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Cover page of the integrated protocol

An open-label non-randomized, phase 1 single dose study to evaluate the pharmacokinetics and safety of copanlisib in subjects with impaired hepatic or renal function in comparison to healthy subjects

Phase 1 study of copanlisib in hepatic or renal impairment

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

- **Original protocol,** Version 1.0, dated 17 Mar 2017
- **Amendment 1** (described in Section 15.1)
  forming integrated protocol Version 2.0, dated 28 Nov 2017

1. Title page

An open-label non-randomized, phase 1 single dose study to evaluate the pharmacokinetics and safety of copanlisib in subjects with impaired hepatic or renal function in comparison to healthy subjects

Phase 1 study of copanlisib in hepatic or renal impairment

Test drug:	Copanlisib / BAY 80-6946		
Study purpose:	To evaluate the effect of impaired hepatic or renal function on copanlisib		
Clinical study phase:	1	Date:	28 Nov 2017
Registration:	EudraCT: 2016-004561-51	Version no.:	2.0
Sponsor's study no.:	18041		
Sponsor:	Bayer AG, D-51368 Leverkusen, Germany		

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

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Signature of the sponsor's medically responsible person

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

Name: PPD Role: Pharmacodynamics Expert

Date: 28 Nov 2017 Signature: PPD

Signature of coordinating investigator

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

Name: PPD

Affiliation: PPD

Date: 28-Nov-2017 Signature:

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

In the protocol document, this page may remain unsigned.

2. Synopsis - amended

Title	An open-label non-randomized, phase 1 single dose study to evaluate the pharmacokinetics and safety of copanlisib in subjects with impaired hepatic or renal function in comparison to healthy subjects
Short title	Phase 1 study of copanlisib in hepatic or renal impairment
Clinical study phase	1
Study objective(s)[1]	The primary objective of this study is to • Investigate the pharmacokinetics (PK) of copanlisib following a single intravenous (i.v.) dose of 12 mg copanlisib in subjects with moderate hepatic (Child Pugh B), severe hepatic (Child Pugh C) or severe renal impairment compared with healthy subjects The secondary objectives of this study is to • Evaluate the PK of M-1 metabolite • Assess the safety and tolerability of copanlisib when administered to subjects with moderate hepatic, severe hepatic or severe renal impairment
Test drug	BAY 80-6946 (Copanlisib)
Name of active ingredient	BAY 80-6946 (Copanlisib)
Dose	12 mg
Route of administration	i.v.
Duration of treatment	Single dose
Indication	Not applicable.

[1] Objectives revised as subjects with severe hepatic impairment will be included into the study according to Amendment 1

Diagnosis and main criteria for inclusion /exclusion	All subjects • Male and female subjects between 18 and 80 years of age with a body mass index above 18.0 and below 34.0 kg / m² and a body weight of above or equal 50 kg. Healthy subjects • Healthy subjects as determined by absence of clinically significant deviation from normal in medical history, physical examination, vital signs, electrocardiograms, and clinical laboratory determinations. • eGFR ≥ 90 mL/min/1.73 m^2 (according to Modification of Diet in Renal Disease [MDRD] formula). Subjects with moderate hepatic impairment • Subjects with confirmed liver cirrhosis by at least one of the following criteria: histologically by prior liver biopsy showing cirrhosis, liver imaging (computer tomography, and/or ultrasound and/or magnetic resonance imaging scans, and/or fibroscan), or laparoscopy. • Child-Pugh Clinical Assessment Score 7 to 9. Subjects with severe hepatic impairment[2] • Subjects with confirmed liver cirrhosis by at least one of the following criteria: histologically by prior liver biopsy showing cirrhosis, liver imaging (computer tomography, and/or ultrasound and/or magnetic resonance imaging scans, and/or fibroscan), or laparoscopy. • Child-Pugh Clinical Assessment Score 10-15. Subjects with severe renal impairment • Subjects with severe renal impairment with an estimated glomerular filtration rate 15-29 mL/min/1.73 m^2 according to MDRD formula. • Subjects with stable renal disease: no significant change in renal function as evidenced by serum creatinine value within ±25% from the last determination, obtained within at least 3 months before study entry and the absence of the need to start dialysis in the next 3 months.
Study design	Multi-center, non-randomized, open-label, single-dose, parallel group, study consisting of 4 groups (control group: normal hepatic and renal function group, Group A: moderate hepatic impairment group, Group B: severe renal impairment group, Group C severe hepatic impairment group)[3]
Methodology	Pharmacokinetics, safety, and tolerability

[2] Inclusion criteria for subjects with severe hepatic impairment included as those subjects will be included into the study according to Amendment 1
[3] Study design revised as subjects with severe hepatic impairment will be included into the study according to Amendment 1

Type of control	Uncontrolled
Number of subjects[4]	Up to 44 evaluable male and female subjects with 8-22 evaluable subjects in the control group, 8 evaluable subjects each in the moderate hepatic impairment and in the severe renal impairment investigational group, and 6 evaluable subjects in the severe hepatic impairment investigational group. A minimum of 30 subjects (8/group except for severe hepatic impairment: 6) valid for PK of copanlisib (i.e., all blood samples for PK should be available up to 1 week [168 h]) will be required. Additional healthy subjects may be enrolled to achieve demographic matching between healthy and impaired groups until up to 22 healthy subjects valid for PK of copanlisib (i.e., up to 1 week [168 h]).
Primary variables	C_{max}, AUC and AUC(0-168) of copanlisib in plasma
Time point/frame of measurement for primary variables	Blood samples for PK will be collected before start of infusion as well as at 10 min and 1 h (end of infusion), 1.5, 2, 2.5, 3, 5, 8, 24, 48, 72, 96, 120 and 168 h after start of infusion.
Plan for statistical analysis	To investigate the primary objective of this study regarding hepatic and renal impairment, analysis of variance appropriate for a parallel design will be fitted to the natural logarithmic transformation of PK parameters (AUC(0-168), AUC and C_{max}) of copanlisib. The test/reference comparison ratio of geometric least-squares means and associated 90% confidence intervals (CIs) for each PK parameter in the moderate hepatic, severe hepatic[5] or severe renal impairment group versus the respectively matched healthy subject group will be calculated by exponentiation of the natural-log scale point estimate and the associated 90% CI.

[4] Number of subjects revised as subjects with severe hepatic impairment will be included into the study according to Amendment 1

[5] Included as subjects with severe hepatic impairment will be included into the study according to Amendment 1

Table of contents

Table of tables

Table of figures

List of abbreviations – amended

%AUC(t_{last}-∞)	percentage of AUC from the last data point > LLOQ to infinity
AE	adverse event
$A_{E,ur}$	amount excreted into urine from 0 to infinity
$A_{E,ur}$(0-24)	amount excreted into urine from 0 to 24h
AKT	protein kinase B
ALT	alanine aminotransferase
anti HCV	Hepatitis C virus antibody
Anti-HCV	hepatitis C virus antibodies
AP	alkaline phosphatase
AST	aspartate aminotransferase
AUC	area under the concentration vs. time curve from zero to infinity after single dose
AUC(0-168)	AUC from time 0 to 168h
$AUC(0\text{-}168)_u$	AUC of unbound drug (not protein-bound) from time 0 to 168h
AUC(0-t_{last})	AUC from time 0 to the last data point > LLOQ
AUC_u	area under the concentration vs. time curve of unbound drug (not protein-bound) from zero to infinity after single dose
BCRP	breast cancer resistance protein
BMI	body mass index: weight [kg] / (height [m])²
BPM	beats per minute
C-G	Cockcroft-Gault
CI	confidence interval
CK	creatine phosphokinase
CKD	Chronic Kidney Disease
CL	total body clearance of drug from measured matrix (volume/time) or (volume/time/body weight) calculated after intravenous administration
C_{last}	last observed concentration value above lower limit of quantitation
CLcr	creatinine clearance
CL_R	renal body clearance of drug
C_{max}	maximum observed drug concentration in measured matrix after single dose administration

$C_{max,u}$	maximum observed concentration of unbound drug (not protein-bound or free) in measured matrix after single dose administration
CR	complete response
CRF	case report form
CRO	contract research organization
CTCAE	common terminology criteria for AEs
CV	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction
DLBCL	diffuse large Bcell lymphoma
e.g.	exempli gratia (for example)
ECG	electrocardiogram
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EoI	End of infusion
ePRO	electronic subject-reported outcome
E2	estradiol[6]
EU	European Union
EudraCT	EU data repository for clinical trials
F	absolute bioavailability of drug administered via the extravascular route
FDA	Food and Drug Administration
FL	follicular lymphoma
FU	follow-up
GCP	good clinical practice
GGT	gamma glutamyl transpeptidase
GMP	good manufacturing practice
h	hour
HbA1c	glycated hemoglobin

[6] Presentation revised (in protocol Version 1.0 “estradiol” was shown in the left column and “E2” in the right column)

HBsAg	Hepatitis B surface antigene
HCT	hematopoietic cell transplant
HCV	hepatitis C virus
HIV	human immunodeficiency virus
i.e.	id est (that is)
i.v.	intravenous
IB	investigator's brochure
IC_{50}	half maximal inhibitory concentration
ICH	International Conference on Harmonization
IEC	independent ethics committee
INR	international normalized ratio (reagent-independent prothrombin ratio)
IRB	institutional review board
K/DOQI	Kidney Disease Outcomes Quality Initiative
kg	kilogram
L	liter
LDH	lactate dehydrogenase
LLOQ	lower limit of quantitation
LSLV	last subject last visit
M-1	metabolite M-1
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDRD	modification of diet in renal disease
MedDRA	medical dictionary for regulatory activities
mg	milligram
min	minute
mL	milliliter
mmHg	millimeter of mercury
msec	millisecond
mTOR	mammalian target of rapamycin
NCI	National Cancer Institute

NCT	number connection test
NHL	non-Hodgkin's lymphoma
nM	nanomolar
OTC	over-the-counter
PBPK	physiologically based pharmacokinetics
P-gp	permeability glycoprotein
pH	Pondus hydrogenii (log of the ion concentration)
PI3K	phosphatidylinositol 3-kinase
PIP3	phosphoinositol-3-phosphate
PK	pharmacokinetics
PKS	PK analysis set
popPK	population PK
PR	PR interval in ECG
PT	preferred term
QA	Quality Assurance
QC	quality control
QT	QT interval in ECG
QTcB	QT interval frequency-corrected according to Bazett's formula
QTcF	QT interval frequency-corrected according to Fridericia's formula
R_{end}	last time point for λ_z calculation
R_{start}	first time point for λ_z calculation
SAE	serious adverse event
SAF	safety analysis set
SAS	Statistical Analysis System
SD	standard deviation
sec	second
SNR	screening number
SoI	Start of infusion
SUSAR	suspected unexpected serious adverse reaction
T1	tumor invades lamina propria
$t_{1/2}$	half-life associated with the terminal slope

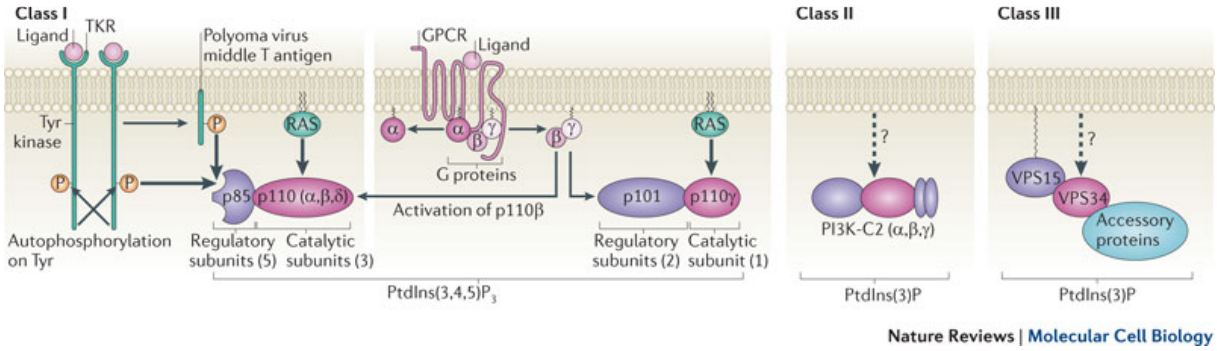
Ta	non-invasive tumor
TEAE	treatment-emergent adverse event
Tis	carcinoma in situ
t_{last}	time of last observed concentration value above lower limit of quantitation
t_{max}	time to reach C_{max} (in case of two identical C_{max} values, the first t_{max} will be used)
u	unbound (i.e. based on free / not protein bound concentration) (used as index for other parameters)
ULN	upper limit of norm (upper limit of normal laboratory values)
V_z	volume of distribution during terminal phase after intravascular administration
WBC	white blood cell (count)

3. Introduction - amended

Background

The phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway is one of the prominent pathways that promote cellular survival and is constitutively activated in many types of cancer. Class I PI3K receptor is downstream of most cancer associated tyrosine kinase growth factor receptors. PI3K inhibitors are expected to be effective not only in PI3K pathway-driven tumors but also in combination with other chemotherapy agents. Four PI3K isoforms (PI3Kα, PI3Kβ, PI3Kγ, and PI3Kδ) are categorized as class I enzymes (Figure 3-1) because they can use phosphatidylinositol-4, 5-bisphosphate as a substrate to generate phosphoinositol-3-phosphate (PIP3). Elevated PIP3 in cellular membranes drives several hallmarks of the cancer phenotype: cell proliferation, survival, metabolic reprogramming, and migration. PI3Kα and PI3Kβ are ubiquitous, while PI3Kγ and PI3Kδ are expressed mostly in the hematopoietic tissue.

Figure 3-1: The distinct classes of mammalian PI3Ks.
From Nature Reviews Molecular Cell Biology 13, 195-203, 2012



Copanlisib (BAY 80-6946[7], approved by the Food and Drug Administration [FDA] in September 2017[8]) is a novel, highly selective, -panclass- PI3K inhibitor with potent activity against both α and δ isoforms, with *in vitro* IC_{50} of 0.5 nM and 0.7 nM, respectively. This PI3K inhibitor is being developed for the treatment of advanced and refractory malignancies either as a single agent or in combination with other investigational agents. Copanlisib is the active ingredient (free base) of BAY 84-1236, the dihydrochloride salt, which for clinical use is formulated as an intravenous (i.v.) drug product solution.

[7] "BAY 806946" replaced by "BAY 80-6946" according to Amendment 1
[8] Included according to Amendment 1

Previous experience in humans

Safety and efficacy

Copanlisib is currently investigated in multiple trials enrolling cancer subjects. As of today, approximately 675 subjects with advanced cancer have been treated with copanlisib in eight different Phase 1 studies, three Phase 2 studies and three Phase 3 studies as a single agent or in combination with other agents [1].

As a single agent, 0.8 mg/kg [Study 12871 dose escalation: 0.1, 0.2, 0.4, 0.8 and 1.2 mg/kg] of copanlisib is the maximum tolerated dose in nondiabetic subjects given i.v. in a 3 weeks on/1 week off schedule (total dose should not exceed 65 mg, in order to control copanlisib exposure in overweight subjects).

The dose limiting toxicity was serious left ventricular systolic dysfunction following the copanlisib dose of 1.2 mg/kg (~ absolute dose 93mg) The recommended (Phase 2) dose of monotherapy with copanlisib is 60 mg given i.v. over 1 h weekly for the first 3 weeks (on Days 1, 8, and 15) of a 28-day cycle, followed by a 1-week break (3 weeks on/1 week off schedule) based on an evaluation of pharmacokinetic and clinical data from ongoing single agent studies.

Clinical antitumor activity was observed in subjects of the Phase 1 monotherapy Study 12871 and in the Phase 2 Study 16349A. In Study 12871 complete response (CR) as best overall response was achieved in 3 subjects (5.3%); partial response in 7 subjects (12.3%) and stable disease in 15 subjects (26.3%). In the Phase 2 Study 16349 (Part A) overall response rate was achieved in 25 subjects (32.9%).

When copanlisib was given as a single agent (Study 12871), the most common drugrelated adverse events of all grades that occurred in ≥20% of the 57 subjects (all cohorts) were: hyperglycemia (63.2%), nausea (36.8%), and hypertension (21.1%). In the phase 2 Study 16349(Part A), transient hyperglycemia (64.5%) and hypertension (60.5%) of maximum common terminology criteria for adverse events (CTCAE) Grade 3 were the most frequent adverse events (AEs) observed following administration of copanlisib. Further AEs occurring with an incidence of >20% observed in this study were: fatigue (51.3%), diarrhea (42.1%), neutrophil count decreased (35.5%), nausea (34.2%), anemia (30.3%), and oral mucositis (23.7%). In the mass balance study, 6 healthy subjects received a single dose of 12 mg copanlisib i.v. In this study, 3 out of the 6 subjects (50%) who received treatment had at least one TEAE. A total of 5 gastrointestinal TEAEs (MedDRA PT: abdominal pain, nausea, flatulence, frequent bowel movements and diarrhea) as well as one event each of myalgia and oropharyngeal pain were reported. Of the 6 subjects, 2 subjects (33.3%) experienced TEAEs which were assessed as being related to copanlisib. These TEAEs were all of grade 1, and included abdominal pain and diarrhea in 1 subject and nausea in another subject. No serious or fatal TEAEs were reported in this study and no subject prematurely discontinued the study participation due to an AE. No TEAEs of specific interest were defined in this study. No clinically relevant changes in laboratory values, vital signs and no abnormal findings in ECG were found.

Pharmacokinetics

Copanlisib demonstrated dose-proportional increases in C_{max} and area under the plasma concentration vs time curve (AUC) from time zero to 25 h (AUC(0-25)) over the dose range of 0.1 to 1.2 mg/kg (absolute dose range: 5 to 93 mg). AUC(0-25) was chosen to assess the dose-linearity because plasma concentrations can be measured during that interval in all subjects dosed at the lower dose to the higher dose level and the exposure represents more than 50% of the AUC covering the 1week dosing interval. Inter-subject variability in copanlisib C_{max} and AUC(0-25) at 0.8 mg/kg was moderate to high with a %CV of 64.4% for C_{max} and 38.4% for AUC(0-25) (Study 12871). Copanlisib has a large volume of distribution of 838 L (range: 437-2150 L) and a reversible-free fraction plasma protein binding of 15.8%.

Albumin was the main binding protein. The blood-to-plasma ratio was approximately 1.7. The geometric mean halflife ($t_{1/2}$) of the terminal phase of copanlisib elimination was 38.2 h (% coefficient of variation [%CV]: 42.5%, range: 16.9 - 72.7 h). The geometric mean population systemic clearance was 15.2 L/h (range: 7.85 - 27.9, %CV: 42.1%) (Study 12871). No accumulation or time-dependency in the PK of copanlisib was observed.

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

A human mass balance study in healthy subjects (Study 16353) was conducted with a single i.v. dose of 12 mg [^{14}C] copanlisib in six healthy subjects. Approximately 86% of the administered dose was recovered, with 64% in feces and 22% in urine within a collection interval of 20 to 34 days. Unchanged copanlisib represented approximately 30% of the administered dose in feces and 15% in urine, respectively. Metabolites resulting from oxidation metabolism accounted for 41% of the administered dose. Metabolite M-1 (morpholinone derivative) was the only relevant circulating metabolite in human plasma. The ratio M-1/total radioactivity was less than 5 % in human plasma. Conclusively, M-1 is considered as a minor metabolite according to ICH M3.

Copanlisib is excreted as unchanged compound and metabolites (about 50:50) in human. Metabolism of copanlisib is mediated by cytochrome P450 CYP3A4 (> 90%) and to a minor extent by CYP1A1 (< 10%). Therefore, a low DDI potential due to several clearance pathways is anticipated.

Further details can be found in the latest available version of the investigator's brochure (IB) [1], which contains comprehensive information on the study drug.

Rationale of the study

Liver infiltration in subjects with advanced malignancies including non-Hodgkin's lymphoma (NHL) is common, and various degree of hepatic dysfunction may occur in the later stages of malignancy [2].

Renal failure in cancer subjects is often multifactorial including renal parenchymal invasion, tumor lysis syndrome, glomerular diseases, chemotherapy associated thrombocytic microangiopathy or hematopoietic cell transplant (HCT)-associated renal failure [3].

