the Copa/R arm versus 72.4% in the Pbo/R arm. It is therefore possible that patients in the treatment arm may be healthier than those in the control arm at baseline, potentially impacting efficacy results.

Immature OS data

Median OS has not yet been reached, thus the OS data is considered immature.

Monotherapy

The pivotal study to support monotherapy copanlisib in the treatment of MZL is a single-arm trial performed in iNHL patients, in which MZL is a small subgroup. The study design, with no comparator hampers the interpretation of the results.

The number of patients in the MZL-subgroup is very limited (n=23) and 13 (56.6%) discontinued, mostly due to AEs not associated with PD and withdrawal by subject.

Eleven patients in the FAS did not meet the in-/exclusion criteria, but still entered treatment, and narratives for these patients are requested. Eleven of the 23 patients with MZL were excluded from PP analysis due to major protocol deviations. Only 13 patients had their MZL diagnosis confirmed by central laboratory exploratorily, of these, 2 each (15.4%) had MALT lymphoma and nodal MZL and for 9 (69.2) the subtype could not be specified.

There is overall low concordance between independent review and investigator assessment of response in the FAS, 63.38%. In the MZL subgroup, there were 3 CRs as assessed by independent review (1 CR among those diagnosed by central pathology), while investigator did not observe any CRs in the MZL patients.

Dosing

Dose-response, and exposure-response for efficacy is to a large extent undescribed.

5.4. Unfavourable effects

Combination therapy

The safety population consisted of 453 patients with relapsed iNHL (307 patients in Copa/R-arm and 146 in Pbo/R arm). This included 94 patients with marginal zone lymphoma (65 in the Copa/R-arm and 29 in Pbo/R arm). Overall, the safety profile of copanlisib in combination with rituximab was generally consistent between the total iNHL study population and the FL and MZL subpopulations, although the frequency of SAEs seemed to be higher for the MZL- than for the iNHL-population

All patients in the Copa/R-arm and almost all patients (91.8%) in the Pbo/R-arm experienced at least one AE. The most common AEs in the Copa/R arm compared to the Pbo/R arm were: Hyperglycaemia (69.4% vs. 23.3%), hypertension (49.2% vs. 19.2%), diarrhoea (33.6% vs. 9.6%), neutrophil count decreased (33.2% vs. 23.3%), nausea (22.5% vs. 11.6%), neutropenia (20.8% vs. 16.4%), and pyrexia (20.5% vs. 7.5%). Events with a ≥15 % point higher incidence were hyperglycaemia, hypertension, and diarrhoea.

The most common AEs with a worst grade of 3 in the copanlisib/rituximab arm were (Copa/R arm vs. Pbo/R arm): hyperglycaemia (48.2% vs. 8.2%/ Grade 4; 8.1% vs. 0%), hypertension (39.7% vs. 8.9%), neutrophil count decreased (11.1% vs. 6.8%/ Grade 4; 11.7% vs. 6.8%), neutropenia (6.8% vs. 6.2%/ Grade 4; 8.8% vs. 6.2%), and white blood cell count decreased (6.5% vs. 3.4%) (Table 10-8). The AEs occurring with a ≥15 percentage point higher incidence in the Copa/R arm than in the Pbo/R arm were hyperglycaemia and hypertension.

The frequency of SAEs was 47.2% (Copa/R) and 18.5% (Pbo/R). The SAEs occurring in ≥2% of patients in the Copa/R arm vs. Pbo/R were: hyperglycaemia (6.8% vs. 0%), pneumonia (5.5% vs. 3.4%), pneumonitis (4.9% vs. 0%), and Pneumocystis jirovecii pneumonia (2.6% vs. 0%).

Key safety concerns are hyperglycaemia, hypertension, non-infections pneumonitits (NIP), infections and neutropenia. These are known side effects of other PI3K-inhibitors. With the exception of NIP, these events are also listed for rituximab.

Oral PI3K-inhibitors have been associated with serious cases of diarrhoea and colitis. As copanlisib is administered intravenously and intermittently, the applicant claims that this is a less problem with copanlisib. Although gastrointestinal AEs of Copa/R were mostly of low grade (≤2), serious cases of diarrhoea and colitis have been reported that were considered to be related to copanlisib. For the same reason "Serious diarrhoea" should be included as an important identified risk and "Serious colitis" as an important potential risk in the RMP.