Metabolism of copanlisib is primarily mediated by the CYP3A4 isozyme. Co-administration of copanlisib at 12 mg and 60 mg with the potent inhibitor of CYP3A4 itraconazole resulted in an increased copanlisib AUC by 1.41-fold and 1.53-fold, respectively, with no effect on the C_{max} at both doses [1]. A human mass balance study (Study 16353) indicates the elimination of copanlisib is primarily via feces with 64% in feces and 22% in urine within a collection interval of 20 to 34 days. Based on the population PK (popPK) analysis, mild hepatic impairment, mild and moderate renal impairment had no significant effect on copansilib clearance (CL). The PK of copanlisib has not been studied in moderate and severe hepatic impairment and severe renal impairment.

This study will evaluate the PK and safety of a single 12-mg dose of copanlisib in subjects with moderate or severe[9] hepatic impairment or severe renal impairment of copanlisib and in age-, gender-, and weight-matched healthy controls. The results of this study will provide guidance for drug labeling recommendations for copanlisib in these subjects.

Benefit-risk assessment

As of today approximately 675 subjects with advanced cancer have been treated with copanlisib (BAY 80-6946[10]) in eight different Phase 1 studies, three Phase 2 studies and three Phase 3 studies. In addition to these, a mass balance study was conducted in healthy subjects (Study 16353): 6 healthy male subjects were treated with a single i.v. administration of 12 mg [^{14}C] copanlisib. For this class of drug, the following AEs are expected based on its mechanism of action: hyperglycemia, hypertension, nausea, vomiting and diarrhea.

Even if the probability that these TEAEs occur is very low after a single dose of 12 mg copanlisib, the monitoring and treatment of adverse events will ensure that subjects will not be exposed to undue risk and the inclusion and exclusion criteria will ensure that subjects who might be predisposed to higher risk of drug-related TEAEs are either excluded or identified and treated with caution.

The toxicologic and safety-pharmacologic investigations identified the need for monitoring cardiovascular, hepatic, renal and metabolic functions during early studies in humans.

Practically, this will be addressed in this study through repeated physical examinations including check of vital signs, ECGs, monitoring of clinical chemistry laboratory including close monitoring of glucose especially within the next hours after the infusion.

Because of changes in the reproductive system and adverse effects on development, including embryo-lethality and teratogenicity, women of childbearing potential and men must agree to use adequate contraception from signing of the informed consent form until at least 3 months after dosing. The investigator or a designated associate is requested to advise the subject how to achieve an adequate contraception. Adequate contraception is defined for this study as any medically recommended method (or combination of methods) consistent with standard of care.

[9] Included as subjects with severe hepatic impairment will be included into the study according to Amendment 1
[10] "BAY 806946" replaced by "BAY 80-6946" according to Amendment 1

An adequate contraception includes a hormonal contraception with implants or combined oral, transdermal, or injectable contraceptives, certain intrauterine devices, bilateral tubal ligation or oophorectomy, hysterectomy, or vasectomy of the partner. In addition, the use of condoms for subjects or their partners is required unless the woman is postmenopausal or permanently sterilized (hysterectomy, bilateral oophorectomy).

No direct benefit is to be expected for the study subjects since they have no malignancies susceptible to respond to copanlisib. However, the benefit of this trial will be to get further information on copanlisib in regards to PK and safety in this specific population: copanlisib is supposed to be used for the treatment of subjects with advanced cancer who are at high risk of liver and/or renal injury due to the cancer dissemination and exposure to cytotoxic systemic anticancer therapy. Therefore, this information will be important for the safety of the cancer subjects with hepatic or renal impairment treated with this drug in the future (and hence will provide recommendation on dose adjustment, if needed). This is also required for approval of the drug by the health authorities.

4. Study objectives - amended[11]

The primary objective of this study is to

- Investigate the PK of copanlisib following a single i.v. dose of 12 mg copanlisib in subjects with moderate hepatic (Child Pugh B), severe hepatic (Child Pugh C) or severe renal impairment compared with healthy subjects

The secondary objective of this study is to

- Evaluate the PK of M-1 metabolite
- Assess the safety and tolerability of copanlisib when administered to subjects with moderate hepatic, severe hepatic or severe renal impairment

The exploratory objectives are to explore the relationship between PK and hepatic and renal function parameters:

- Hepatic: Relationship between PK parameters of copanlisib AUC(0-168), AUC, C_{max}, $AUC(0\text{-}168)_u$, AUC_u and $C_{max,u}$ and baseline hepatic function parameters (Child-Pugh Score, total bilirubin, prothrombin time, alpha 1-acid glycoprotein and albumin)
- Renal: Relationship between PK parameters of copanlisib AUC(0-168), AUC, C_{max}, $AUC(0\text{-}168)_u$, AUC_u and $C_{max,u}$ and eGFR (MDRD formula) and estimated creatinine clearance (Cockcroft-Gault formula)

[11] Objectives revised as subjects with severe hepatic impairment will be included into the study according to Amendment 1

5. Study design - amended

Design overview[12]

This will be a multi-center, non-randomized, open-label, single-dose, parallel group, study consisting of 4 groups. The effect of moderate hepatic impairment (Child Pugh B), severe hepatic impairment (Child Pugh C) and severe renal impairment on the PK of copanlisib and M-1 will be investigated. In total, up to 44 evaluable male and female subjects with 8-22 evaluable subjects in the control group, 8 evaluable subjects each in the moderate hepatic and severe renal impairment investigational group, and 6 evaluable subjects in the severe hepatic investigational group will participate in the study (Table 5-1). Each subject will be administered 12 mg of copanlisib (i.v. over 1 h).

Table 5-1: Groups - amended

Group	Description	Number of evaluable subjects
Control group	Normal hepatic and renal function group matched to the groups of hepatic and renal impairment	8-22
Group A	Moderate hepatic impairment group: Child-Pugh B (score 7-9) at the screening visit	8
Group B	Severe renal impairment group: eGFR 15-29 mL/min/1.73 m^2 at the screening visit based on the Modification of Diet in Renal Disease (MDRD) equation	8
Group C	Severe hepatic impairment group: Child-Pugh C (score 10-15) at the screening visit	6

The control group (normal hepatic and renal function) should match with the groups of hepatic and renal impairment. Matching criteria will be age, body weight, and gender. Mean age and body weight between the control group and the groups with hepatic and renal impairment should not vary by more than ±10 years and ±10 kg. Therefore, enrollment in the control group will remain open until the enrollment in the moderate and severe hepatic and severe renal impairment groups is complete and a sufficient number of matching controls have been achieved for comparison.

In all groups, the complete study is divided into several sections: screening, pre-dose, treatment period, end-of-treatment visit, and safety FU (telephone interview). Screening starts with the subject's signature on the informed consent form and ends with the eligibility for pre-dose assessment.

[12] Study design revised as subjects with severe hepatic impairment will be included into the study according to Amendment 1

The in- / exclusion criteria will be finally checked after the results of the safety laboratory from the morning of Day -1 are available (evening of Day -1/morning of the dosing day).[13] During the treatment phase the study objectives will be followed, and the related measures will be performed. The subjects will be monitored for adverse events and concomitant medication. All post-treatment examinations will be conducted during end-of-treatment visit and safety FUs (for details, see Section 16.1, where the study flowcharts are presented).

Starting from approximately 24 h before until 48 h after dosing (i.e. start of infusion), the subjects will stay at the study site (in-house phase of 4 days).

The total duration of the study will be approximately 7 weeks per subject.

For time of measurements, blood samplings, and activities see study flow chart in Section 16.1.

Primary variables

- $C_{max,}$ AUC and AUC(0-168) of copanlisib in plasma

Secondary variables:

- Number of subjects with study-drug-related treatment-emergent adverse event (TEAE)

Justification of the design[14]

This study will investigate the PK of copanlisib and M-1 after administration of 12 mg of copanlisib i.v. over 1 h to subjects with moderate hepatic impairment, with severe hepatic impairment or subjects with severe renal impairment compared to healthy subjects. The choice of the trial design was made based on the following:

- The PK measurements are the primary focuses of the study, therefore a non-randomized, open-label, parallel group design with 4 groups is considered adequate.
- The study will be carried out in accordance with FDA guidance [4][5].
- Enrolling only individuals of an age range similar to the target subject population will provide a consistent and homogeneous study population.

For study objectives please see Section 4.

For justification of study population, see Section 6.3.

For level of blinding, see Section 7.5.

For selection of doses, see Section 7.4.1.

For handling of missing data, see Section 11.4.

[13] Time point of final check of inclusion and exclusion criteria revised according to Amendment 1 (protocol Version 1.0 specified in the evening prior to the administration of the study medication)

[14] Justification of the design revised as subjects with severe hepatic impairment will be included into the study according to Amendment 1

End of study

The end of the study according to the EU Clinical Trial Directive will be reached when the last visit of the last subject (LSLV) for all centers in the respective country has occurred.

As for this study, important data will be collected after last subject last visit (LSLV), the end of the study as a whole will be the date when the clean database is available.

Primary completion

The primary completion event for this study is LSLV.

6. Study population

6.1 Inclusion criteria

Subjects must fulfill all of the following criteria before receiving the study medication:

6.1.1 All subjects

1. Written informed consent obtained, dated and signed prior to any screening procedures
2. Male or female subjects aged 18 to 80 years at the first screening visit
3. Women must have a negative pregnancy test (in blood or urine) within 7 days prior to the dose of study drug or be surgically or biologically sterile or postmenopausal. Postmenopausal women are defined as:
   - Age >50 years with amenorrhea for at least 12 months or
   - Age ≤50 years with 6 months of spontaneous amenorrhea and follicle stimulating hormone level within postmenopausal range (>40 mI U/mL) or
   - Permanently sterilized women (hysterectomy, bilateral oophorectomy)
4. Women and men of reproductive potential must agree to use adequate contraception when sexually active. This applies for the time period between signing of the informed consent form and at least 3 months after administration of the study medication. The investigator or a designated associate is requested to advise the subject how to achieve an adequate contraception. Adequate contraception is defined for this study as any medically recommended method (or combination of methods) consistent with standard of care. An adequate contraception includes a hormonal contraception with implants or combined oral, transdermal, or injectable contraceptives, certain intrauterine devices, bilateral tubal ligation or oophorectomy, hysterectomy, or vasectomy of the partner. In addition, the use of condoms for subjects or their partners is required unless the woman is postmenopausal or permanently sterilized (hysterectomy, bilateral oophorectomy).
5. Men agree to refrain from sperm donation during the whole study (starting after informed consent) and for at least 3 months after the end of treatment with copanlisib.

6. Body Mass Index (BMI): above 18.0 and below 34.0 kg / m² with a body weight of above or equal 50 kg at the first screening visit.
7. Subject must be willing to comply with dietary and fluid restriction from Day -1 to the end-of-treatment visit.
8. Subjects must have venous access sufficient to allow blood sampling as required by the protocol.
9. Subject must be willing to undergo multiple blood draws as required by the protocol.
10. Results of alcohol tests are negative at screening and on Day -1.

6.1.2 Subjects in the control group: healthy subjects

11. Healthy subjects as determined by absence of clinically significant deviation from normal in medical history, physical examination, vital signs, electrocardiograms, and clinical laboratory determinations.
12. eGFR ≥ 90 mL/min/1.73 m^2 (according to MDRD formula, see Section 16.5).
13. Adequate liver function as defined by:
    - Total bilirubin and international normalized ratio (INR) lower or equal to 1.5x upper limit of normal (≤ 1.5 ULN)
    - Alkaline phosphatase (AP) ≤1.5 ULN, alanine aminotransferase (ALT) ≤1.5 ULN, aspartate aminotransferase (AST) ≤1.5 ULN

6.1.3 Subjects in Group A: moderate hepatic impairment (Child-Pugh B)

14. Subjects with confirmed liver cirrhosis by at least one of the following criteria:
    - Histologically by prior liver biopsy showing cirrhosis.
    - Liver imaging (computer tomography, and/or ultrasound and/or magnetic resonance imaging scans, and/or fibroscan).
    - Laparoscopy.
15. Child-Pugh Clinical Assessment Score 7 to 9 at screening (see Section 16.3).
16. Subjects with stable liver disease: no acute decompensation (hemorrhage, encephalopathy, new onset ascites) in the last 2 months.
17. Subjects with active Hepatitis B or hepatitis C virus (HCV) can be included into the study but only in stable condition without ongoing or indicator of immediate antiviral treatment.
18. History of alcohol abuse is permissible providing that the results of alcohol test are negative at screening and on Day -1.

6.1.4 Subjects in Group B: severe renal impairment

19. Subjects with severe renal impairment defined as an eGFR 15 - 29 mL/min/1.73 m^2 (according to MDRD formula, see Section 16.5)

20. Subjects with stable renal disease: no significant change in renal function as evidenced by serum creatinine value within ±25% from the last determination, obtained within at least 3 months before study entry and the absence of the need to start dialysis in the next 3 months.
21. Stable treatment regimen for renal impairment for at least 14 days prior to treatment start. Diuretics are allowed when needed.

6.1.5 Subjects in Group C: severe hepatic impairment - amended[15]

22. Subjects with confirmed liver cirrhosis by at least one of the following criteria:
    - Histologically by prior liver biopsy showing cirrhosis.
    - Liver imaging (computer tomography, and/or ultrasound and/or magnetic resonance imaging scans, and/or fibroscan).
    - Laparoscopy.
23. Child-Pugh Clinical Assessment Score 10 to 15 at screening (see Section 16.3). For subjects with hepatic encephalopathy, the condition does not, in the investigator's opinion, interfere with the participant's ability to provide an appropriate informed consent.
24. Subjects with active Hepatitis B or Hepatitis C virus (HCV) can be included into the study but only in stable condition without ongoing or indicator of immediate antiviral treatment.
25. History of alcohol abuse is permissible providing that the results of alcohol test are negative at screening and on Day -1.

6.2 Exclusion criteria

Subjects are to be excluded from the study if they display any of the following criteria:

6.2.1 All subjects - amended

Medical and surgical history

1. Active coronary artery disease or myocardial infarction within 6 months of study entry; unstable angina (angina symptoms at rest) or new-onset angina or congestive heart failure of grade III-IV according to New York Heart Association (NYHA) within 3 months of study entry.
2. Immuno-compromised subjects including known history/seropositivity of human immunodeficiency virus (HIV).
3. Other concurrent severe and/or uncontrolled medical conditions (e.g. current diagnosis of type 1 or type 2 diabetes mellitus with HbA1c >8.5%) that could cause unacceptable safety risks or compromise compliance with protocol.

[15] Inclusion criteria for subjects with severe hepatic impairment included as those subjects will be included into the study according to Amendment 1

4. Previous or concurrent history of malignancies within 5 years prior to study treatment except for curatively treated cervical cancer *in situ*, non-melanoma skin cancer, superficial bladder cancer (Ta [non-invasive tumor], Tis [carcinoma *in situ*] and T1 [tumor invades lamina propria]) as well as localized prostate cancer.
5. Known or suspected allergy or hypersensitivity to copanlisib.
6. Significant illness within 1 week prior to dosing (e.g. fever).
7. Known severe allergies (e.g. allergies to more than 3 allergens, allergies affecting the lower respiratory tract – allergic asthma, allergies requiring therapy with corticosteroids).
8. Uncontrolled hypertension despite optimal medical management (per investigator's assessment).
9. Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis or pulmonary embolism within 6 months before the start of study medication.
10. Active, clinically serious infections.
11. History or concurrent condition of interstitial lung disease of any severity and/or severely impaired lung functions (as judged by the investigator).
12. Subjects with evidence or history of bleeding diathesis. Any hemorrhage or moderate bleeding event within 4 weeks of start of study medication.

Medication, drug use and special behavioral pattern

13. Administration of strong CYP3A4 inhibitors or inducers within 2 weeks prior to dosing until 7 days after dosing (A list of these medications can be found in Section 16.8 of the protocol. However, this list may not be comprehensive); the label of the respective co-medications should therefore be checked).
14. Use of immunosuppressive drugs.
15. Administration of medications that prolong the QT interval within 2 weeks prior to dosing and during the study (A list of agents that prolong the QT interval can be found at https://crediblemeds.org/healthcare-providers/. However, this list may not be comprehensive); the label of the respective co-medications should therefore be checked).
16. Intake of foods or beverages containing grapefruit, pomelo or Seville oranges within 7 days before study drug administration and 7 days thereafter. The juices and products containing these fruits must also be avoided.
17. Regular daily consumption of more than 1 L of methylxanthine-containing beverages.
18. Unable to abstain from alcohol and methylxanthine-containing beverages or food (coffee, tea, cola, chocolate, "powerdrinks") from 48 h prior to dosing of study drug until Day 7.
19. Subjects with known drug abuse within 1 month prior to dosing or evidence of such abuse as indicated by the laboratory assays conducted during the screening or baseline evaluations.
20. Donation or loss of 400 mL or more of blood within 4 weeks prior to dosing.

Electrocardiogram (ECG)

21. Abnormal finding in the 12-lead electrocardiogram (ECG), such as QTcF (Fridericia correction) interval over 500 msec, or any other finding that increases the risk associated with study participation, as judged by the investigator.

Laboratory examination

22. Neutrophils <1500/µL[16] at inclusion.
23. Positive urine drug screening at screening and Day -1.

Other exclusion criteria

24. Previous assignment to treatment during this study.
25. Close affiliation with the investigational site; e.g. a close relative of the investigator, dependent person (e.g. employee or student of the investigational site).
26. Criteria which in the opinion of the investigator preclude participation for scientific reasons, for reasons of compliance, or for reasons of the subject's safety.
27. Inability to understand the protocol requirements, instructions and study related restrictions, the nature, scope, and possible consequences of the study.
28. Subject is in custody by order of an authority or a court of law.
29. Use of investigational drugs (i.e. participation in any clinical investigation) within 30 days prior to dosing or longer if required by local regulation, or within 5-half-lives of the investigational agent taken (whichever is longer).

6.2.2 Subjects in the control group: healthy subjects

Medical and surgical history

30. Incompletely cured pre-existing diseases for which it can be assumed that the absorption, distribution, metabolism, elimination, and effects of the study drugs will not be normal.
31. A history of relevant diseases of vital organs, the central nervous system, or other organs.

Medication, drug use and special behavioral pattern

32. Regular use of recreational drugs, e.g. carnitin products, anabolics, high dose vitamins.
33. Use of any prescription drug or over-the-counter (OTC) medication within 2 weeks or 5-half-lives prior to dosing (whichever is longer), except for acetaminophen within 7 days before dosing.

[16] "<1000 µL" replaced by "<1500 µL" according to Amendment 1

Physical examination

34. Clinically relevant findings in the physical examination as judged by the Investigator.

Laboratory examination

35. Positive results for hepatitis B virus surface antigen (HBsAg), hepatitis C virus antibodies (anti-HCV).
36. Clinically relevant deviations of the screened laboratory parameters from reference ranges at screening or before study drug administration according to the opinion of the investigator.

6.2.3 Subjects in Group A: moderate hepatic impairment (Child-Pugh B)

Medical and surgical history

37. Symptoms or history of encephalopathy (Grade III or worse, time needed in the number connection test exceeds 80 sec) within 2 months prior to dosing. (For number connection test, please see Section 16.7).
38. Clinical evidence of severe ascites more than 6 L by ultrasound.
39. Subjects with primary and secondary biliary cirrhosis.
40. Subjects with sclerosing cholangitis.
41. Failure of any other major organ other than the liver; severe infection, or any clinically significant illness within 4 weeks prior to study drug administration.
42. Renal failure with an eGFR <35 mL/min/1.73 m^2 (according to MDRD formula, see Section 16.5).

Medication, drug use and special behavioral pattern

43. Subjects with a change of their chronic medication less than 4 weeks prior to study drug administration.

Laboratory examination

44. INR >2.5 or prothrombin time more than 6 sec prolonged.
45. Any evidence of progressive liver disease (within the last 4 weeks) as indicated by liver transaminases (>4 x ULN), alkaline phosphatase (>4 x ULN), and gamma glutamyl transpeptidase (GGT) (>4 x ULN) (an isolated elevation of GGT above 4 times ULN will not exclude the subject).
46. Serum albumin <20 g/L.
47. Hemoglobin <8 g/dL.
48. Platelet count <50 x 10^9/L.
49. Clinically relevant deviations of the other screened laboratory parameters from reference ranges at screening or before study drug administration according to the opinion of the investigator.

6.2.4 Subjects in Group B: severe renal impairment

Medical and surgical history

50. Acute renal failure at study entry.
51. Acute nephritis at study entry.
52. Nephrotic syndrome.
53. Acute hepatorenal syndrome.
54. History of renal transplant.
55. Failure of any other major organ other than the kidney.
56. Severe infection or any clinically significant illness within 4 weeks prior to study drug administration.

Medication, drug use and special behavioral pattern

57. Imminent renal replacement therapy (i.e., during the trial period).

Laboratory examination

58. Positive results for HBsAg, anti-HCV.
59. Platelet count <50 x 10^9/L.
60. Hemoglobin < 8 g/dL.
61. Serum albumin < 20 g/L.
62. Aspartate aminotransferase (AST) or ALT in conjunction with GGT ≥4 times the ULN (an isolated elevation of GGT above 4 times ULN will not exclude the subject).
63. Clinically relevant deviations of the other screened laboratory parameters from reference ranges at screening or before study drug administration according to the opinion of the investigator.

6.2.5 Subjects in Group C: severe hepatic impairment - amended[17]

Medical and surgical history

64. Has active encephalopathy Grade III or IV (time needed in the number connection test at screening or admission exceeds 80 sec) within 2 months prior to dosing. (For number connection test, please see Section 16.7).
65. Subjects with sclerosing cholangitis.
66. Failure of any other major organ other than the liver; severe infection, or any clinically significant illness within 4 weeks prior to study drug administration.

[17] Exclusion criteria for subjects with severe hepatic impairment included as those subjects will be included into the study according to Amendment 1

67. Renal failure with an eGFR <35 mL/min/1.73 m^2 (according to MDRD formula, see Section 16.5).
68. Clinical evidence of severe ascites more than 6 L by ultrasound.
69. Esophageal variceal bleeding within 3 months prior to dosing.

Medication, drug use and special behavioral pattern

70. Subjects with a change of their chronic medication less than 4 weeks prior to study drug administration.

Laboratory examination

71. Any evidence of progressive liver disease (within the last 4 weeks) as indicated by liver transaminases (>4 x ULN), alkaline phosphatase (>4 x ULN), and GGT (>4 x ULN) (an isolated elevation of GGT above 4 times ULN will not exclude the subject).
72. Serum albumin <20 g/L.
73. Hemoglobin <8 g/dL.
74. Platelet count <50 x 10^9/L.

6.3 Justification of selection criteria

The selection criteria are chosen to ensure that subjects with specific risks for administration of the study drugs and/ or subjects with conditions which may have an impact on the aims of the study are excluded.

Justification of gender selection

Male and female subjects will be included in so far as they meet all the criteria for inclusion and do not fulfill any of those for exclusion. No sex-specific effects of the treatment are anticipated.

6.4 Withdrawal of subjects from study

6.4.1 Withdrawal

Withdrawal criteria

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

- At their own request or at the request of their legally acceptable representative. At any time during the study and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- If, in the investigator's opinion, continuation of the study would be harmful to the subject's well-being
- At the specific request of the sponsor and in liaison with the investigator (e.g. obvious non-compliance, safety concerns).

- Violation of in- / exclusion criteria: if the subject develops conditions which would have prevented his / her entry into the study according to the in- / exclusion criteria, he / she must be withdrawn immediately if safety is concerned; in other cases, the investigator will decide whether there is a conflict with the study objectives.

Depending on the time point of withdrawal, a withdrawn subject is referred to as either "screening failure" or "dropout" as specified below:

Screening failure

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

For those subjects who underwent screening procedures and cannot meet eligibility within the 28day screening period, screening procedures may be repeated within the indicated time window before the first dose in case the medical conditions preventing the subject's initial attempt to participate have changed. Re-screening must be performed within 28 days of the initial screening and with approval from the sponsor.

In this case, the investigator has to ensure that the repeated general screening procedures do not expose the subject to an unjustifiable health risk. In addition, for general re-screening, the subject has to be re-consented and sign the informed consent form, even if it was not changed after the subject's previous general screening.

Dropout

A subject who discontinues study participation prematurely for any reason is defined as a "dropout" if the subject has already been administered the study drug.

General procedures

In all cases, the reason for withdrawal must be recorded in the CRF and in the subject's medical records.

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

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

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

6.4.2 Replacement - amended

Subjects who drop out may be replaced to obtain a minimum of 30 subjects (8/group except for severe hepatic impairment: 6) valid for PK of copanlisib (i.e., all blood samples for PK should be available up to 1 week [168 h]). Additional healthy subjects may be enrolled to achieve demographic matching between healthy and impaired groups in up to 22 healthy subjects valid for PK of copanlisib (i.e., up to 1 week [168 h]).[18]

6.5 Subject identification - amended

At the beginning of screening every subject is given a screening number (9 digit number consisting of: Digits 1 to 5 = Unique center number Digits 6 to 9 = Current subject number within the center).

In the morning of the dosing day before start of infusion and after assessing the pre-dose blood pressure and glucose values[19], subjects who meet the entry criteria will be sequentially assigned to a unique number in ascending order (treatment number).

7. Treatments

7.1 Treatments to be administered - amended

All eligible subjects will receive 12 mg of copanlisib i.v. over 1 h.

The treatments to be administered during the study are displayed in Table 7-1.

Table 7-1: Treatments administered - amended[20]

Group	Dose of copanlisib / route	Frequency of administration	No. of evaluable subjects
Control group (healthy subjects)	12 mg i.v. over 1 h	Single dose on Day 1	8-22
Group A (moderate hepatic impairment group)	12 mg i.v. over 1 h	Single dose on Day 1	8
Group B (severe renal impairment group)	12 mg i.v. over 1 h	Single dose on Day 1	8
Group C (severe hepatic impairment group)	12 mg i.v. over 1 h	Single dose on Day 1	6

The cumulative dose per subject is 12 mg copanlisib.

[18] Replacement strategy revised as subjects with severe hepatic impairment will be included into the study according to Amendment 1

[19] Timepoint of treatment assignment revised according to Amendment 1 (protocol Version 1.0 specified in the evening of day -1 after final check of inclusion and exclusion criteria)

[20] Table revised as subjects with severe hepatic impairment will be included into the study and to clarify that in Group B subjects with severe renal impairment will be included according to Amendment 1

7.2 Identity of study treatment – amended

The details of the study drug are presented in Table 7-2.

Table 7-2: Identity of copanlisib – amended[21]

Chemical name	2amino-N[7methoxy-8(3morpholin-4ylpropoxy)-2,3dihydroimidazo [1,2-c]quinazolin-5yl]pyrimidine-5carboxamide dihydrochloride
Substance code number	BAY 80-6946 (free base)
Appearance	white to slightly yellowish lyophilisate
Formulation	Freeze-dried product containing 78.8 mg BAY 84-1236 (= Copanlisib dihydrochloride; equivalent to 68.4 mg copanlisib, free base, BAY 80-6946) in a 6 mL injection vial
Composition	Copanlisib dihydrochloride, citric acid, mannitol, sodium hydroxide
Type of primary packaging	Glass vial for injections (6 mL)

Reconstitution and dilution should be performed under laminar air flow conditions and according to separate handling instructions.

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

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

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

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

7.3 Treatment assignment - amended

Before administration of the study drug (after assessing the pre-dose blood pressure and glucose values), subjects who meet the entry criteria will be sequentially assigned to a unique number in ascending order ("treatment number"). All subjects will receive the same treatment.

Subjects will be assigned to the following treatment numbers:[22]

- Subjects with moderate hepatic impairment (site PPD

[21] "BAY 806946" replaced by "BAY 80-6946" according to Amendment 1

[22] Treatment numbers revised as subjects with severe hepatic impairment will be included into the study and as a third study center will recruit subjects according to Amendment 1

- Subjects with moderate hepatic impairment (site PPD
- Subjects with severe renal impairment (site PPD
- Subjects with severe renal impairment (site PPD
- Subjects with severe hepatic impairment (site PPD
- Subjects with severe hepatic impairment (site PPD
- Subjects with severe hepatic impairment (site PPD
- Control subjects (site PPD
- Control subjects (site PPD
- Control subjects (site PPD

Additional numbers will be used in case of replacements being needed; the replacing participant will receive the original subject's treatment number PPD (site PPD or PPD (site PPD or PPD (site PPD

7.4 Dosage and administration

Regarding the selection of dose in this study, refer to Section 7.4.1.

Regarding dose(s), route / mode of administration, formulation(s) and duration of treatment(s), refer to Table 7-1 and Table 7-2.

7.4.1 Selection of doses in the study - amended

Each subject will be given 12 mg of copanlisib (i.v. over 1 h).

Rationale for copanlisib 12 mg dose

The 12 mg dose has been chosen (not the Recommended Phase II Dose of 60 mg) to assess the effects of moderate hepatic, severe hepatic or severe renal impairment on copanlisib PK. The rationale for this is the observed dose-linear PK of copanlisib and also the favorable safety profile of 12 mg copanlisib dose in healthy subjects (Human mass balance study 16353). Therefore, the 12 mg dose can be used across all four groups in this study. The results from a clinical study evaluating the effect of the strong CYP3A4 inhibitor itraconazole (as a perpetrator) on copanlisib (as a victim) at 12 mg and 60 mg showed the effect of itraconazole was independent of the dose suggesting the use of 12 mg dose can be predictive of results at higher doses given that the PK of copanlisib is linear. [23]

The popPK data for copanlisib demonstrates no statistically significant difference in copanlisib clearance in patients with mild hepatic impairment (total bilirubin [TB] ≤ upper limit of normal [ULN] and aspartate aminotransferase [AST] > ULN, or TB < 1-1.5 x ULN and any AST, N = 47) and patients with normal liver function (TB ≤ ULN and AST ≤ ULN, N = 250).

[23] Paragraph revised as subjects with severe hepatic impairment will be included into the study according to Amendment 1

Further, the popPK data for copanlisib in patients with renal impairment demonstrates no statistically significant difference in copanlisib clearance in patients with mild (CLcr = 60-90 mL/min, N = 112) or moderate renal impairment (CLcr = 30-60 mL/min, N = 58) and patients with normal renal function (CLcr ≥ 90 mL/min, N = 125).

Based on the above discussion, the study will be conducted in all subjects at 12 mg dose.

7.4.2 Selection and timing of dose for each subject

Each of the subjects will receive one single dose of 12 mg of copanlisib i.v. over 1 h.

In case of a blood pressure value of ≥ 150/90 mmHg before the planned time point of dosing administration will be delayed until recovery to < 150/90 mmHg. Instructions for blood pressure measurements are given in Section 9.6.3.

Antihypertensive medication may be given to control arterial hypertension. Dosing can proceed on the scheduled day if at least 2 consecutive blood pressure values measured at 5 to 10 min interval prior to copanlisib dosing show BP <150/90 mmHg. Otherwise, dosing must be delayed. Guidance for the treatment of arterial hypertension is given in Section 9.6.1.7.2.

Subject's fasting pre-dose glucose level should be ≤125 mg/dL (non-diabetic subjects) or <160 mg/dL (diabetic subjects) before copanlisib infusion (see Section 3, benefit-risk assessment). Guidance for the treatment of transient glucose increase is given in Section 9.6.1.7.1.

Food and drink on the day with dosing will be standardized. For details on meals, see Section 9.2.6.2.

7.5 Blinding

This study will be performed in a non-blinded design, as the primary objective of this trial is the investigation of PK and because the PK results will neither be affected by the subjects nor by the investigator(s).

7.6 Drug logistics and accountability - amended

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

[24] Third study site included according to Amendment 1

Receipt, distribution, return and destruction (if any) of the study drug must be properly documented according to the sponsor's agreed and specified procedures.

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

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

7.7 Treatment compliance

The administration of the study medication will be done by a member of the investigator's team. This person will ascertain and document that the subject receives the treatment as planned.

Further information about the subject's treatment compliance can be derived from drug concentration measurements in plasma and urine.

8. Non-study therapy

8.1 Prior and concomitant therapy

All prior medication used within 6 weeks before treatment will be documented (medication history). Copanlisib is metabolized by CYP3A4. Therefore, concomitant use of strong inhibitors of CYP3A4 or strong inducers of CYP3A4 is not permitted from 14 days before the administration of study drug until 7 days after dosing (end of blood sampling period for PK). Refer to Section 6.2 for medication representing exclusion criteria. A list of these medications can be found in Section 16.8 of the protocol.

Use of medication for concomitant therapy is not planned. Especially the use of medication that may have an impact on the study objectives is not permitted. This comprises any medication (including herbal remedies or food supplements), which could affect the pharmacokinetics and / or pharmacodynamics of the study drug. The subjects will be instructed to report any concomitant medication used to the investigator. All concomitant medication will be documented.

The subjects with hepatic and renal impairment will be allowed to continue their medications a long as they are in line with the enrollment criteria.

8.2 Post-study therapy

Subjects will not receive post-study medication by the sponsor. Subjects with renal and hepatic impairment will continue their treatment for their disease as before.

9. Procedures and variables

9.1 Tabular schedule of evaluations

See study flow chart in Section 16.1.

Regarding protocol deviations, the processes and responsibilities defined by the sponsor will be followed. Respective details (e.g. identification and classification of protocol deviations) are described separately.

9.2 Visit description

If not stated otherwise, the measures / actions listed in the following Sections 9.2.1 to 9.2.5 will be performed by or under the supervision of an investigator.

9.2.1 Screening visit - amended

Due to the fact that not all subjects may fulfill the inclusion / exclusion criteria, a higher number of subjects than needed to be valid for the evaluation of the study, will be asked to participate in the screening examinations.

A subject information session will be held. If the (first) screening procedures already start on the same day (same date) as the subject signs the informed consent form, the time of the subject's signature must be recorded in the source documents.

Note: No screening procedures may be performed unless written informed consent has been obtained.

After

- Obtaining the subject's signature on the consent form

the below listed screening procedures will be performed and the respective results will be assessed within 28 days prior to treatment.

- Allocation of screening number, SNR (see Section 6.5)
- Demographic data collection
- Weight, height, body mass index
- Medical and surgical history
- Questioning for special behavior (e.g. smoking history, alcohol consumption, dietary habits)
- Participation in previous clinical studies
- Current and previous medication (relevant medication history)
- Adverse events before start of treatment (e.g. signs / symptoms of the subject; results of physical examination)
- Physical examination (complete)
- Vital signs: blood pressure and pulse rate after resting for at least 10 min in supine[25] position and body temperature

[25] Corrected to supine position according to Amendment 1 (protocol Version 1.0 specified sitting position)

- 12-lead ECG after resting for at least 10 min in a supine position
- Urine drug screen and alcohol breath test (see Section 16.2 for details)
- Blood and urine sample (fasting) for the laboratory examinations described in Section 16.2
- Virology examination (i.e. HIV, hepatitis B and C virus)
- For hepatic impaired subjects: Child Pugh Scoring and number connection test
- For all subjects: eGFR calculation according to MDRD

Based on the information obtained from the above assessments, i.e. once all results (including laboratory data) are available, the subject's eligibility will be decided upon:

- Eligibility check

No subject may start study treatment unless adherence to all selection criteria as given in Section 6.1 and Section 6.2 is established.

In case of abnormal results caused by intercurrent diseases, short-term treatable conditions or other temporary health disorders (e.g. acute infection, iron deficiency, blood pressure outside defined range), the investigator may decide to repeat the respective screening parameter(s). As a rule, up to two repetitions are acceptable.

As soon as fulfillment of all criteria is confirmed, the subject is included into the trial. In case all subjects are equally qualified, decision will be made casting lots. In case of not being included in the trial the data of the additional subjects will not be listed.

9.2.2 Pre-dose (Study Day -1, relative time: day -01)

The subjects will arrive at the study site in the morning of Study Day -1 (relative time: day -01) (start of in-house period).

The following measures/ actions will be carried out:

- Medical history (update)
- Pregnancy test in blood or urine for women with reproductive potential (including women whose partners are sterilized) (within 7 days prior to dosing)
- Complete physical examination
- Urine drug screen
- Alcohol breath test;
  the subjects will be instructed to continue abstaining from alcohol consumption until Day 7
- Urine (Urinalysis) and blood samples (chemistry, hematology and coagulation) in fasted state for safety laboratory examinations. Results of laboratory tests will be checked in the afternoon /evening.
- 12-lead ECG after at least 10 min rest in supine position
- Vital signs: Blood pressure and pulse rate after resting in supine position for at least 10 min and body temperature

- Open questioning for / documentation of AEs and previous/concomitant medication (update)
- Reminder about the restrictions imposed on the subjects
- Final check of applicable inclusion/ exclusion criteria
- Start overnight fasting for 8 h before the procedures for the dosing start (drinking of water and beverages with artificial sweeteners is allowed)

9.2.3 Randomization

Not applicable. For allocation of treatment number, refer to Section 7.3.

9.2.4 Treatment period

In case more than one measure/ action to be performed coincide at a given time point, the following order will be adhered to: ECG, blood pressure / pulse rate, blood sample for PK at defined time points, blood sample for safety.

Any meal will be served after the study-related measures / actions for a given time point have been completed.

9.2.4.1 Dosing and profile day (Study Day 1, relative time: day 00) - amended

The following measures / actions will be performed at the time points given in the study flow chart in Section 16.1.

- Fasting to be continued until the capillary glucose pre-dose is performed (drinking of water and beverages with artificial sweeteners is allowed)
- Abbreviated physical examination
- After a bed rest for at least 10 min, the following baseline measurements will be carried out: 12-lead ECG, vital signs (blood pressure/pulse rate, body temperature), blood sample (fasting capillary blood glucose, PK[26])
- Open questioning for / documentation of AEs and previous/concomitant medication (update)
- Low glycemic breakfast at 1.5 h prior to start of the infusion (for details, see Section 9.2.6.2)
- BP will be measured at least 2 times with 5-10 min intervals prior to the administration of the study drug until 2 consecutive values are <150/90 mmHg (see Sections 7.4 and 9.6.3 for further details)
- Study drug administration i.v. (approximately 8 a.m. for the first subject) (see Section 7.4.2)

[26] "Protein binding assessment" deleted before dosing according to Amendment 1

- Throughout the day until 12 h p.a.:
  - Capillary glucose 1h after start of copanlisib infusion (end of infusion), 1, 2, 3,[27] 6, 8 h after start of infusion, further capillary glucose if necessary
  - Further capillary glucose assessment at the discretion of the investigator (based of previous blood glucose levels)
  - Vital signs (blood pressure/pulse rate, body temperature) after a least 10 min in supine position at 1 h after start of copanlisib infusion (end of infusion) and at 6 h after start of infusion
  - 12-lead ECG after a least 10 min in supine position at 1 h after start of copanlisib infusion (end of infusion) and at 6 h after start of infusion
  - blood sampling for pharmacokinetics at 10 min after start of copanlisib infusion, at 1 h after start of copanlisib infusion (end of infusion) and at 1.5, 2, 2.5, 3, 5, and 8 h after start of infusion
  - blood sampling for protein binding at 1 h after start of copanlisib infusion (end of infusion)
- Urine sampling for pharmacokinetics (0-8 h and 8-24 h)
- Documentation on meal time (whole day)
- Open questioning for and documentation of AEs and update on concomitant medication.

9.2.4.2 Observation day (Study Day 2 and 3, relative time: day 01 and day 02)

The following measures / actions will be performed at the time points given in the study flow chart in Section 16.1.

- Abbreviated physical examination
- 12-lead ECG after at least 10 min rest in supine position
- Vital signs: Blood pressure and pulse rate after resting in supine position for at least 10 min; Body temperature
- Blood and urine sample for safety laboratory examinations
- Blood sampling for PK and protein binding assessment
- Further capillary glucose assessment at the discretion of the investigator (based of previous blood glucose levels)
- Documentation of meal´s timing in case of hyperglycemia
- Open questioning for and documentation of AEs and update on concomitant medication.