Adverse events leading to permanent discontinuation of copanlisib treatment occurred more commonly in the Copa/R arm (31.3%) than AEs leading to permanent discontinuation of placebo in the Pbo/R arm (8.2%). The frequency of copanlisib interruptions were Copa/R 67.4% and Pbo/R 35.6% and for dose-reductions Copa/R 26.7%, Pbo/R 6.8%. Additionally, the frequency of AEs leading to permanent discontinuation of rituximab was Copa/R 20.8% and Pbo/R 3.4%.

Monotherapy

The monotherapy safety population included in total 514 subjects organised into five pools according to the underlying malignancy (iNHL, FL, MZL, NHL/CLL and NHL/CLL/ST). Pool 1 is considered the main pool for adverse events evaluation as this pool contained the iNHL patients, including 29 MZL patients and 161 FL patients. Of the 207 patients in the iNHL Pool 1 the dose of copanlisib was either 60 mg IV or 0.8 mg/kg (max 65 mg IV) D. 1, 8, and 15 of a 28-day cycle (3 patients received 45 mg IV). The overall median time of copanlisib treatment (including drug holidays and drug interruptions or delays) was 5.52 months in Pool 1, and similar in FL Pool 1b, and MZL Pool 1c.

In the iNHL Pool 1, the most common AEs were hyperglycaemia (59.9%), hypertension (39.1%), diarrhoea (37.2%), fatigue (27.5%), neutropenia and pyrexia (26.6% each), nausea (24.6%), and anaemia (20.3%); the most frequent AEs are in line the combination study as is also the case for AEs by SOC.

The most common AEs with a worst grade of 3 in Pool 1 were hyperglycaemia (35.3%), hypertension (28.5%), neutropenia (9.2%), pneumonia (8.7%), white blood cell count decreased (7.7%), diarrhoea (6.3%), and anaemia (5.8%). The most common AEs with a worst grade of 4 in iNHL Pool 1 were neutropenia (11.6%), neutrophil count decreased (5.3%), and hyperglycaemia (4.8%).

SAEs occurred in 51.7% of the patients in the iNHL Pool 1. SAEs occurring in ≥2% of patients in iNHL Pool 1 were pneumonia (11.1%), pneumonitis and pyrexia (5.3%, each), hyperglycaemia (4.3%), and interstitial lung disease (2.4%).

The frequency of discontinuations due to TEAEs were identical for combination and monotherapy, (31.3% and 32.4%). The AEs that led to permanent discontinuation of copanlisib in ≥2% of patients in iNHL Pool 1 were pneumonia (3.4%), pneumonitis (2.9%), and neutropenia (2.4%) (Table 2B-12/SCS). Frequencies of AEs leading to interruptions and dose reductions of copanlisib were 68.6% and 25.1%.

Overall, the safety profile of copanlisib seems to be rather similar for monotherapy compared to combination therapy. The most common AEs, SOCs infection and infestations (72.6% vs 65.2%), hyperglycaemia (71.0% vs 62.3%), neutropenia (51.8% vs 41.1%) and hypertension (51.1% vs 39.1%) occurred more frequently for combination therapy than for monotherapy, while more gastrointestinal AEs were seen for monotherapy (64.5% vs 68.1%).

5.5. Uncertainties and limitations about unfavourable effects

Oral PI3K-inhibitors are associated with serious cases of diarrhoea and colitis. As copanlisib is administered intravenously and intermittently, the applicant claims that this is a less problem for this drug. Although gastrointestinal AEs of copanlisib were mostly of low grade (≤2), cases of serious diarrhoea and colitis have been reported that were considered to be related to copanlisib.

Serious cases of exfoliative skin reactions have been reported. Serious cutaneous AEs are known side effects of oral PI3K-inhibitors.

Results from the ECG sub-study indicate that copanlisib may have the potential to cause changes in the QTc interval. More detailed information has been requested from the applicant.

During therapy an increase in the mean HbA1c values from baseline to end of treatment was seen, and some patients shifted from baseline normal to diabetic status. Follow-up data have been requested to gain information on the course and outcome of these events.

No evidence was found for an increased risk of renal impairment in either treatment arm in study 17067, but patients with severe and end-stage renal disease were not included in the study. The SPC states that the pharmacokinetics in patients with end-stage renal disease are unknown.

Copanlisib is predominantly eliminated by the liver. Therefore, patients with hepatic impairment may experience increased copanlisib exposure. Dose recommendations for patients with hepatic impairment are based on population pharmacokinetic analysis and a dedicated pharmacokinetic study evaluating a single IV dose of 12 mg copanlisib, but proposed dose regimens in patients with moderate and severe hepatic impairment are currently not considered adequately justified. It is whether the results of the latter study can be transferred to the recommended dose of 60 mg.