Provided there are no medical objections, the subjects are released from the ward in the morning of day 02 after having breakfast (48 h post-administration).

[27] Capillary glucose at 4h after start of infusion deleted according to Amendment 1

9.2.4.3 Ambulatory visits (Study Day 4 to 6, relative time: day 03 to day 05)

The following measures / actions will be performed at the time points given in the study flow chart in Section 16.1.

- Blood sampling for PK
- Further capillary glucose assessment at the discretion of the investigator (based of previous blood glucose levels)
- Open questioning for and documentation of AEs and update on concomitant medication.

Provided there are no medical objections, the subjects are released.

9.2.4.4 End-of-treatment (Study Day 8 to 11, relative time: day 07(+3))

The following measures / actions will be performed 7+3 days after administration of the study medication:

- Complete physical examination
- 12-lead ECG after at least 10 min rest in supine position
- Vital signs: Blood pressure and pulse rate after resting in supine position for at least 10 min; Body temperature
- Blood and urine sample for safety laboratory examinations.
- Blood sampling for PK
- Open questioning for and documentation of AEs and update on concomitant medication.

Provided there are no medical objections, the subjects are released from the study ward.

If required in case of elevated or decreased laboratory parameters out of the normal range additional visits will be performed after the follow-up visit.

9.2.5 Safety follow-up (relative time: day 14 (±3) and day 30 (+3))

There will be a telephone interview 14 ± 3 and 30 + 3 days after study drug administration (see also study flow chart in Section 16.1). The following measures / actions will be performed:

- Open questioning for and documentation of AEs and update on concomitant medication.
- Any AEs ongoing at Safety Follow-up visit should be followed until resolution or stabilization unless, in the investigator's opinion, the condition is unlikely to resolve due to the subject's underlying disease

All SAEs (including deaths) occurring up to 30 days after the single dose should be reported to the sponsor per usual SAE reporting procedures.

9.2.6 Special conditions during the study

9.2.6.1 Restrictions - amended

Restrictions to be observed by the subjects are displayed in Table 9-1 below:

Table 9-1: Restrictions during the study - amended

What?	Restriction
Smoking	not allowed during the in-house phase of the study[28]
Alcohol	not permitted from 48 h prior to the dosing until Day 7
Food and beverages containing grapefruit, pomelo or Seville oranges	not permitted within 7 days before dosing and 7 days thereafter.
Methylxanthin-containing food and drinks (coffee, tea, cola, cacao)	not permitted from 48 h prior to dosing until Day 7
Physical activity	usual activities are permitted, strenuous exercise not allowed from 72 h before admission to the study site until 96 h after study drug administration

9.2.6.2 Food and drinks

The subjects will be required to follow the alimentary restrictions listed in Table 9-1, otherwise they are allowed to eat and drink as usual. On the visit day of screening, the subjects need to come in fasting state. During their stay at the study site, the subjects will be served non-standardized meals considering the imposed restrictions – except for the day when the study medication will be administered.

Starting in the evening preceding the day with administration of the study medication, the subjects have to keep to the standardized food and drink presented in Table 9-2.

Table 9-2: Food and drink before and after dosing

Time	Food and drink
Approximately 8 h until the capillary glucose pre-dose is performed (before dosing)	Fasting (drinking of water and beverages with artificial sweeteners is allowed)
Approximately 1.5 h before dosing	Low glycemic breakfast (eggs, cheese and/or plain yoghurt, vegetables, meat). The breakfast should be completed 1h before start of infusion
During the last hour before dosing and during infusion	Nothing by mouth
During the first 2 h after EoI	Water consumption ad libitum
Approx. 2 h after EoI[a]	Standard lunch

[28] Smoking restriction revised (protocol Version 1.0 specified that smoking is not allowed during the study)

Table 9-2: Food and drink before and after dosing

Time	Food and drink
Approximately 8 h until the capillary glucose pre-dose is performed (before dosing)	Fasting (drinking of water and beverages with artificial sweeteners is allowed)
Approximately 1.5 h before dosing	Low glycemic breakfast (eggs, cheese and/or plain yoghurt, vegetables, meat). The breakfast should be completed 1h before start of infusion
During the last hour before dosing and during infusion	Nothing by mouth
Whenever appropriate (no specific timepoint)	Standard dinner

[a] after the study-related measures / actions of that time point have been performed

9.2.6.2.1 Accommodation

In-house phase: 4 days

Overnight stay: 3 nights

Ambulant visits: 5 visits (screening, Study Days 4 to 6, and end of treatment visit)

Number of periods: 1

9.3 Population characteristics

9.3.1 Demographic

For demographic assessment, the following parameters will be recorded:
Year of birth / age, sex, race / ethnicity, body weight and height.

- **Body weight and height, BMI**

Body weight will be measured by a member of the investigator's team under the following conditions:

- Subject in underwear and without shoes after having emptied his / her bladder
- Electronic physician (column) scale with digital display, measurement units 0.1 kg

The subject's height will be measured (without shoes) to calculate the BMI.

9.3.2 Medical history

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

- Start before signing of the informed consent
- Considered relevant for the subject's study eligibility.

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

9.3.3 Other baseline characteristics

Information on smoking and alcohol consumption will be collected.

9.4 Efficacy

Not applicable.

9.5 Pharmacokinetics / pharmacodynamics

9.5.1 Pharmacokinetics

9.5.1.1 Drug measurements

Blood samples for pharmacokinetic analyses of copanlisib and its metabolite BAY 84-5795 (M-1) in plasma will be collected at the time points given below and in the study flow chart, see Section 16.1. Urine for PK analyses of copanlisib and its metabolite M-1 will be collected in intervals given below and in the study flow chart (Section 16.1).

Blood samples for PK will be collected before start of infusion as well as at 10 min and 1 h (end of infusion [EoI]), 1.5, 2, 2.5, 3, 5, 8, 24, 48, 72, 96, 120 and 168 h after start of infusion (SoI).

Urine samples for PK will be collected in two sampling intervals from 0-8 and >8 up to 24 h after start of copanlisib infusion.

For all subjects, additional blood sample for evaluation of protein binding of copanlisib will be collected at 1 h after SoI (at EoI) on Day 1, and at 24 h after SoI on Day 2. These samples will be used for determination of fraction unbound and concentrations of total plasma protein, albumin and alpha 1-acid glycoprotein.

Whenever possible, all efforts should be made to adhere to the planned blood sampling schedule for PK. However, based on practical considerations, the following time ranges are provided as guidance:

- Pre-dose samples should be collected within 30 min before SoI.
- The end-of infusion sample for copanlisib and M-1 metabolite should be collected within 5 min after the end of infusion (EoI) of copanlisib for adequate characterization of C_{max}.
- For planned time points ≤6 h post-dose, PK samples should be collected within ±15 min of the planned time.
- For planned time points >6 h and ≤24 h, PK samples should be collected within ±30 min.
- For planned time points >24 h, the PK sample should be taken within ±3 h.

It is of importance that the actual date and time of blood sampling are thoroughly documented in the electronic case report form (eCRF) because PK calculations will be based on the actual sampling times relative to dosing times. Deviations from the specified time points will be documented and taken into account when calculating the PK parameters.

Cumulated substantial deviations of sampling times and/or consecutive, missing PK samples may lead to an insufficient description of the concentration-time profile(s) of the analyte(s), and thus affect the quality of the PK evaluation of the respective subject(s). In this case these deviations should be classified as “important” and may lead to as declared “validity findings” to the exclusion of the respective subject(s) from the PK analysis set.

Time points for PK samples may be adapted when data from this or another study become available (e.g. by adding up to five blood sampling time points per subject, or moving or deleting sampling time points). The decision on modification of sampling time points as well as the rationale for this will be described in detail in the Clinical Study Report, if applicable.

Regarding handling of the samples collected, refer to Section 16.2. The bioanalytical analyses of the samples will be performed using validated analytical methods. Quality control (QC) and calibration samples will be analyzed concurrently with study samples. The results of calibration samples and QC samples will be reported in the Bioanalytical Report which will be included in the Clinical Study Report for this study. Concentrations are calculated from the chromatographic raw data in accordance with current Bayer guidelines.

9.5.1.2 Pharmacokinetic evaluation

Non compartmental analysis (NCA)

The PK parameters will be calculated according to the Sponsor’s current guidelines using the pharmacokinetic software WinNonlin (version 5.3 or higher). Based on the concentration time data, the following PK parameters will be calculated.

Parameters based on unbound plasma concentrations will be calculated for copanlisib. The calculation of these parameters ($AUC(0\text{-}24)_u$, $AUC(0\text{-}168)_u$, AUC_u, , and $C_{max,u}$) will be performed by Data Management (see Section 11.3).

Main parameters:	
Copanlisib	C_{max}, AUC(0-168) and AUC
Additional parameters:	
Copanlisib	AUC(0-24), $AUC(0\text{-}t_{last})$, $t_{1/2}$, t_{max}, t_{last}, V_z, CL, $A_{E,ur}(0\text{-}24)$, CL_R, $C_{max,u}$, $AUC(0\text{-}24)_u$, $AUC(0\text{-}168)_u$, and AUC_u based on average value of unbound fraction in the 1h and 24h samples
BAY 84-5795 (M-1)	AUC(0-168), $AUC(0\text{-}t_{last})$, AUC, $t_{1/2}$, C_{max}, t_{max}, t_{last}, $A_{E,ur}(0\text{-}24)$
Other parameters:	
Copanlisib and BAY 84-5795 (M-1)	number of points terminal, $\%AUC(t_{last}\text{-}\infty)$, R_{start}, R_{end}, C_{last}

9.5.2 Pharmacodynamics

Not applicable.

9.5.3 Pharmacometric analysis

In addition to the NCA analysis, all PK and /or safety data may be used for additional pharmacometric analyses, e.g. a population PK analysis, which describes the relationship between dose, time, and copanlisib concentrations, and/or evaluations of exposure- safety-relationships for relevant safety parameters. If a popPK analysis will be conducted, the analysis will be described in a separate Modelling and Simulating (M&S) Analysis Plan and the results will be described in a separate M&S Report. Other pharmacometric analyses will also be reported separately.

9.6 Safety

9.6.1 Adverse events

9.6.1.1 Definitions

Definition of adverse event (AE)

In a clinical study, an AE is any untoward medical occurrence (i.e. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

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

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

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

Definition of serious adverse event (SAE)

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

a. Results in death

b. Is life-threatening

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

c. Requires in-subject hospitalization or prolongation of existing hospitalization

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

   – The admission results in a hospital stay of less than 12 h

   – The admission is pre-planned
     (e.g. elective or scheduled surgery arranged prior to the start of the study; admission is part of the study procedures as described in Section 9.2)

   – The admission is not associated with an AE
     (e.g. social hospitalization for purposes of respite care).

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

d. Results in persistent or significant disability / incapacity

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

e. Is a congenital anomaly / birth defect

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

9.6.1.2 Classifications for adverse event assessment

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

9.6.1.2.1 Seriousness

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

9.6.1.2.2 Intensity

The intensity of an AE is classified according to the following categories:

- Mild (A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living)
- Moderate (A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant)
- Severe (A type of AE that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects clinical status. The event possesses a significant risk of harm to the research participant and hospitalization may be required)

9.6.1.2.3 Causal relationship

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

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

Possible answers are “yes” or “no”

An assessment of “no” would include:

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

or

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

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

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

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on drug discontinuation (de-challenge), recurrence on drug re-introduction (rechallenge): Subject’s response after de-challenge or re-challenge should be considered in view of the usual clinical course of the event in question.

- Underlying, concomitant, intercurrent diseases:
  Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication or treatment:
  The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them might have caused the event in question.
- Known response pattern for this class of drug: Clinical/preclinical
- Exposure to physical and/or mental stresses: The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event
- The pharmacology and pharmacokinetics of the study treatment:
  The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the study treatment, coupled with the individual subject's pharmacodynamics should be considered.

Causal relationship to protocol-required procedure(s)

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

Possible answers are "yes" or "no"

9.6.1.2.4 Action taken with study treatment

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

- Drug withdrawn (not applicable in this study)
- Drug interrupted
- Dose reduced (not applicable in this study)
- Dose not changed (not applicable in this study)
- Dose increased (not applicable in this study)
- Not applicable
- Unknown

9.6.1.2.5 Other specific treatment(s) of adverse events

- None
- Remedial drug therapy
- Other

9.6.1.2.6 Outcome

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

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

9.6.1.3 Assessments and documentation of adverse events

The investigator has to record on the respective CRF pages all adverse events occurring in the period between the signing of the informed consent and the end of the follow-up phase; after the end of the follow-up phase there is no requirement to actively collect AEs including deaths.

Any AEs ongoing at Safety Follow-up visit should be followed until resolution or stabilization unless, in the investigator's opinion, the condition is unlikely to resolve due to the subject's underlying disease

All SAEs (including deaths) occurring up to 30 days after the single dose should be reported to the sponsor per usual SAE reporting procedures.

The type of information that should be assessed and recorded by the investigator for each AE is listed in Section 9.6.1.2.

"Death" should generally not be recorded as an AE on the AE page. Instead, "death" is the outcome of underlying AE(s) which should be reported. Death should be reported as a SAE only if the underlying event which resulted in death is unknown.

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

9.6.1.4 Reporting of serious adverse events

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

Investigator's notification of the sponsor

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

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

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

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

It is not mandatory to report SAEs occurring after the protocol defined observation period (see Section 9.6.1.3); however, at the investigator's discretion these may be reported if considered potentially relevant. In such cases, the SAEs will be processed by the sponsor according to all applicable regulations.

An isolated laboratory abnormality is not reportable as an SAE, unless the investigator assesses that the event meets standard International Conference on Harmonization (ICH) criteria for an SAE (see SAE definition in Section 9.6.1.1).

Notification of the IECs / IRBs

Notification of the independent ethics committee (IECs) / institutional review board (IRBs) about all relevant events (e.g. SAEs, suspected, unexpected, serious adverse reactions [SUSARs]) will be performed by the sponsor and/or by the investigator according to all applicable regulations.

Notification of the authorities

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

Sponsor's notification of the investigational site

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

9.6.1.5 Expected adverse events

For this study, the applicable reference document is the most current version of the IB of Copanlisib [1].

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

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

- **Expected conduct-related AEs**

The frequent blood sampling (by single vein puncture and / or indwelling cannula) may be accompanied by mild pain, hematoma and in rare cases inflammation of the vessel wall or injury of a nerve. Awareness should be raised to the possibility of a vasovagal attack or syncope (marked by pallor, nausea, sweating, bradycardia, and decrease in arterial blood pressure which, when below critical level, results in dizziness and /or loss of consciousness) during the sampling procedure.

The use of adhesive electrodes (ECG leads) and / or adhesive dressings may be accompanied by mild and transient reddening and / or itching of the skin.

9.6.1.6 Adverse events of special safety interest

Not applicable.

9.6.1.7 Recommendations for the management of specific adverse events

9.6.1.7.1 Management of glucose increases that can occur with study treatment

Management of transient post-infusion glucose increases in non-diabetic subjects

- Asymptomatic transient glucose increases
  Mild to moderate asymptomatic increases of blood glucose may occur after study drug infusion, with larger increases potentially occurring post-prandial. Transient asymptomatic glucose increases that are ≤250 mg/dL do generally not require treatment with glucose-lowering medication. Subjects with post-dose blood glucose >250 mg/dL should have repeated laboratory glucose measurements to verify if the values are persistent or decreasing. If the repeated glucose values are decreasing, glucose levels may be followed without glucose-lowering medication if the subject is asymptomatic and if hydration status is normal as clinically assessed.
- Symptomatic or persisting glucose increases
  Hydration status: If the subject has symptomatic glucose increase of any grade, hydration status should be clinically assessed. If the clinical assessment is consistent with dehydration, fluids should be given as clinically appropriate (orally or IV).
  Glucose-lowering medication: Subjects with post-dose blood glucose >250 mg/dL should have repeated laboratory glucose measurements to verify if values are persistent or decreasing. If a blood glucose level of >250 mg/dL persists upon confirmation by repeated laboratory analysis, and/or the subject is symptomatic, and/or the hydration status indicates the need for hydration, glucose-lowering medication should be administered: Rapid or short-acting (regular) insulin may be given for blood glucose levels that are persisting at >250 mg/dL, or if the subject is symptomatic during the infusion day. “Sliding scale” short-acting or (regular) insulin coverage of blood glucose levels that are persisting at >250 mg/dL is recommended, with oral or IV hydration as clinically appropriate. Only the use of short-acting (rapid-acting) insulin is recommended for treatment of glucose increases after the single dose copanlisib infusion in non-diabetic subjects.
  Meal timing is added to the glucose management log used by the investigator and to be continued as long as hyperglycemia induced by the copanlisib infusion persists.

Management of transient post-infusion glucose increases in diabetic subjects

For subjects with diabetes mellitus (types 1 and 2), the regimen of oral glucose-lowering medication and/or insulin (short-acting, intermediate, or long-acting) may be adjusted at the investigator's discretion after the single copanlisib infusion.

The management of these subjects may require, if needed the input of a diabetes specialist. Adjustment of the subject's glucose-lowering regimen (whether prior use of oral hypoglycemic medication, insulin, or a combination of both) with special attention to post-copanlisib infusion meal coverage should be considered for postprandial glucose increases.

Monitoring during the study

All subjects (diabetic and non-diabetic) should be kept on ward as long as the post-dose glucose level is >250 mg/dL and until the glucose level decreases to <200 mg/dL non-fasting. All diabetic subjects as well as non-diabetic subjects who experience a glucose level of >250 mg/dL or require insulin administration post-infusion will have capillary glucose monitoring including fasting plasma glucose (morning before breakfast) and 2 further capillary glucose measurements approximately 2 h after intake of food. If after the required 48 h the glucose values are not at goal (post-prandial glucose <200 mg/dL), this monitoring will continue until blood glucose values are at goal.

9.6.1.7.2 Treatment of arterial hypertension associated with copanlisib

Subjects with pre-existing arterial hypertension should adhere to their regular antihypertensive medication schedule, and take their usual doses on the day of the copanlisib infusion. The management of acute arterial hypertension following copanlisib will need to be individualized for each subject, but the experience in Phase I studies on copanlisib has suggested the benefit of dihydropyridine calcium channel blockers (i.e. amlodipine, felodipine). Topical nitrates, verapamil and diltiazem (nondihydropyridine calcium channel blockers) can be also considered.

In general, antihypertensive medication should be readily available if needed. If arterial hypertension ≥150/90 mmHg occurs during the copanlisib infusion, antihypertensive treatment is suggested as indicated above. If arterial hypertension (≥160/100 mmHg) occurs during copanlisib IV infusion, the copanlisib IV infusion should be interrupted or slowed down, administration of anti-hypertensive therapy initiated and copanlisib infusion may be resumed when BP has returned to <150/90 mmHg.

9.6.1.7.3 Treatment of vomiting and diarrhea

Adequate hydration through appropriate fluid maintenance is essential for the treatment of diarrhea or vomiting. Anti-diarrhea medications may be introduced if symptoms occur. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2 to 4 h until diarrhea-free for 12 h, a maximum daily dose of 16 mg is not to be exceeded. If clinically indicated diphenoxylate or Lomotil, which contains diphenoxylate plus atropine might also be used. The routine use of standard antiemetics, including 5-HT_3 blockers is allowed, see Section 8.1 for permitted concomitant therapy.

9.6.2 Pregnancies

A subject's participation is to be terminated immediately if a pregnancy is supposed (i.e. in case her pregnancy test becomes positive).

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

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

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

9.6.3 Safety examinations

The following safety examinations will be performed at the time points specified in the study flowchart, see Section 16.1.

- **Physical examination**

The physical examination (by means of inspection, palpation, auscultation) will be performed by a physician at the study site according to the schedule summarized in the flow chart in Section 16.1.

Complete physical examination includes the NYHA classification (see Section 16.9) and complete reviews of body systems.

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

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

- General appearance
- Skin (paleness, jaundice, redness / rush, acneiform changes)
- Hand and feet (signs of hand-foot syndrome / palmar-plantar erythrodysesthesia)
- Eyes (accommodation, double images, abnormal sensitivity to light, jaundice)
- Ears, nose, throat (presence of petechial bleedings, gingiva bleeding)
- Head and neck
- Lungs
- Heart
- Abdomen (pain, tenderness, peristaltic, ascites, organomegaly)
- Lymph nodes
- Musculoskeletal system and spine
- Lower legs (petechial bleedings, ulcer, signs of thrombosis)
- Neurologic findings

Abbreviated physical examinations will be performed (by inspection, palpation, and auscultation) by a physician at the study center according to the schedule summarized in the flow chart in Section 16.1.

Abbreviated physical examination includes pertinent organ systems and brief interim history (change of symptoms). At the minimum, the following aspects / regions need to be assessed as well:

- Skin (paleness, jaundice, redness / rush, acneiform changes)
- Hand and feet (signs of hand-foot syndrome / palmar-plantar erythrodysesthesia)
- Throat (presence of petechial bleedings, gingiva bleeding)
- Lungs
- Abdomen (pain, tenderness, peristaltic, ascites, organomegaly)
- Neurologic findings
- Other clinical signs and regions might be investigated as well if clinically indicated.

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

- **Vital Signs**
  - Blood pressure (BP) / pulse rate (supine)

Systolic / diastolic blood pressure and pulse rate will be measured by a member of the investigator's team under the following conditions:

- Position: Supine (small pillow under head allowed) for at least 10 min
- Measuring site: cuff to be placed on the right / left upper arm (if possible, the same arm will be used for all measurements in one subject)
- Method: oscillometric by automatic measurement device

Body temperature, BP, and pulse rate will be assessed according to the schedule summarized in the flow chart in Section 16.1. If clinically indicated, it is at the investigator's discretion to perform these measurements more frequently.

BP will be measured every 5 to 10 min before the copanlisib dose until 2 consecutive values are <150/90 mmHg. A single BP measurement will be performed at the end of the copanlisib IV infusion.

For details about the management of arterial hypertension, see also Section 9.6.1.7.2 (treatment of arterial hypertension).

- **Body temperature**

Body temperature will be measured by a member of the investigator's team using always the same method according to local practice. The measured values are to be recorded in the electronic CRF in degree Celsius (°C).

- **Electrocardiogram**

A complete standard 12-lead ECG will be recorded by a member of the investigator's team under the following conditions:

- Position: supine (small pillow under head allowed) for at least 15 min
- Device: computerized ECG device
- Automatic calculation of the following parameters: RR interval, heart rate, P-duration, PR (PQ) interval, QRS-duration, QT (uncorrected). For data analysis by the sponsor, the frequency-corrected QT interval will be calculated according to both the formula of Fridericia (QTcF) and Bazett (QTcB) by data management.
- Evaluation of ECG by a physician providing an ECG diagnosis and overall assessment (including clinical relevance)

- **Laboratory examinations**

Blood and urine samples will be collected by a member of the investigator's team, for time points and parameters see Section 16.1 and Section 16.2 in the appendix.

The MDRD equation will be used for the eligibility assessment in Group B (see Section 16.5). The creatinine clearance will be calculated from the creatinine concentration measured in serum according to the Cockroft-Gault formula after the study (see Section 16.6).

In the event of implausible results, the laboratory may measure additional parameters to assess the quality of the sample (e.g. clotted or hemolyzed) and to verify the results.

The results from such additional analyses may neither be included in the clinical database of this study nor evaluated further. If the results are relevant, the investigator will be informed to determine follow-up activities outside of this protocol.

9.7 Other procedures and variables

For virology and urine drug screen parameters and pregnancy test, please refer to Table 16-2.

9.8 Appropriateness of procedures / measurements

All PK and safety parameters, as well as the methods to measure them, are standard variables/ methods in clinical studies and/ or clinical practice. They are widely used and generally recognized as reliable, accurate and relevant.

10. Statistical methods and determination of sample size

10.1 General considerations

The statistical evaluation will be performed by using the SAS software package. All data will be listed and trial summary tables will be provided.

All data will be listed and study summary tables will be provided where appropriate. Quantitative data will be described by the following summary statistics: arithmetic mean, standard deviation, median, minimum and maximum. Whenever appropriate, summary statistics will be provided for the original data as well as for the change versus baseline. Graphical illustrations will be provided where appropriate. Frequency tables will be provided for qualitative data. Baseline is defined as the last pre-dose assessment before study drug administration.

10.2 Analysis sets

All subjects who received at least one dose of the study medication will be included in the safety analysis set (SAF).

All subjects with a PK profile allowing calculation of the main PK parameters will be included in the PK analysis set (PKS1).

All hepatically impaired subjects and gender, age- and weight-matched healthy subjects with a PK profile allowing calculation of the main PK variables will be included in the PK analysis set for hepatic impairment assessment (PKS2).

All renally impaired subjects and gender, age- and weight-matched healthy subjects with a PK profile allowing calculation of the main PK variables will be included in the PK analysis set for renal impairment assessment (PKS3).

10.3 Variables and planned statistical analyses - amended

Primary and secondary variables are specified in Section 5.

Statistical and analytical plans

- **Demographic and other baseline characteristics**

Analysis for population characteristics will be performed for the SAF population, unless otherwise specified.

Disposition at the end of screening will be summarized for all enrolled subjects. Disposition at the end of treatment will be summarized by group and overall for the SAF population.

Demographics will be summarized by group and overall. Quantitative data will be summarized by arithmetic mean, standard deviation, median, minimum and maximum. Frequency tables will be provided for qualitative data. Analysis of demographic data will also be performed for the PKS1 population if this population differs from SAF.

- **Adverse events**

Individual listings of AEs will be provided. The incidence of TEAEs and drug-related TEAEs, respectively, will be summarized by group and overall using MedDRA terms. Listings of deaths and SAEs will be provided.

Adverse events are considered to be treatment-emergent if they have started or worsened after first application of study medication up to 30 days after end of treatment with study medication.

- **Safety parameters**

Quantitative data for safety (hematology, clinical chemistry, coagulation, urinalysis, vital signs, ECG) will be described by descriptive statistics (arithmetic mean, standard deviation, median, minimum and maximum) and will be presented by each group for the original data as well as for the difference to baseline. Frequency tables will be provided for qualitative data.

Laboratory data outside the reference range will be listed and flagged with 'L' for low and'H' for high.

Graphical displays of individual data as well as mean values with standard deviation will be included.

- **Pharmacokinetic variables**

The plasma concentration vs time courses of copanlisib (and its metabolite) will be summarized by group. The following statistics will be calculated for each plasma sampling point: arithmetic mean, standard deviation (SD) and coefficient of variation (CV), geometric mean, geometric standard deviation (re-transformed standard deviation of the logarithms) and CV, minimum, median, maximum value and the number of measurements. Means at any time will only be calculated if at least 2/3 of the individual data were measured and were above the lower limit of quantification (LLOQ). For the calculation of the mean value a data point below LLOQ will be substituted by one half of this limit. This rule also applies for means shown in figures. In tables showing mean values, where values below LLOQ are included in the calculation of mean values, these means will be marked.

Individual and mean concentration versus time profiles of all analytes will be plotted using both linear and semi-logarithmic scale.

Pharmacokinetic characteristics (t_{max} and t_{last} excluded) will be summarized by the statistics mentioned above. T_{max} and t_{last} will be described utilizing minimum, maximum and median as well as frequency counts.

To investigate the primary objective of this study regarding hepatic and renal impairment, analysis of variance appropriate for a parallel design will be fitted to the natural logarithmic transformation of PK parameters (AUC(0-168), AUC and C_{max}) of copanlisib .

The test/reference comparison ratio of geometric least-squares means and associated 90% confidence intervals (CIs) for each PK parameter in the moderate hepatic, severe hepatic[29] or severe renal impairment group versus the matched healthy subjects group will be calculated by exponentiation of the natural-log scale point estimate and the associated 90% CI.

[29] Included as subjects with severe hepatic impairment will be included into the study according to Amendment 1

10.4 Determination of sample size - amended[30]

The study population will consist of up to 44 evaluable male and female subjects with 8-22 evaluable subjects in the control group, 8 evaluable subjects each in the moderate hepatic and severe renal impairment investigational group, and 6 evaluable subjects in the severe hepatic impairment investigational group. The sample size of 8 subjects in each of the groups with impaired moderate hepatic and severe renal function and 6 subjects in the severe hepatic impairment group has been selected based on practical consideration and following the FDA guidance [4][5].

In copanlisib studies 12871 and 16270, the SD for log-transformed AUC(0-168) or AUC was estimated between 0.33 and 0.40. For the current study, we assume the SD of 0.40 for log-transformed AUC(0-168). The PK parameter AUC(0-168) is considered appropriate for sample size estimation as in Study 16270 the extrapolation for calculation of AUC was only 4.8% of AUC(0-168). Further, based on the PK data from study 12871, the inter-subject variability for copanlisib PK exposure was estimated to be 46.5% for AUC(0-168) and 73.3% for C_{max} in terms of geometric coefficient of variation (CV). In study 16270, the inter-subject variability for C_{max} was 63.2% in terms of geometric mean CV. The AUC(0-168) value has been considered for sample size estimation as a suitable PK parameter because of the higher uncertainty around of the C_{max} especially for an i.v. drug. For AUC(0-168), a sample size of 8 eligible subjects each in the control, moderate hepatic and severe renal impairment investigational group would provide an approximately 90% chance for the 90% confidence interval for the ratio of geometric least-squares means between impaired subjects and healthy subjects to be within a 2-fold difference, that is, within limits of 50% to 200% for AUC(0-168). This can be shown in Table 10-1 based on different observed ratios.

Table 10-1: 90% Confidence interval for copanlisib with N=8 per group - amended

Observed Ratio	90% CI for the ratio
1	(0.685, 1.461)
1.1	(0.753, 1.607)
1.2	(0.822, 1.753)
1.3	(0.890, 1.899)

A sample size of 6 eligible subjects per each in the control and severe hepatic impairment investigational group would provide an approximately 90% chance for the 90% confidence interval for the ratio of geometric least-squares means between impaired subjects and healthy subjects to be within an approximately 2-fold difference, that is, within limits of 50% to 207% for AUC(0-168) as shown in Table 10-2 based on different observed ratios.

[30] Sample size determination revised as subjects with severe hepatic impairment will be included into the study according to Amendment 1

Table 10-2: 90% Confidence interval for copanlisib with N=6 per group - amended

Observed Ratio	90% CI for the ratio
1	(0.628, 1.593)
1.1	(0.691, 1.752)
1.2	(0.753, 1.911)
1.3	(0.816, 2.07)

10.5 Planned interim analyses - amended

An interim analysis will be conducted after 8 evaluable subjects with moderate hepatic impairment and 8 evaluable subjects with severe renal impairment with their corresponding matching healthy volunteers have completed the study to fulfill the first part of the post marketing requirement as agreed with the FDA (July 2019) based on the accelerated approval of copanlisib (September 14, 2017). This interim analysis will also serve as a final analysis on the moderate hepatic impairment and severe renal impairment groups in the final clinical study report. The results of the final report will include subjects with severe hepatic impairment as agreed with FDA (July 2021).[31]

11. Data handling and quality assurance

11.1 Data recording

The data collection tool for this study will be a validated electronic data capture system called RAVE. Subject data necessary for analysis and reporting will be entered/ transmitted into a validated database or data system (SAS).

Data required according to this protocol will be recorded by investigational site personnel via data entry into the internet based electronic data capture (EDC) software system RAVE, which has been licensed from Medidata Solutions Worldwide. RAVE has been validated by Medidata Solutions Worldwide for use in Bayer clinical studies. RAVE allows for the Integrated Clinical application of software logic to set-up data entry screens and data checks to ensure the completeness and accuracy of the data entered by the site personnel. The logic has been extensively applied to ensure data are complete and reflect the clinical data requirements of the study. Data queries resulting from the application of the software logic are resolved by the site personnel. The data are stored at a secure host facility maintained by Medidata Solutions Worldwide.

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

[31] Interim analysis included according to Amendment 1

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

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

Source documentation

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

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

Data recorded from screening failures

At minimum, the following data should be recorded in the CRF:

- Demographic information (subject number; year of birth / age; sex; if applicable race / ethnicity)
- Date of informed consent
- Relevant inclusion/exclusion criteria
- Reason for premature discontinuation
- Date of last visit

These data will be transferred to the respective database.

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

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

11.2 Monitoring

In accordance with applicable regulations, GCP, and sponsor's/CRO's procedures, monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and sponsor's requirements. When reviewing data collection procedures, the discussion will also include identification and documentation of source data items.

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

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

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

11.3 Data processing

Bioanalytical results for PK evaluation will electronically be transferred from the Bioanalytical Department to Data Management using a predefined uniform file format. Data Management will include these data in the corresponding SAS data repository. Data Management will create a transfer file containing the bioanalytical results, demographic data, dosing data, and actual dosing and sample collection times and will electronically send this file to Clinical Pharmacokinetics. Clinical Pharmacokinetics will calculate the PK parameters indicated in this protocol as described in Section 9.5.1.2 except for the parameters derived from unbound concentrations. The finalized evaluation will electronically be transferred to Data Management where all data will be included in the corresponding SAS data repository. Pharmacokinetic parameters for unbound copanlisib (AUC_u, $C_{max,u}$) will be calculated by Data Management by multiplying the pertinent parameters for copanlisib as calculated by Clinical Sciences with / by the individual free fraction provided by the Preclinical Pharmacokinetics Department. All electronic file transfer processes will follow validated procedures.

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

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

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

11.4 Missing data

No imputation of missing data is planned. All available data will be used for statistical analysis.

11.5 Audit and inspection

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

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

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

11.6 Archiving

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

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

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

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

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

12. Premature termination of the study

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

- If risk-benefit ratio becomes unacceptable owing to, for example,
  - Safety findings from this study (e.g. SAEs)
  - Results of any interim analysis
  - Results of parallel clinical studies
  - Results of parallel animal studies
    (on e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity).

- If the study conduct (e.g. recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.

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

For any of the above closures, the following applies:

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

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

13. Ethical and legal aspects

13.1 Investigator(s) and other study personnel

Sponsor's **Medical Expert**

Name: PPD
Title: PPD
Address: Bayer AG,
SBU Oncology, Pharmaceuticals
Muellerstrasse 178
13353 Berlin, Germany
Phone: PPD
Fax: PPD

Coordinating Investigator for the Study

Name: PPD
Title: PPD
Address: PPD
Germany
Phone: PPD
Fax: PPD

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

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

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

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

13.2 Funding and financial disclosure

Funding

This study will be funded by its sponsor.

Financial disclosure

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

13.3 Ethical and legal conduct of the study

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

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

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

Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator or the sponsor may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior IEC/IRB/sponsor approval/favorable opinion.

As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IEC/IRB/head of medical institution/sponsor. Any deviations from the protocol must be explained and documented by the investigator.

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

13.4 Subject information and consent

All relevant information on the study will be summarized in an integrated subject information sheet and informed consent form provided by the sponsor or the study center. A sample subject information and informed consent form is provided as a document separate to this protocol.

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

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

Each subject will be informed about the following aspects of premature withdrawal:

- Each subject has the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.
- The subject's consent covers end-of-study examinations as specified in the visit description described in Section 9.2 to be conducted after withdrawal of consent.
- The subject's data that have been collected until the time of withdrawal will be retained and statistically analyzed in accordance with the statistical analysis plan.
- Subject-specific data on the basis of material obtained before withdrawal may be generated after withdrawal (e.g. image reading, analysis of biological specimen such as blood, urine or tissues); these data would also be retained and statistically analyzed in accordance with the statistical analysis plan. The subject has the right to object to the generation and processing of this post-withdrawal data. The subject's oral objection may be documented in the subject's source data.

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

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

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

In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or subject´s clinical record must clearly show that informed consent was obtained prior to these procedures.

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

13.5 Publication policy and use of data

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

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

Regarding public disclosure of study results, the sponsor will fulfill its obligations according to all applicable laws and regulations. The sponsor is interested in the publication of the results of every study it performs.

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

13.6 Compensation for health damage of subjects / insurance

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

13.7 Confidentiality

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

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

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

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

14. Reference list

[1] Investigator's Brochure: BAY 80-6946 (Copanlisib), current version.

[2] Walz-Mattmueller R, Horny HP, Ruck P, Kaiserling E. Incidence and pattern of liver involvement in haematological malignancies. Pathol Res Pract. 1998;194(11):781–789.

[3] Humphreys BD, Soiffer RJ, Magee CC. Renal failure associated with cancer and its treatment: an update. J Am Soc Nephrol. 2005 Jan;16(1):151-61. Epub 2004 Dec 1.

[4] Guidance for Industry: Pharmacokinetics in patients with impaired hepatic function: study design, data analysis, and impact on dosing and labeling. Food and Drug Administration. May 2003.

[5] Draft Guidance for Industry: Pharmacokinetics in patients with impaired renal function: study design, data analysis, and impact on dosing and labeling. Food and Drug Administration. March 2010.

[6] National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. Am J Kidney Dis 39:S1-S266, 2002 (suppl 1).

15. Protocol amendments

15.1 Amendment 1

Amendment 1 (substantial) is dated 28 Nov 2017.

15.1.1 Overview of changes to the study

This amendment is issued as a result of the FDA's comment in the e-mail from 03 Aug 2017.

- Modification 1 (Enrollment of subjects with severe hepatic impairment): As copanlisib is mainly metabolized and excreted by the liver subjects with severe hepatic impairment (Child-Pugh C) will additionally be enrolled in this study. A total of 6 evaluable subjects with severe hepatic impairment will be included in Group C. An interim analysis will be conducted after 8 evaluable subjects with moderate hepatic impairment and 8 evaluable subjects with severe renal impairment with their corresponding matching healthy volunteers have completed the study to fulfill the post marketing requirement as agreed upon with the FDA after the accelerated approval of copanlisib in September 2017. The subject number ranges were revised (Sections 2 [synopsis], 3, 4, 5, 6.1.5, 6.2.5, 6.4.2, 7.1, 7.3, 7.4.1, 10.3, 10.4, 10.5, and 16.3).

In addition, this amendment covers the following modifications:

- Modification 2 (Inclusion of a third study center). A third study center was included PPD The subject number ranges were revised (Section 7.3, 7.6, and 16.2).
- Modification 3 (Revision of abbreviation list): The presentation of the abbreviation E2 for estradiol was revised in the abbreviation list (list of abbreviations).

- Modification 4 (Revision of Table 7-1): In the first column of Table 7-1 “severe” was included to Group B for clarification (Section 7.1).
- Modification 5 (Correction of position for vital sign measurements): The position for vital sign measurements at screening was corrected in Section 9.2.1 from “sitting” to “supine”. Vital signs will be determined in supine position as described in Section 9.6.3 and the flow chart (Section 9.2.1).
- Modification 6 (Addition of follicle stimulating hormone to the table of laboratory parameters): Follicle stimulating hormone was added to the table of laboratory parameters as this parameter will be determined in postmenopausal women ≤50 years of age as described in inclusion criterion no. 3 (Section 16.2).
- Modification 7 (Correction of position of footnote “b” in the flow chart): Footnote “b” (before any study specific tests or procedures are done) applies to “informed consent” and not to “blood pressure” and “pulse rate”. The flow chart was corrected accordingly (Section 16.1).
- Modification 8 (Deletion of protein binding assessment at pre-dose): The protein binding assessment was deleted at pre-dose in the visit description. The assessment will not be performed at pre-dose as described in Section 9.5.1.1 and the flow chart (Section 9.2.4.1).
- Modification 9 (Deletion of assessment of capillary glucose at 4 h): The assessment of capillary glucose was deleted at 4 h after start of infusion in the visit description. The assessment will not be performed at 4 h as described in the flow chart (Section 9.2.4.1).
- Modification 10 (Revision of smoking restriction): It was clarified that smoking will not be allowed during the in-house phase of the study (Section 9.2.6.1).
- Modification 11 (Correction of fasting period after dosing): In the flow chart the fasting period was corrected from 1 h to 2 h after end of infusion. The fasting period will last 2 h as described in Table 9-2 and footnote “i” of the flow chart (Section 16.1).
- Modification 12 (Revision of time points for final check of inclusion and exclusion criteria and treatment assignment): Final assessment of inclusion and exclusion criteria will take place after the results of the safety laboratory from the morning of Day -1 are available (evening of Day -1/morning of the dosing day). Treatment assignment will take place in the morning of the dosing day before start of infusion and after assessing the pre-dose blood pressure and glucose values. The protocol was corrected accordingly (Sections 5, 6.5, and 16.1).
- Modification 13 (Correction of time period in title of the flow chart): The title of the flow chart was corrected from “-00d16h – 07d00h” to “-01d00h – 05d00h” (Section 16.1).
- Modification 14 (Approval of BAY 80-6946 by FDA). BAY 80-6946 was approved by the FDA in September 2017. This information was included (Section 3).