The frequency of AEs leading to permanent discontinuation of copanlisib was high and comparable for combination therapy (31.3%) and monotherapy (32.4%). So were the frequencies of treatment interruptions (67.4% and 68.6%) and dose reductions (26.7% and 25.1%).

Long term safety data is limited.

5.6. Effects Table

Table . Effects table for copanlisib combination therapy (study 17067, data cut-off: 31 AUG 2020).

Effect	**Short Description**	**Unit**	**Copa/R** **n:** 307**/66**	**Pbo/R** **n:** 151**/29**	**Strength of evidence/ Uncertainties**	**References**
Favourable Effects: [iNHL[1] and **MZL[2] subgroup (in bold)**]						
PFS; Primary endpoint	Progression free survival by independent review	Months [95% CI]	21.5 [17.8, 33.0] **22.1 [13.8, A]**	13.8 [10.2, 17.5] **11.5 [5.6, 16.3]**	[1]HR: 0.520 [0.393, 0.688] [3]P: <.000001 **[2]HR: 0.475 [0.245, 0.923]** **[3]P: 0.012291** Efficacy in the Unfit population questioned.	See Results/ primary endpoint section
ORR; Secondary endpoint	Objective response rate	n, (%) [95% CI]	248 (80.8) [75.9, 85.0] **50 (75.8) [63.6, 85.5]**	72 (47.7) [39.5, 56.0] **12 (41.4) [23.5, 61.1]**	[4]Difference: 32.99 [23.95, 42.03] [5]P: <.000001 **34.38 [13.69, 55.07]** **[6]P: 0.000596**	See Results/ secondary endpoint section
CRR; Secondary endpoint	Complete response rate	n, (%) [95% CI]	104 (33.9) [28.6, 39.5] **26 (39.4) [27.6, 52.2]**	22 (14.6) [9.4, 21.2] **3 (10.3) [2.2, 27.4]**	[4]Difference: 19.27 [28.6, 39.5] [5]P <.000001 **29.05 [12.87, 45.23]** **[6]P: 0.002318**	See Results/ secondary endpoint section
Unfavourable Effects (all iNHL population in study 17067, SAF; Copa/R: n= 307, Pbo/R: n=146)						

Effect	Short Description	Unit	Copa/R n: 307/66	Pbo/R n: 151/29	Strength of evidence/ Uncertainties	References
Hyperglycaemia (MLG)	Any AE Gr. 3-4 AE SAE	% % %	71.0 57.0 6.8	24.7 8.2* 0	Much higher use of anti-glycaemic medication in Copa/R arm	Safety section
Hypertension (MLG)	Any AE Gr. 3 AE*	% %	51.1 41.0	19.9 9.6	Much higher use of anti-hypertensive medication in Copa/R arm	Safety section
Non-infectious pneumonia	Any AE SAE	% %	9.8 7.2	1.4 0		Safety section
Diarrhoea	Any AE Gr. 3 AE*	% %	33.6 4.9	9.6 0		Safety section
Neutropenia (MLG)	Any AE Gr. 3-4 AE	% %	51.8 36.8	34.9 22.6		Safety section

Abbreviations: CMH = Cochran-Mantel-Haenszel, MLG; MedDRA labeling grouping, Pbo; placebo, R; rituximab,

Notes:

[1]: PFS was evaluated with the stratified log-rank test based on stratification factors iNHL histology and entry criterion used for randomization. HR and 95% CI were based on Cox Regression Model, stratified by iNHL histology and entry criterion.

[2]: PFS was evaluated with the unstratified log-rank test. Histology is based on the information entered in the eCRF for randomization. HR and 95% CI were based on unstratified Cox Regression Model.

[3]: One-sided p-value from log rank test

[4]: Difference = copanlisib/rituximab – placebo/rituximab; for the total population CMH-weighted difference is displayed

[5]: P-values from CMH test stratified by iNHL histology and entry criterion based on stratification information used for randomisation.

[6]: P-values are from chi-square test.