- Modification 15 (Change of exclusion criterion regarding neutrophils): In order to be consistent with other copanlisib studies, the upper limit of neutrophils was increased in the exclusion criterion. Subjects will not be included into the study in case of neutrophils <1500/µL instead of <1000/µL at inclusion (Section 6.2.1).
- Modification 16 (Harmonization of name of study drug). The name of the study drug was harmonized (BAY 80-6946 instead of BAY 806946). The name of the study drug should have 7 digits (Section 3 and 7.2).

15.1.2 Changes to the protocol text

In this section on changes to the protocol text, all protocol sections affected by the respective amendment are detailed; the sequence of the sections follows the structure of the most recent previous protocol version. As applicable, changes to the protocol text are highlighted as follows:

- **Addition of a whole new portion** Brief identification of the new portion
- **Removal of a whole portion** Complete display of the removed portion, formatted as ~~crossed out~~
- **Editing of an existing portion** Comparative presentation of "old text" versus "new text", with "old text" referring to the most recent previous protocol version. Deletions are ~~crossed out~~ in the "old text". Additions are underlined in the "new text".
- **Tables / figures** The term "amended" is added to the caption.
- **Terminological changes** Brief specification of the terminological change

Correction of typos or omissions is not highlighted.

15.1.2.1 Section 2 Synopsis

This section was changed as a result of Modification 1.

Old table

[…]	
Study objective(s)	The primary objective of this study is to • Investigate the pharmacokinetics (PK) of copanlisib following a single intravenous (i.v.) dose of 12 mg copanlisib in subjects with moderate hepatic (Child Pugh B) or severe renal impairment compared with healthy subjects The secondary objective of this study is to • Evaluate the PK of M-1 metabolite • Assess the safety and tolerability of copanlisib when administered to subjects with moderate hepatic or severe renal impairment
[…]	
Diagnosis and main criteria for inclusion /exclusion	[…] Subjects with moderate hepatic impairment • Subjects with confirmed liver cirrhosis by at least one of the following criteria: histologically by prior liver biopsy showing cirrhosis, liver imaging (computer tomography, and/or ultrasound and/or magnetic resonance imaging scans, and/or fibroscan), or laparoscopy. • Child-Pugh Clinical Assessment Score 7 to 9. Subjects with severe renal impairment • Subjects with severe renal impairment with an estimated glomerular filtration rate 15-29 mL/min/1.73 m^2 according to MDRD formula. • Subjects with stable renal disease: no significant change in renal function as evidenced by serum creatinine value within ±25% from the last determination, obtained within at least 3 months before study entry and the absence of the need to start dialysis in the next 3 months.
Study design	Multi-center, non-randomized, open-label, single-dose, parallel group, study consisting of ~~3~~ groups (control group: normal hepatic and renal function group, Group A: moderate hepatic impairment group, Group B: severe renal impairment group
[…]	
Number of subjects	Up to ~~32~~ evaluable male and female subjects with 8-~~16~~ evaluable subjects in the control group ~~and~~ 8 evaluable subjects ~~in~~ each ~~investigational group (hepatic and renal impairment)~~ A minimum of ~~24~~ subjects (8/group) valid for PK of copanlisib (i.e., all blood samples for PK should be available up to 1 week [168 h]) will be required. Additional healthy subjects may be enrolled to achieve demographic matching between healthy and impaired groups until up to ~~16~~ healthy subjects valid for PK of copanlisib (i.e., up to 1 week [168 h]).
[…]	

Plan for statistical analysis	To investigate the primary objective of this study regarding hepatic and renal impairment, analysis of variance appropriate for a parallel design will be fitted to the natural logarithmic transformation of PK parameters (AUC(0-168), AUC and C_{max}) of copanlisib. The test/reference comparison ratio of geometric least-squares means and associated 90% confidence intervals (CIs) for each PK parameter in the moderate hepatic or severe renal impairment group versus the respectively matched healthy subject group will be calculated by exponentiation of the natural-log scale point estimate and the associated 90% CI.

New table

[…]	
Study objective(s)	The primary objective of this study is to • Investigate the pharmacokinetics (PK) of copanlisib following a single intravenous (i.v.) dose of 12 mg copanlisib in subjects with moderate hepatic (Child Pugh B), severe hepatic (Child Pugh C) or severe renal impairment compared with healthy subjects The secondary objectives of this study is to • Evaluate the PK of M-1 metabolite • Assess the safety and tolerability of copanlisib when administered to subjects with moderate hepatic, severe hepatic or severe renal impairment
[…]	

Diagnosis and main criteria for inclusion /exclusion	[…] Subjects with moderate hepatic impairment • Subjects with confirmed liver cirrhosis by at least one of the following criteria: histologically by prior liver biopsy showing cirrhosis, liver imaging (computer tomography, and/or ultrasound and/or magnetic resonance imaging scans, and/or fibroscan), or laparoscopy. • Child-Pugh Clinical Assessment Score 7 to 9. Subjects with severe hepatic impairment • Subjects with confirmed liver cirrhosis by at least one of the following criteria: histologically by prior liver biopsy showing cirrhosis, liver imaging (computer tomography, and/or ultrasound and/or magnetic resonance imaging scans, and/or fibroscan), or laparoscopy. • Child-Pugh Clinical Assessment Score 10-15. Subjects with severe renal impairment • Subjects with severe renal impairment with an estimated glomerular filtration rate 15-29 mL/min/1.73 m^2 according to MDRD formula. • Subjects with stable renal disease: no significant change in renal function as evidenced by serum creatinine value within ±25% from the last determination, obtained within at least 3 months before study entry and the absence of the need to start dialysis in the next 3 months.
Study design	Multi-center, non-randomized, open-label, single-dose, parallel group, study consisting of 4 groups (control group: normal hepatic and renal function group, Group A: moderate hepatic impairment group, Group B: severe renal impairment group, Group C severe hepatic impairment group)
[…]	
Number of subjects	Up to 44 evaluable male and female subjects with 8-22 evaluable subjects in the control group, 8 evaluable subjects each in the moderate hepatic impairment and in the severe renal impairment investigational group, and 6 evaluable subjects in the severe hepatic impairment investigational group. A minimum of 30 subjects (8/group except for severe hepatic impairment: 6) valid for PK of copanlisib (i.e., all blood samples for PK should be available up to 1 week [168 h]) will be required. Additional healthy subjects may be enrolled to achieve demographic matching between healthy and impaired groups until up to 22 healthy subjects valid for PK of copanlisib (i.e., up to 1 week [168 h]).
[…]	

Plan for statistical analysis	To investigate the primary objective of this study regarding hepatic and renal impairment, analysis of variance appropriate for a parallel design will be fitted to the natural logarithmic transformation of PK parameters (AUC(0-168), AUC and C_{max}) of copanlisib. The test/reference comparison ratio of geometric least-squares means and associated 90% confidence intervals (CIs) for each PK parameter in the moderate hepatic, severe hepatic or severe renal impairment group versus the respectively matched healthy subject group will be calculated by exponentiation of the natural-log scale point estimate and the associated 90% CI.

15.1.2.2 List of abbreviations

This section was changed as a result of Modification 3.

Old table

[…]

ePRO	electronic subject-reported outcome
~~Estradiol~~	~~E2~~
EU	European Union

[…]

New table

[…]

ePRO	electronic subject-reported outcome
E2	estradiol
EU	European Union

[…]

15.1.2.3 Section 3 Introduction

This section was changed as a result of Modification 1, 14, and 16.

Old text

Background

[…]

Copanlisib (BAY 806946) is a novel, highly selective, -panclass- PI3K inhibitor with potent activity against both α and δ isoforms, with *in vitro* IC_{50} of 0.5 nM and 0.7 nM, respectively.

[…]

Rationale of the study

[…]

This study will evaluate the PK and safety of a single 12-mg dose of copanlisib in subjects with moderate hepatic impairment or severe renal impairment of copanlisib and in age-, gender-, and weight-matched healthy controls. The results of this study will provide guidance for drug labeling recommendations for copanlisib in these subjects.

Benefit-risk assessment

As of today approximately 675 subjects with advanced cancer have been treated with copanlisib (BAY 806946) in eight different Phase 1 studies, three Phase 2 studies and three Phase 3 studies.

[…]

New text

Background

[…]

Copanlisib (BAY 80-6946, approved by the Food and Drug Administration [FDA] in September 2017) is a novel, highly selective, -panclass- PI3K inhibitor with potent activity against both α and δ isoforms, with *in vitro* IC_{50} of 0.5 nM and 0.7 nM, respectively.

[…]

Rationale of the study

[…]

This study will evaluate the PK and safety of a single 12-mg dose of copanlisib in subjects with moderate or severe hepatic impairment or severe renal impairment of copanlisib and in age-, gender-, and weight-matched healthy controls. The results of this study will provide guidance for drug labeling recommendations for copanlisib in these subjects.

Benefit-risk assessment

As of today approximately 675 subjects with advanced cancer have been treated with copanlisib (BAY 80-6946) in eight different Phase 1 studies, three Phase 2 studies and three Phase 3 studies.

[…]

15.1.2.4 Section 4 Study objectives

This section was changed as a result of Modification 1.

Old text

The primary objective of this study is to

- Investigate the PK of copanlisib following a single i.v. dose of 12 mg copanlisib in subjects with moderate hepatic (Child Pugh B) or severe renal impairment compared with healthy subjects

The secondary objective of this study is to

- Evaluate the PK of M-1 metabolite
- Assess the safety and tolerability of copanlisib when administered to subjects with moderate hepatic or severe renal impairment

[…]

New text

The primary objective of this study is to

- Investigate the PK of copanlisib following a single i.v. dose of 12 mg copanlisib in subjects with moderate hepatic (Child Pugh B), severe hepatic (Child Pugh C) or severe renal impairment compared with healthy subjects

The secondary objective of this study is to

- Evaluate the PK of M-1 metabolite
- Assess the safety and tolerability of copanlisib when administered to subjects with moderate hepatic, severe hepatic or severe renal impairment

[…]

15.1.2.5 Section 5 Study design

This section was changed as a result of Modification 1 and 12.

Old text

Design overview

This will be a multi-center, non-randomized, open-label, single-dose, parallel group, study consisting of ~~3~~ groups. The effect of moderate hepatic impairment (Child Pugh B) and severe renal impairment on the PK of copanlisib and M-1 will be investigated. In total, up to ~~32~~ evaluable male and female subjects with 8-~~16~~ evaluable subjects in the control group ~~and~~ 8 evaluable subjects ~~in~~ each ~~investigational group (hepatic and renal impairment)~~ will participate in the study (Table 5-1). Each subject will be administered 12 mg of copanlisib (i.v. over 1 h).

Table 5-1: Groups

Group	Description	Number of evaluable subjects
Control group	Normal hepatic and renal function group matched to the groups of hepatic and renal impairment	8-~~16~~
Group A	Moderate hepatic impairment group: Child-Pugh B (score 7-9) at the screening visit	8
Group B	Severe renal impairment group: eGFR 15-29 mL/min/1.73 m^2 at the screening visit based on the Modification of Diet in Renal Disease (MDRD) equation	8

The control group (normal hepatic and renal function) should match with the groups of hepatic and renal impairment. Matching criteria will be age, body weight, and gender. Mean age and body weight between the control group and the groups with hepatic and renal impairment should not vary by more than ±10 years and ±10 kg. Therefore, enrollment in the control group will remain open until the enrollment in the moderate hepatic and severe renal impairment groups is complete and a sufficient number of matching controls have been achieved for comparison.

[…]

~~At pre-dose, which in this study is the evening prior to the administration of the study medication, t~~he in- / exclusion criteria will be finally checked. During the treatment phase the study objectives will be followed, and the related measures will be performed.

[…]

Justification of the design

This study will investigate the PK of copanlisib and M-1 after administration of 12 mg of copanlisib i.v. over 1 h to subjects with moderate hepatic impairment or subjects with severe renal impairment compared to healthy subjects. The choice of the trial design was made based on the following:

- The PK measurements are the primary focuses of the study, therefore a non-randomized, open-label, parallel group design with ~~3~~ groups is considered adequate.

[…]

New text

Design overview

This will be a multi-center, non-randomized, open-label, single-dose, parallel group, study consisting of 4 groups. The effect of moderate hepatic impairment (Child Pugh B), severe

hepatic impairment (Child Pugh C) and severe renal impairment on the PK of copanlisib and M-1 will be investigated. In total, up to 44 evaluable male and female subjects with 8-22 evaluable subjects in the control group, 8 evaluable subjects each in the moderate hepatic and severe renal impairment investigational group, and 6 evaluable subjects in the severe hepatic investigational group will participate in the study (Table 5-1). Each subject will be administered 12 mg of copanlisib (i.v. over 1 h).

Table 5-1: Groups

Group	Description	Number of evaluable subjects
Control group	Normal hepatic and renal function group matched to the groups of hepatic and renal impairment	8-22
Group A	Moderate hepatic impairment group: Child-Pugh B (score 7-9) at the screening visit	8
Group B	Severe renal impairment group: eGFR 15-29 mL/min/1.73 m^2 at the screening visit based on the Modification of Diet in Renal Disease (MDRD) equation	8
Group C	Severe hepatic impairment group: Child-Pugh C (score 10-15) at the screening visit	6

The control group (normal hepatic and renal function) should match with the groups of hepatic and renal impairment. Matching criteria will be age, body weight, and gender. Mean age and body weight between the control group and the groups with hepatic and renal impairment should not vary by more than ±10 years and ±10 kg. Therefore, enrollment in the control group will remain open until the enrollment in the moderate and severe hepatic and severe renal impairment groups is complete and a sufficient number of matching controls have been achieved for comparison.

[…]

The in- / exclusion criteria will be finally checked after the results of the safety laboratory from the morning of Day -1 are available (evening of Day -1/morning of the dosing day). During the treatment phase the study objectives will be followed, and the related measures will be performed.

[…]

Justification of the design

This study will investigate the PK of copanlisib and M-1 after administration of 12 mg of copanlisib i.v. over 1 h to subjects with moderate hepatic impairment, with severe hepatic impairment or subjects with severe renal impairment compared to healthy subjects.

The choice of the trial design was made based on the following:

- The PK measurements are the primary focuses of the study, therefore a non-randomized, open-label, parallel group design with 4 groups is considered adequate.

[…]

15.1.2.6 Section 6.1.5 Subjects in Group C: severe hepatic impairment

This section was added as a result of Modification 1.

New section

Section 6.1.5: Subjects in Group C: severe hepatic impairment

22. Subjects with confirmed liver cirrhosis by at least one of the following criteria:
    - Histologically by prior liver biopsy showing cirrhosis.
    - Liver imaging (computer tomography, and/or ultrasound and/or magnetic resonance imaging scans, and/or fibroscan).
    - Laparoscopy.
23. Child-Pugh Clinical Assessment Score 10 to 15 at screening (see Section 16.3). For subjects with hepatic encephalopathy, the condition does not, in the investigator's opinion, interfere with the participant's ability to provide an appropriate informed consent.
24. Subjects with active Hepatitis B or Hepatitis C virus (HCV) can be included into the study but only in stable condition without ongoing or indicator of immediate antiviral treatment.
25. History of alcohol abuse is permissible providing that the results of alcohol test are negative at screening and on Day -1.

15.1.2.7 Section 6.2.1: All subjects

This section was changed as a result of Modification 15.

Old text

[…]

Laboratory examination

22. Neutrophils <1~~0~~000/µL at inclusion.
23. Positive urine drug screening at screening and Day -1.

[…]

New text

[…]

Laboratory examination

22. Neutrophils <1500/µL at inclusion.
23. Positive urine drug screening at screening and Day -1.

[…]

15.1.2.8 Section 6.2.5 Subject in Group C: severe hepatic impairment

This section was added as a result of Modification 1.

New section

Section 6.2.5: Subject in Group C: severe hepatic impairment

Medical and surgical history

64. Has active encephalopathy Grade III or IV, (time needed in the number connection test at screening or admission exceeds 80 sec) within 2 months prior to dosing. (For number connection test, please see Section 16.7).
65. Subjects with sclerosing cholangitis.
66. Failure of any other major organ other than the liver; severe infection, or any clinically significant illness within 4 weeks prior to study drug administration.
67. Renal failure with an eGFR <35 mL/min/1.73 m2 (according to MDRD formula, see Section 16.5).
68. Clinical evidence of severe ascites more than 6 L by ultrasound.
69. Esophageal variceal bleeding within 3 months prior to dosing.

Medication, drug use and special behavioral pattern

70. Subjects with a change of their chronic medication less than 4 weeks prior to study drug administration.

Laboratory examination

71. Any evidence of progressive liver disease (within the last 4 weeks) as indicated by liver transaminases (>4 x ULN), alkaline phosphatase (>4 x ULN), and GGT (>4 x ULN) (an isolated elevation of GGT above 4 times ULN will not exclude the subject).
72. Serum albumin <20 g/L.
73. Hemoglobin <8 g/dL.
74. Platelet count <50 x 109/L.

15.1.2.9 Section 6.4.2 Replacement

This section was changed as a result of Modification 1.

Old text

Subjects who drop out may be replaced to obtain a minimum of ~~24~~ subjects (8/group) valid for PK of copanlisib (i.e., all blood samples for PK should be available up to 1 week [168 h]). Additional healthy subjects may be enrolled to achieve demographic matching between healthy and impaired groups in up to ~~16~~ healthy subjects valid for PK of copanlisib (i.e., up to 1 week [168 h]).

New text

Subjects who drop out may be replaced to obtain a minimum of 30 subjects (8/group except for severe hepatic impairment: 6) valid for PK of copanlisib (i.e., all blood samples for PK should be available up to 1 week [168 h]). Additional healthy subjects may be enrolled to achieve demographic matching between healthy and impaired groups in up to 22 healthy subjects valid for PK of copanlisib (i.e., up to 1 week [168 h]).

15.1.2.10 Section 6.5 Subject identification

This section was changed as a result of Modification 12.

Old text

[…]

In the ~~evening of day -01 after final check of inclusion and exclusion criteria~~, subjects who meet the entry criteria will be sequentially assigned to a unique number in ascending order (treatment number).

New text

[…]

In the morning of the dosing day before start of infusion and after assessing the pre-dose blood pressure and glucose values, subjects who meet the entry criteria will be sequentially assigned to a unique number in ascending order (treatment number).

15.1.2.11 Section 7.1 Treatments to be administered

This section was changed as a result of Modification 1 and 4.

Old table

Table 7-1: Treatments administered

Group	Dose of copanlisib / route	Frequency of administration	No. of evaluable subjects
Control group (healthy subjects)	12 mg i.v. over 1 h	Single dose on Day 1	8-~~16~~
Group A (moderate hepatic impairment group)	12 mg i.v. over 1 h	Single dose on Day 1	8
Group B (renal impairment group)	12 mg i.v. over 1 h	Single dose on Day 1	8

New table

Table 7-1: Treatments administered

Group	Dose of copanlisib / route	Frequency of administration	No. of evaluable subjects
Control group (healthy subjects)	12 mg i.v. over 1 h	Single dose on Day 1	8-22
Group A (moderate hepatic impairment group)	12 mg i.v. over 1 h	Single dose on Day 1	8
Group B (severe renal impairment group)	12 mg i.v. over 1 h	Single dose on Day 1	8
Group C (severe hepatic impairment group)	12 mg i.v. over 1 h	Single dose on Day 1	6

15.1.2.12 Section 7.2 Identiy of study drugs

This section was changed as a result of Modification 16.

Old table

Table 7-2: Identity of copanlisib

Chemical name	2amino-N[7methoxy-8(3morpholin-4ylpropoxy)-2,3dihydroimidazo [1,2-c]quinazolin-5yl]pyrimidine-5carboxamide dihydrochloride
Substance code number	BAY 806946 (free base)
Appearance	white to slightly yellowish lyophilisate
Formulation	Freeze-dried product containing 78.8 mg BAY 84-1236 (= Copanlisib dihydrochloride; equivalent to 68.4 mg copanlisib, free base, BAY 806946) in a 6 mL injection vial
Composition	Copanlisib dihydrochloride, citric acid, mannitol, sodium hydroxide
Type of primary packaging	Glass vial for injections (6 mL)

New table

Table 7-2: Identity of copanlisib

Chemical name	2amino-N[7methoxy-8(3morpholin-4ylpropoxy)-2,3dihydroimidazo [1,2-c]quinazolin-5yl]pyrimidine-5carboxamide dihydrochloride
Substance code number	BAY 80-6946 (free base)
Appearance	white to slightly yellowish lyophilisate
Formulation	Freeze-dried product containing 78.8 mg BAY 84-1236 (= Copanlisib dihydrochloride; equivalent to 68.4 mg copanlisib, free base, BAY 80-6946) in a 6 mL injection vial
Composition	Copanlisib dihydrochloride, citric acid, mannitol, sodium hydroxide
Type of primary packaging	Glass vial for injections (6 mL)

15.1.2.13 Section 7.3 Treatment assignment

This section was changed as a result of Modification 1 and 2.

Old text

[…]

Subjects will be assigned to the following treatment numbers:

- Subjects with moderate hepatic impairment (site PPD
- Subjects with moderate hepatic impairment (site PPD
- Subjects with severe renal impairment (site PPD
- Subjects with severe renal impairment (site PPD
- Control subjects (site PPD
- Control subjects (site PPD

Additional numbers will be used in case of replacements being needed; the replacing participant will receive the original subject's treatment number PPD (site PPD or + PPD (site PPD

New text

[…]

Subjects will be assigned to the following treatment numbers:

- Subjects with moderate hepatic impairment (site PPD
- Subjects with moderate hepatic impairment (site PPD
- Subjects with severe renal impairment (site PPD
- Subjects with severe renal impairment (site PPD
- Subjects with severe hepatic impairment (site PPD
- Subjects with severe hepatic impairment (site PPD
- Subjects with severe hepatic impairment (site PPD

- Control subjects (site PPD
- Control subjects (site PPD
- Control subjects (site PPD

Additional numbers will be used in case of replacements being needed; the replacing participant will receive the original subject's treatment number PPD (site PPD or PPD (site PPD or PPD (site PPD

15.1.2.14 Section 7.4.1 Selection of doses in the study

This section was changed as a result of Modification 1.

Old text

Each subject will be given 12 mg of copanlisib (i.v. over 1 h).

Rationale for copanlisib 12 mg dose

The 12 mg dose has been chosen (not the Recommended Phase II Dose of 60 mg) to assess the effects of moderate hepatic or severe renal impairment on copanlisib PK. The rationale for this is the observed dose-linear PK of copanlisib and also the favorable safety profile of 12 mg copanlisib dose in healthy subjects (Human mass balance study 16353). Therefore, the 12 mg dose can be used across all ~~three~~ groups in this study.

[…]

New text

Each subject will be given 12 mg of copanlisib (i.v. over 1 h).

Rationale for copanlisib 12 mg dose

The 12 mg dose has been chosen (not the Recommended Phase II Dose of 60 mg) to assess the effects of moderate hepatic, severe hepatic or severe renal impairment on copanlisib PK. The rationale for this is the observed dose-linear PK of copanlisib and also the favorable safety profile of 12 mg copanlisib dose in healthy subjects (Human mass balance study 16353). Therefore, the 12 mg dose can be used across all four groups in this study.

[…]

15.1.2.15 Section 7.6 Drug logistics and accountability

This section was changed as a result of Modification 2.

Old text

All study drugs will be stored at the contracted pharmacy PPD or at the study site PPD in accordance with Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP) requirements and the instructions given by the clinical supplies department of the sponsor (or its affiliate/contract research organization [CRO]), and will be inaccessible to unauthorized personnel.

[…]

New text

All study drugs will be stored at the contracted pharmacy PPD or at the study site PPD in accordance with Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP) requirements and the instructions given by the clinical supplies department of the sponsor (or its affiliate/contract research organization [CRO]), and will be inaccessible to unauthorized personnel.

[…]

15.1.2.16 Section 9.2.1 Screening visit

This section was changed as a result of Modification 5.

Old text

- […]
- Physical examination (complete)
- Vital signs: blood pressure and pulse rate after resting for at least 10 min in ~~sitting~~ position and body temperature
- 12-lead ECG after resting for at least 10 min in a supine position
- […]

New text

- […]
- Physical examination (complete)
- Vital signs: blood pressure and pulse rate after resting for at least 10 min in supine position and body temperature
- 12-lead ECG after resting for at least 10 min in a supine position
- […]

15.1.2.17 Section 9.2.4.1 Dosing and profile day (Study Day 1, relative time: day 00)

This section was changed as a result of Modification 8 and 9.

Old text

- […]
- Abbreviated physical examination
- After a bed rest for at least 10 min, the following baseline measurements will be carried out: 12-lead ECG, vital signs (blood pressure/pulse rate, body temperature), blood sample (fasting capillary blood glucose, PK~~, protein binding assessment~~)
- Open questioning for / documentation of AEs and previous/concomitant medication (update)

- […]
- Throughout the day until 12 h p.a.:
  - Capillary glucose 1h after start of copanlisib infusion (end of infusion), 1, 2, 3, ~~4,~~ 6, 8 h after start of infusion, further capillary glucose if necessary
  - Further capillary glucose assessment at the discretion of the investigator (based of previous blood glucose levels)
  - […]

New text

- […]
- Abbreviated physical examination
- After a bed rest for at least 10 min, the following baseline measurements will be carried out: 12-lead ECG, vital signs (blood pressure/pulse rate, body temperature), blood sample (fasting capillary blood glucose, PK)
- Open questioning for / documentation of AEs and previous/concomitant medication (update)
- […]
- Throughout the day until 12 h p.a.:
  - Capillary glucose 1h after start of copanlisib infusion (end of infusion), 1, 2, 3, 6, 8 h after start of infusion, further capillary glucose if necessary
  - Further capillary glucose assessment at the discretion of the investigator (based of previous blood glucose levels)
  - […]

15.1.2.18 Section 9.2.6.1 Restrictions

This section was changed as a result of Modification 10.

Old table

Table 9-1: Restrictions during the study

What?	Restriction
Smoking	not allowed during the study
Alcohol	not permitted from 48 h prior to the dosing until Day 7
[…]	

New table

Table 9-1: Restrictions during the study

What?	Restriction
Smoking	not allowed during the in-house phase of the study
Alcohol	not permitted from 48 h prior to the dosing until Day 7
[…]	

15.1.2.19 Section 10.3 Variables and planned statistical analyses

This section was changed as a result of Modification 1.

Old text

[…]

- **Pharmacokinetic variables**

[…]

To investigate the primary objective of this study regarding hepatic and renal impairment, analysis of variance appropriate for a parallel design will be fitted to the natural logarithmic transformation of PK parameters (AUC(0-168), AUC and C_{max}) of copanlisib . The test/reference comparison ratio of geometric least-squares means and associated 90% confidence intervals (CIs) for each PK parameter in the moderate hepatic or severe renal impairment group versus the matched healthy subjects group will be calculated by exponentiation of the natural-log scale point estimate and the associated 90% CI.

New text

[…]

- **Pharmacokinetic variables**

[…]

To investigate the primary objective of this study regarding hepatic and renal impairment, analysis of variance appropriate for a parallel design will be fitted to the natural logarithmic transformation of PK parameters (AUC(0-168), AUC and C_{max}) of copanlisib . The test/reference comparison ratio of geometric least-squares means and associated 90% confidence intervals (CIs) for each PK parameter in the moderate hepatic, severe hepatic or severe renal impairment group versus the matched healthy subjects group will be calculated by exponentiation of the natural-log scale point estimate and the associated 90% CI.

15.1.2.20 Section 10.4 Determination of sample size

This section was changed as a result of Modification 1.

Old text/table

The study population will consist of up to ~~32~~ evaluable male and female subjects with 8-~~16~~ evaluable subjects in the control group ~~and~~ 8 evaluable subjects ~~in~~ each ~~investigational group (hepatic and renal impairment)~~. The sample size of 8 subjects in each of the groups with impaired hepatic and renal function has been selected based on practical consideration and following the FDA guidance [4][5].

[…]

For AUC(0-168), a sample size of 8 eligible subjects ~~per~~ each group would provide an approximately 90% chance for the 90% confidence interval for the ratio of geometric least-squares means between impaired subjects and healthy subjects to be within a 2-fold difference, that is, within limits of 50% to 200% for AUC(0-168). This can be shown in ~~the table below~~ based on different observed ratios.

Table 10-1: 90% Confidence interval for copanlisib

Observed Ratio	90% CI for the ratio
1	(0.685, 1.461)
1.1	(0.753, 1.607)
1.2	(0.822, 1.753)
1.3	(0.890, 1.899)

New text/tables

The study population will consist of up to 44 evaluable male and female subjects with 8-22 evaluable subjects in the control group, 8 evaluable subjects each in the moderate hepatic and severe renal impairment investigational group, and 6 evaluable subjects in the severe hepatic impairment investigational group. The sample size of 8 subjects in each of the groups with impaired moderate hepatic and severe renal function and 6 subjects in the severe hepatic impairment group has been selected based on practical consideration and following the FDA guidance [4][5].

[…]

For AUC(0-168), a sample size of 8 eligible subjects each in the control, moderate hepatic and severe renal impairment investigational group would provide an approximately 90% chance for the 90% confidence interval for the ratio of geometric least-squares means between impaired subjects and healthy subjects to be within a 2-fold difference, that is, within limits of 50% to 200% for AUC(0-168). This can be shown in Table 10-1 based on different observed ratios.

Table 10-1: 90% Confidence interval for copanlisib with N=8 per group

Observed Ratio	90% CI for the ratio
1	(0.685, 1.461)
1.1	(0.753, 1.607)
1.2	(0.822, 1.753)
1.3	(0.890, 1.899)

A sample size of 6 eligible subjects per each in the control and severe hepatic impairment investigational group would provide an approximately 90% chance for the 90% confidence interval for the ratio of geometric least-squares means between impaired subjects and healthy subjects to be within an approximately 2-fold difference, that is, within limits of 50% to 207% for AUC(0-168) as shown in Table 10-2 based on different observed ratios.

Table 10-2: 90% Confidence interval for copanlisib with N=6 per group

Observed Ratio	90% CI for the ratio
1	(0.628, 1.593)
1.1	(0.691, 1.752)
1.2	(0.753, 1.911)
1.3	(0.816, 2.07)

15.1.2.21 Section 10.5 Planned interim analyses

This section was changed as a result of Modification 1.

Old text

~~A formal interim analysis is not planned. However; all data will be reviewed during the study on an ongoing basis for potential deviations from expected safety and pharmacokinetics results~~.

New text

An interim analysis will be conducted after 8 evaluable subjects with moderate hepatic impairment and 8 evaluable subjects with severe renal impairment with their corresponding matching healthy volunteers have completed the study to fulfill the first part of the post marketing requirement as agreed with the FDA (July 2019) based on the accelerated approval of copanlisib (September 14, 2017). This interim analysis will also serve as a final analysis on the moderate hepatic impairment and severe renal impairment groups in the final clinical study report. The results of the final report will include subjects with severe hepatic impairment as agreed with FDA (July 2021).

15.1.2.22 Section 16.1 Study flow chart

This section was changed as a result of Modification 7, 11, 12, and 13.

Old table

Table 16-1: Study flow chart: Screening (all subjects) (continued)

	Screening[a]
Study Day	**-28 to -2**
Relative time day	**- 28 to -02**
Informed consent (date of written informed consent)	X
[…]	
Blood pressure ~~[b,c]~~, pulse rate ~~[b,c]~~, body temperature	X
[…]	

[…]
b Before any study specific tests or procedures are done
[…]

New table

Table 16-1: Study flow chart: Screening (all subjects) (continued)

	Screening[a]
Study Day	**-28 to -2**
Relative time day	**- 28 to -02**
Informed consent (date of written informed consent)[b]	X
[…]	
Blood pressure [c], pulse rate [c], body temperature	X
[…]	

[…]
b Before any study specific tests or procedures are done
[…]

Old table

Table 16-1: Study flow chart (continued): -~~00~~d~~16~~h – ~~07~~d00h (all subjects) (continued)

Study period		**Treatment Period**																			
Study Day		**-1**							**1**								**2**	**3**	**4**	**5**	**6**
Relative time	**day**	**-01**	**-00**	**-00**	**00**	**00**	**00**	**00**	**00**	**00**	**00**	**00**	**00**	**00**	**00**	**00**	**01**	**02**	**03**	**04**	**05**
	hour	**00**	**01**	**00**	**00**	**00**	**01**	**01**	**02**	**02**	**03**	**05**	**06**	**08**	**10**	**12**	**00**	**00**	**00**	**00**	**00**
	minute	**00**	**30**	**30**	**00**	**10**	**00**	**30**	**00**	**30**	**00**	**00**	**00**	**00**	**00**	**00**	**00**	**00**	**00**	**00**	**00**
Approximate 24-hour clock time 1st subject		*08:00*	*06:30*	*07:30*	*08:00*	*08:10*	*09:00*	*09:30*	*10:00*	*10:30*	*11:00*	*13:00*	*14:00*	*16:00*	*18:00*	*20:00*	*08:00*	*08:00*	*08:00*	*08:00*	*08:00*
In-house		X		→	→	→	→	→	→	→	→	→	→	→	→	→	→	X			
Ambulatory follow-up visits																			X	X	X
Final check of inclusion/exclusion criteria		X																			
[…]																					
Fasting[i]				X	→	→	→	→	→~~X~~												
[…]																		X			

[…]

New table

Table 16-1: Study flow chart (continued): -01d00h – 05d00h (all subjects) (continued)

Study period		**Treatment Period**																			
Study Day		**-1**							**1**								**2**	**3**	**4**	**5**	**6**
Relative time	**day**	**-01**	**-00**	**-00**	**00**	**00**	**00**	**00**	**00**	**00**	**00**	**00**	**00**	**00**	**00**	**00**	**01**	**02**	**03**	**04**	**05**
	hour	**00**	**01**	**00**	**00**	**00**	**01**	**01**	**02**	**02**	**03**	**05**	**06**	**08**	**10**	**12**	**00**	**00**	**00**	**00**	**00**
	minute	**00**	**30**	**30**	**00**	**10**	**00**	**30**	**00**	**30**	**00**	**00**	**00**	**00**	**00**	**00**	**00**	**00**	**00**	**00**	**00**
Approximate 24-hour clock time 1st subject		*08:00*	*06:30*	*07:30*	*08:00*	*08:10*	*09:00*	*09:30*	*10:00*	*10:30*	*11:00*	*13:00*	*14:00*	*16:00*	*18:00*	*20:00*	*08:00*	*08:00*	*08:00*	*08:00*	*08:00*
In-house		X		→	→	→	→	→	→	→	→	→	→	→	→	→	→	X			
Ambulatory follow-up visits																			X	X	X
Final check of inclusion/exclusion criteria		X[l]																			
[…]																					
Fasting[i]				X	→	→	→	→	→	→	→X										
[…]																		X			

[…]

l Final check of inclusion and exclusion criteria takes place after availability of the safety laboratory results (evening of Day -1 or morning of Day 1)

15.1.2.23 Section 16.2 Laboratory analyses

This section was changed as a result of Modification 2 and 6.

Old table

Table 16-2: Parameters of laboratory analyses

[…]	
Urinalysis - dipstick: Hemoglobin/erythrocytes, pH, protein, glucose, bilirubin, urobilinogen, ketone, nitrite, leukocytes (semi-quantitatively/dipstick)	PPD None (to be performed at the study site) PPD Local laboratory
[…]	
Pregnancy test in blood or urine beta-hCG (within 7 days prior to dosing), in women with reproductive potential including women whose partners are sterilized)	Blood: Local laboratory Urine: None (to be performed at the study site)
Urine drug screen: Methadone, cocaine, amphetamines and methamphetamine/ecstacy, cannabinoids, barbiturates, benzodiazepines, tricyclic antidepressants, phencyclidin, morphine/opiates	None (to be performed at the study site)
[…]	

New table

Table 16-2: Parameters of laboratory analyses

[…]	
Urinalysis - dipstick: Hemoglobin/erythrocytes, pH, protein, glucose, bilirubin, urobilinogen, ketone, nitrite, leukocytes (semi-quantitatively/dipstick)	PPD None (to be performed at the study site) PPD Local laboratory PPD local laboratory
[…]	
Pregnancy test in blood or urine beta-hCG (within 7 days prior to dosing), in women with reproductive potential including women whose partners are sterilized)	Blood: Local laboratory Urine: None (to be performed at the study site)
Follicle stimulating hormone in blood In postmenopausal women ≤ 50 years of age	Local laboratory
Urine drug screen: Methadone, cocaine, amphetamines and methamphetamine/ecstacy, cannabinoids, barbiturates, benzodiazepines, tricyclic antidepressants, phencyclidin, morphine/opiates	None (to be performed at the study site)
[…]	

15.1.2.24 Section 16.3 Assessment of hepatic impairment

This section was added as a result of Modification 1.

Old text

In Group A, subjects with moderate hepatic impairment will be included (Child-Pugh B: score 7-9).

[…]

New text

In Group A, subjects with moderate hepatic impairment will be included (Child-Pugh B: score 7-9) and in Group C, subjects with severe hepatic impairment will be included (Child-Pugh C: score 10-15).

[…]

16. Appendices

16.1 Study flow chart - amended

The reference point (relative time: day 00 : hour 00 : minute 00) for the time matrix to be used for data evaluation will be the administration of copanlisib. All measures / actions to be performed **before this reference point** will be assigned to **negative** time points, all subsequent measures / actions will have positive time points. Table 16-1 in the following provides a flow chart presenting the time points for the study related measures / actions.