*: No grade 4 AEs

Table . Effects Table for copanlisib monotherapy in MZL (study 16349 Part B)

Effect	Short Description	Unit	Copanlisib	Strength of evidence/ Uncertainties	Ref.
ORR; Primary endpoint	Objective response rate	n, (%) [95% CI]	10 (76.9) [46.2, 95.0]		See Results
Unfavourable effects (safety from ISS Pool 1), N=207					
Hyperglycaemia (MLG)	Any AE Gr. 3-4 AE SAE	% % %	62.3 41.5 4.3		Safety section
Hypertension (MLG)	Any AE Gr. 3 AE*	% %	39.1 28.5		Safety section

Effect	Short Description	Unit	Copanlisib	Strength of evidence/ Uncertainties	Ref.
Non-infectious pneumonia	Any AE SAE	% %	10.1 7.7		Safety section
Diarrhoea	Any AE Gr. 3 AE*	% %	37.2 14.5		Safety section
Neutropenia (MLG)	Any AE Gr. 3-4 AE	% %	41.1 29.9		Safety section

*no Grade 4 AEs

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

Combination therapy

MZL is an indolent orphan disease with potentially several relapses, years apart. In the phase 3 study CHRONOS-3, combination therapy with copanlisib and rituximab extended PFS in the total iNHL population (n=458), meeting the primary endpoint of the study. This was supported by ORR, CRR, and DOR results. While no confirmatory statistical testing was performed in the MZL subpopulation (n=95), which is the indication sought, the results in this subpopulation largely agreed with those in iNHL. In the MZL population, PFS was extended by 10.6 mo in the Copa/R arm relative to the Pbo/R arm. The observed increase in PFS is substantial, and, along with ORR, compares favourably with other available treatments not specifically approved for MZL, such as lenalidomide in combination with rituximab (ORR 65% in AUGMENT; ORR 51% in MAGNIFY) and ibrutinib in combination with rituximab (ORR 46% in PCYC-1121). The efficacy results are thus likely to translate into a clinical benefit in this patient group. However, some uncertainties remain and further clarification of the significance of protocol deviations, differences between local and central assessment of efficacy endpoints, baseline health status and the impact of different censoring approaches for PFS will be required to ensure that the observed positive effect on primary and secondary efficacy endpoints is robust.

The main risks include hyperglycaemia, hypertension, and non-infectious pneumonitis (NIP). Infections and neutropenia are also concerns, but these are common adverse events in haematology both due to the diseases and treatment. Both hyperglycaemia and hypertension demand close observation as well as treatment, the latter illustrated by the higher need for medication in the Copa/R arm compared to the Pbo/R arm. NIP is rare but may be fatal and awareness is crucial as not to mistake NIP for pneumonia.

The frequency of permanent discontinuations due to AEs was high and identical for combination and monotherapy, (31.3% and 32.4%). The tolerability profile and benefit/risk balance could potentially be improved with less intense start dosing. However, as less intense start dosing has not been prospectively tested, and the dose-response relationship or target exposure has not been characterised, it is unknown whether reduced initial doses, or dose intensity, would maintain similar clinical benefit.

Serious cases of diarrhoea and colitis have been reported that were considered related to copanlisib. More information about these cases have been requested, and the applicant should include a warning against these AEs in section 4.4 of the SmPC.

More information is also requested from the applicant on possible serious cutaneous AEs as serious cases of exfoliative skin reactions have been reported.

Monotherapy

An ORR of ~70% is encouraging from a clinical point of view. However, the small and heterogenous subgroup of relapsed-refractory MZL patients, the lack of a comparator together with large diversions in diagnosis and response assessment, the extent of major protocol deviations, and the fact that more than half of the patients in this subgroup ended treatment for other reasons than PD, does not allow the evaluation of the treatment's benefit/risk. In light of the limited data and the concerning safety profile of Aliqopa as monotherapy in patients with R/R MZL, updated efficacy (ORR, DOR, PFS and OS) and safety data from CHRONOS-1 are requested. The applicant is also invited to provide additional supportive data for the use of Aliqopa as monotherapy in iNHL/MZL.

The same risks as discussed for combination therapy are also applicable for monotherapy.

5.7.2. Balance of benefits and risks

Combination therapy

It is considered that the benefit outweighs the risks provided that satisfactory answers to the LoQs are given by the applicant.

Monotherapy

The benefit/risk for the MZL population is considered negative.

5.7.3. Additional considerations on the benefit-risk balance

Not applicable.

Conditional marketing authorisation

Not applicable.

Marketing authorisation under exceptional circumstances

Not applicable.

5.8. Conclusions

The overall B/R of Aliqopa in combination with rituximab for adult patients with previously treated marginal zone lymphoma could be considered positive subject to the LoQ.

The overall B/R of Aliqopa as monotherapy for the treatment of adult patients with marginal zone lymphoma who have received at least two prior therapies is considered negative.