Table 16-1: **Study flow chart: Screening (all subjects) (continued) - amended**

	Screening[a]
Study Day	**-28 to -2**
Relative time day	**- 28 to -02**
Informed consent (date of written informed consent)[b][32]	X
Allocation of screening number	X
Demographic data collection	X
Height, weight, body mass index	X
Medical and surgical history	X
Smoking history, alcohol / diet	X
Participation in previous clinical studies	X
Current and previous medication	X
Complete physical examination	X
Blood pressure [c], pulse rate [c], body temperature	X
12-lead electrocardiogram [c]	X
Blood sampling	
- Safety (clinical chemistry, hematology, coagulation) [d]	X
- HbA1C	X
- Virology: HIV, HBs-Ag, Anti HCV-AB	X
Urine sampling	
- Safety (dipstick ± sediment) [d]	X
- Drug screen	X
Alcohol breath test	X
Child Pugh Scoring (for hepatic impaired subjects)	X
Number connection test (for hepatic impaired subjects)	X
eGFR calculation [e]	X
Adverse events	X
Eligibility check	X

anti HCV-AB=hepatitis C virus antibodies, eGFR=estimated glomerular filtration rate, HbA1c=glycated hemoglobin, HBs-AG=Hepatitis B surface antigen, HIV=human immunodeficiency virus

X To be done at the time point indicated
a Within 28 days prior to treatment
b Before any study specific tests or procedures are done
c After at least 10 min rest in supine position
d In fasted state
e For all subject calculation according to MDRD

[32] Footnote “b” shifted from blood pressure and pulse rate to informed consent according to Amendment 1

Table 16-1: Study flow chart (continued): -01d00h – 05d00h[33] (all subjects) (continued) - amended

Study period		**Treatment Period**																				
Study Day		**-1**							**1**									**2**	**3**	**4**	**5**	**6**
Relative time	**day**	**-01**	**-00**	**-00**	**00**	**00**	**00**	**00**	**00**	**00**	**00**	**00**	**00**	**00**	**00**	**00**	**00**	**01**	**02**	**03**	**04**	**05**
	hour	**00**	**01**	**00**	**00**	**00**	**01**	**01**	**02**	**02**	**03**	**05**	**06**	**08**	**10**	**12**		**00**	**00**	**00**	**00**	**00**
	minute	**00**	**30**	**30**	**00**	**10**	**00**	**30**	**00**	**30**	**00**	**00**	**00**	**00**	**00**	**00**		**00**	**00**	**00**	**00**	**00**
Approximate 24-hour clock time 1st subject		*08:00*	*06:30*	*07:30*	*08:00*	*08:10*	*09:00*	*09:30*	*10:00*	*10:30*	*11:00*	*13:00*	*14:00*	*16:00*	*18:00*	*20:00*		*08:00*	*08:00*	*08:00*	*08:00*	*08:00*
In-house		X		→	→	→	→	→	→	→	→	→	→	→	→	→		→	X			
Ambulatory follow-up visits																				X	X	X
Final check of inclusion/exclusion criteria		X[!]																				
Medical History		X[a]																				
Pregnancy test in blood or urine		X[f]																				
Complete physical examination		X																				
Abbreviated physical examination				X														X	X			
Urine drug screen, alcohol breath test		X																				
Fasting[i]				X	→	→	→	→	→	→	→X[34]											
Low glycemic breakfast[i]			X																			
Study drug administration[i]					X	→	→X															
Blood sampling																						
- PK assessment of copanlisib and M-1				X		X	X	X	X	X	X	X		X				X	X	X	X	X
- Protein binding/ fraction unbound (fu) calculation							X											X				
- Safety[d] (clinical chemistry, hematology, coagulation)		X																X	X			
Urine sampling																						
- PK of copanlisib and M-1					X	→	→	→	→	→	→	→	→	→X	→	→		→X				

[33] Time period revised in title according to Amendment 1

[34] Fasting period prolonged until 2 h after end of infusion according to Amendment 1 (protocol Version 1.0 stated fasting lasts until 1 h after end of infusion)

Table 16-1: Study flow chart (continued): -01d00h – 05d00h[33] (all subjects) (continued) - amended

Study period		**Treatment Period**																				
Study Day		**-1**							**1**								**2**	**3**	**4**	**5**	**6**
Relative time	**day**	**-01**	**-00**	**-00**	**00**	**00**	**00**	**00**	**00**	**00**	**00**	**00**	**00**	**00**	**00**	**00**	**01**	**02**	**03**	**04**	**05**
	hour	**00**	**01**	**00**	**00**	**00**	**01**	**01**	**02**	**02**	**03**	**05**	**06**	**08**	**10**	**12**	**00**	**00**	**00**	**00**	**00**
	minute	**00**	**30**	**30**	**00**	**10**	**00**	**30**	**00**	**30**	**00**	**00**	**00**	**00**	**00**	**00**	**00**	**00**	**00**	**00**	**00**
Approximate 24-hour clock time 1st subject		*08:00*	*06:30*	*07:30*	*08:00*	*08:10*	*09:00*	*09:30*	*10:00*	*10:30*	*11:00*	*13:00*	*14:00*	*16:00*	*18:00*	*20:00*	*08:00*	*08:00*	*08:00*	*08:00*	*08:00*
- Safety[d] (dipstick ± sediment)		X															X	X			
12-lead electrocardiogram [c]		X		X			X						X				X	X			
Vital signs (body temperature, blood pressure/pulse rate)[c]		X		X			X						X				X	X			
Capillary glucose			X[k]				X		X		X		X	X	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]
Documentation of meal time				X	→	→	→	→	→	→	→	→	→	→	→	→X	X[j]	X[j]			
Adverse events		X		→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Previous/Concomitant medications		X		→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Discharge from ward																		X			

EoI=end of infusion, PK=pharmacokinetics

X To be done at the time point indicated

→ To be done continuously, starting from the time point indicated

a Medical History: update only

c After at least 10 min rest in supine position

d In fasted state

f Within 7 days prior to dosing in women with reproductive potential (including women whose partners are sterilized

g Not mandatory, depends on result of prior capillary glucose results

h End-of-treatment: within 7 + 3 days after administration

i Subjects will receive a low glycemic breakfast at 1.5 h prior to start of the infusion. The breakfast should be completed 1 h prior to start of the infusion. Subjects should remain fasted until 2 h after the end of infusion. During the fasting period after the infusion water may be consumed.

j Only in case of hyperglycemia

k Prior to glycemic breakfast

l Final check of inclusion and exclusion criteria takes place after availability of the safety laboratory results (evening of Day -1 or morning of Day 1).[35]

[35] Footnote added according to Amendment 1

Table 16-1: Study flow chart (continued): End-of-treatment and safety follow-up (all subjects)

	End-of treatment	Telephone interview	
Study Day	**8 (+3)**	**15 (±3)**	**31 (+3)**
Relative day time	**7 (+3)**	**14 (±3)**	**30 (+3)**
Ambulatory follow-up visits	X		
Complete physical examination	X		
Vital signs	X		
12-lead ECG	X		
Blood sampling			
- safety (clinical chemistry, hematology, coagulation)	X		
- PK assessment of copanlisib and M-1	X		
Urine sampling			
- Safety[d] (dipstick ± sediment)	X		
Adverse events	X	X[a]	X[a]
Concomitant medication	X	X	X

a Any AEs ongoing at Safety Follow-up visit should be followed until resolution or stabilization unless, in the investigator's opinion, the condition is unlikely to resolve due to the subject's underlying disease. All SAEs (including deaths) occurring up to 30 days after the single dose should be reported to the sponsor per usual SAE reporting procedures.

d In fasted state

16.2 Laboratory analyses - amended

Detailed information about the volume, collection, processing, storage and shipment of the samples will be provided separately (e.g. sample handling sheets and / or laboratory manual).

The amount of blood planned to be withdrawn during the course of this study will be below 500 mL. The approximate volume will be given in the Subject Information Sheet and Consent Form. The calculation sheet of the total amount of blood to be withdrawn per subject will be stored in the study files.

Table 16-2 provides information on the parameters to be analyzed, and indicates the laboratories to be used.

Samples relevant for the subject's safety evaluation will be immediately analyzed, and the respective results will be made promptly available to the investigator. Samples collected for non-safety purposes may be stored under pre-defined conditions until final analysis.

Sampling in the morning for the laboratory examinations will be done on a fasting state of the subjects, i.e. an overnight fast of ≥ 10 h has to be adhered to: nothing to eat or drink except for water. During the treatment period, refer to Section 9.2.6.1 and Section 9.2.6.2 for alimentary restrictions imposed.

Table 16-2: Parameters of laboratory analyses - amended

Parameters (by group)	**Sample destination**
Hematology: Leukocytes, erythrocytes, hemoglobin, hematocrit, MCV, MCH, MCHC, platelets, WBC with differential to include absolute neutrophil, lymphocyte, monocyte, basophil and eosinophil counts.	Local laboratory
Coagulation: Prothrombin time (Quick), reagent-independent prothrombin ratio (INR, international normalized ratio), activated partial thromboplastin time	Local laboratory
Clinical chemistry: AST, ALT, AP, GGT, LDH, CK, total amylase, lipase, plasma glucose (fasted), cholesterol (total), triglycerides, creatinine, urea, uric acid, total bilirubin, total protein, albumin, sodium, potassium, calcium (total/corrected calcium or ionized calcium), chloride, magnesium, inorganic phosphate	Local laboratory
Glucose metabolism: HbA1c	Local laboratory
Virology: Hepatitis B surface antigen, hepatitis C virus antibodies, human immunodeficiency virus antibodies 1/2 (at screening)	Local laboratory
Urinalysis - dipstick: Hemoglobin/erythrocytes, pH, protein, glucose, bilirubin, urobilinogen, ketone, nitrite, leukocytes (semi-quantitatively/dipstick)	PPD None (to be performed at the study site) PPD Local laboratory PPD local laboratory[36]
Urinalysis - sediment: Urine sediment only if dipstick indicates abnormalities	Local laboratory
Pregnancy test in blood or urine beta-hCG (within 7 days prior to dosing), in women with reproductive potential including women whose partners are sterilized)	Blood: Local laboratory Urine: None (to be performed at the study site)
Follicle stimulating hormone in blood In postmenopausal women ≤ 50 years of age[37]	Local laboratory
Urine drug screen: Methadone, cocaine, amphetamines and methamphetamine/ecstacy, cannabinoids, barbiturates, benzodiazepines, tricyclic antidepressants, phencyclidin, morphine/opiates	None (to be performed at the study site)
Alcohol breath test	None (to be performed at the study site)
Bioanalysis: Copanlisib and its metabolite M1 in plasma (including assessment of protein binding)	Bioanalytical laboratories

[36] Included according to Amendment 1
[37] Included according to Amendment 1

16.3 Assessment of hepatic impairment - amended

Child Pugh system

In Group A, subjects with moderate hepatic impairment will be included (Child-Pugh B: score 7-9) and in Group C, subjects with severe hepatic impairment will be included (Child-Pugh C: score 10-15).[38]

Hepatic impairment will be assessed using the classification of Child Pugh (Table 16-3): 5 factors will be scored from 1 point to 3 points. The Child Pugh score is calculated by adding the scores of the 5 factors and can range from 5 to 15.

Table 16-3: Child Pugh system

	Points scored for observed findings		
	1	**2**	**3**
Encephalopathy grade*	None	1 or 2	3 or 4
Ascites	absent	slight	moderate
Serum bilirubin (mg/dL)	<2	2 to 3	>3
Serum albumin (g/dL)	>3.5	2.8 to 3.5	<2.8
Prothrombin time (sec prolonged)	<4	4 to 6	>6

* Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity
Assessment as A or mild if 5 or 6 points; B or moderate if 7 to 9 points; and C or severe if 10 to 15 points.

Assessment of hepatic encephalopathy

The exclusion of a possible hepatic encephalopathy will be performed using a trailmaking test, the number connection test (NCT) (see Section 16.7). This test measures cognitive motor abilities. In the NCT, subjects have to connect numbers printed on paper consecutively from 1 to 25, as quickly as possible. Errors are not enumerated, but subjects are instructed to return to the preceding correct number and then carry on. The test score is the time the subject needs to perform the test, including the time needed to correct the errors. A low score indicates a good performance.

If the time needed exceeds 80 sec, subjects will be excluded from the study. If the subject needs <30 sec, hepatic encephalopathy can be excluded. An example of the NCT will be given in the clinical study report.

In addition, an experienced physician will assess hepatic encephalopathy by performing a standard neurological examination, which includes handwriting and common amnestic testing.

[38] Included as subjects with severe hepatic impairment will be included into the study according to Amendment 1

16.4 Assessment of renal impairment

Stages of renal impairment are based on Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines for Chronic Kidney Disease (CKD) from the National Kidney Foundation in 2002; GFR: glomerular filtration rate [6] (Table 16-4).

Table 16-4: Stages of chronic kidney disease[a]

Stage	Description[b]	eGFR[b] (mL/min/1.73m^2)
1	Kidney damage with normal or increased GFR	≥90
2	Kidney damage with mild decrease in GFR	60-89
3	Moderate decrease in GFR	30-59
4	Severe decrease in GFR	15-29
5	Kidney failure	<15 (or dialysis)

a = Chronic kidney disease is defined as either kidney damage or GFR <60 mL/min/1.73 m^2 for ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.
b = eGFR: estimate of GFR based on an MDRD equation

16.5 Estimation of glomerular filtration rate (eGFR) using modification of diet in renal disease

In accordance with established nephrology practice and guidelines, renal function at baseline and throughout the study will be assessed by means of the eGFR, calculated using the abbreviated MDRD Study equation.

This equation of 4 variables (serum creatinine level, age, sex, and ethnicity) is recommended by the National Kidney Foundation for use in individuals 18 years or older. The formula is as follows:

GFR (mL/min/1.73 m^2) = k × $(S_{cr})^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female) × (1.212 if African American),

where

k=175 if serum creatinine was measured by methods calibrated to an IDMS reference method.

For the purpose of the study, it is recommended to use the Bayer-verified calculator (preferred) or online MDRD GFR calculator at http://mdrd.com/

16.6 Estimated creatinine clearance (CLcr) using Cockcroft-Gault (C-G) equation

The CL_{cr} expressed as mL/min, is yielded by Cockcroft- Gault Equation, relating serum creatinine with age (in years) and body weight (in kg).

CL_{cr} is estimated from a spot serum creatinine determination. The C-G Equation assumes that women have a 15% lower CL_{cr} compared to men.

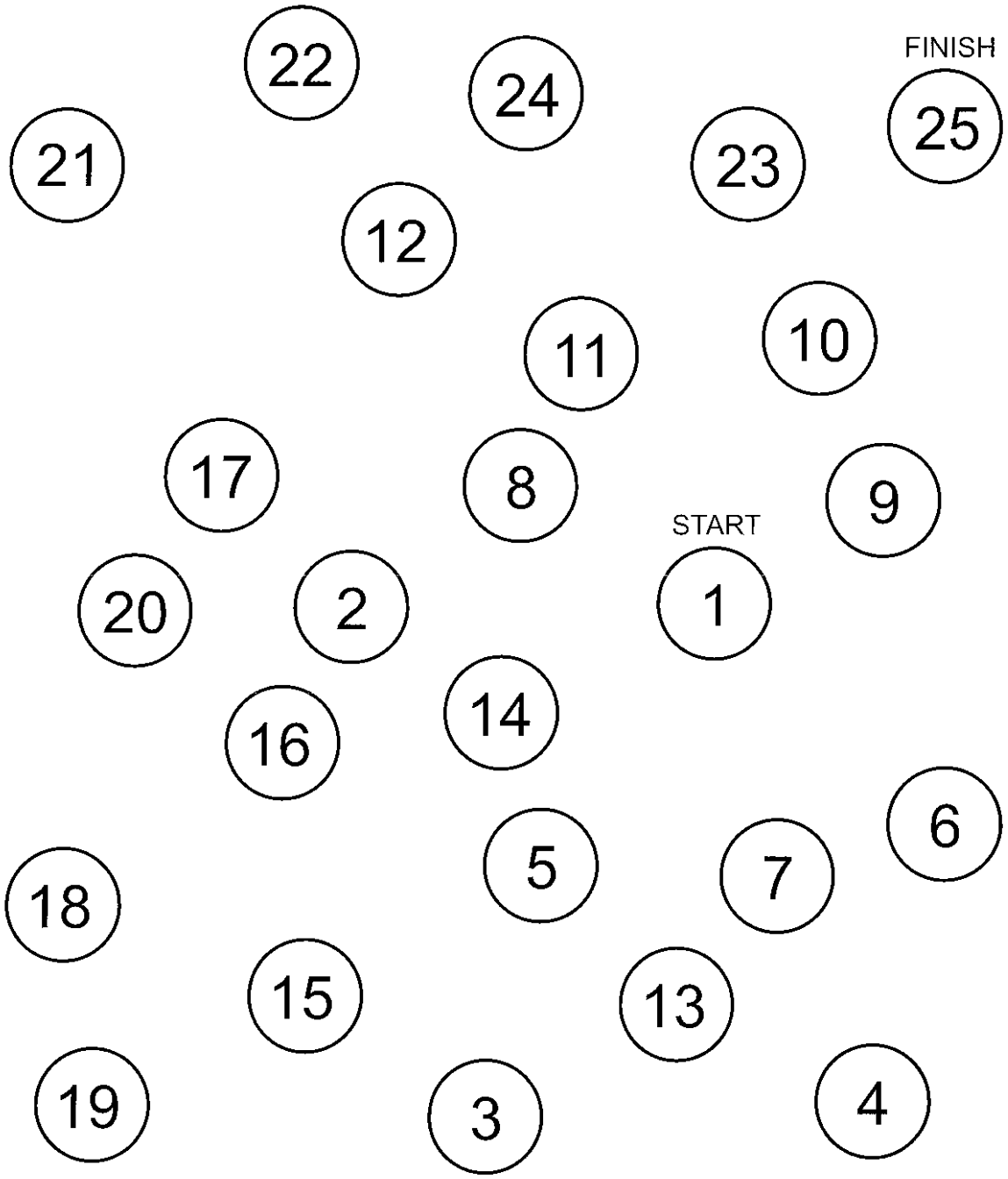
$$CLcr\ (mL/min) = \frac{[140 - age\ (years)] \times weight\ (kg)}{72 \times serum\ creatinine\ (mg/dL)} \{\times 0.85\ for\ female\ patients\}$$

16.7 Number connection test at screening

In subjects with hepatic impairment only

Time to complete: _____ sec.

Investigator's signature: _____


22
24
FINISH
25
21
23
12
11
10
17
8
9
START
20
2
1
14
16
6
5
7
18
15
13
19
3
4

16.8 List of CYP3A4 inhibitors and inducers for reference. Only STRONG CYP3A4 inhibitors and inducers are not allowed in this study

Table 16-5: CYP3A4 inhibitors

Substance name	Inhibitor strength
Amiodarone	Weak
Amlodipine	Weak
Amprenavir	Moderate
Aprepitant	Moderate
Atazanavir	Moderate
Azithromycine	Weak
Berberine	Weak
Boceprevir[1]	**Strong**
Bicalutamide	Weak
Casopitant	Moderate
Chloramphenicol	Moderate
Chlorzoxazone	Weak
Ciclosporine/Cyclosporine	Weak
Cilostazol	Weak
Cimetidine	Weak
Clarithromycin[1]	**Strong**
Citrus and grape fruit juice	Depends on dose
Cobicistat[1]	**Strong**
Conivaptan[1]	**Strong**
Crizotinib	Moderate
Darunavir	Moderate
Dasatinib	Weak
Delavirdine	Moderate
Diltiazem	Moderate
Dronedarone	Moderate
Erythromycin	Moderate
Everolimus	Weak
Fluconazole	Moderate
Fluoxetine	Moderate
Fluvoxamine	Weak
Fosamprenavir	Moderate
Fosaprepitant	Weak
Ginkgo biloba	Weak
Idealisib[1]	Strong
Imatinib	Moderate
Indinavir[1]	**Strong**
Isoniazid	Weak
Itraconazole[1]	**Strong**
Ivacaftor	Weak
Ketoconazole[1]	**Strong**
Lapatinib	Weak
Lomitapide	Weak

Table 16 5: CYP3A4 inhibitors (continued)

Substance name	Inhibitor strength
Lopinavir[1]	**Strong**
Mibefradil[1]	**Strong**
Miconazole[1]	**Strong**
Mifepristone	Moderate
Nefazodone[1]	**Strong**
Nelfinavir[1]	**Strong**
Nilotinib	Weak
Pazopanib	Weak
Posaconazole[1]	**Strong**
Quinupristin/dalfopristin	Moderate
Propiverine	Weak
Ranitidine	Weak
Ranolazine	Moderate
Ritonavir[1]	**Strong**
Roxithromycin	Weak
Saquinavir[1]	**Strong**
Schisanda sphenantera	Moderate
Sitaxentan	Weak
Tabimorelin	Weak
Tacrolimus	Weak
Telaprevir[1]	**Strong**
Telithromycin	**Strong**
Ticagrelor	Weak
Tipranavir[1]	**Strong**
Tofisopam	Moderate
Tolvaptan	Weak
Valproic acid (valproate)	Moderate
Verapamil	Moderate
Voriconazole[1]	**Strong**

[1] Only strong CYP3A4 inhibitors will be forbidden.

Table 16-6: CYP3A4 inducers

Substance name	Inducer strength
Phenobarbital[1]	**Strong**
Armodafinil	Weak
Avasimibe[1]	**Strong**
Bexarotene	Weak
Bosentan	Moderate
Carbamazepine[1]	**Strong**
Clobazam	Weak
Dexamethasone	Weak
Enzalutamide	Potent
Efavirenz	Moderate
Etravirine	Moderate
Genistein	Weak
Hypericum[1]	**Strong**
Lersivirine	Weak
Lopinavir	Moderate
Lumacaftor[1]	**Strong**
Mephenytoin	Moderate
Methylphenobarbital	Potent
Mitotane	Potent
Modafinil	Moderate
Nafcillin	Moderate
Nevirapine	Weak
Oxcarbazepine	Weak
Phenytoin[1]	**Strong**
Pleconaril	Weak
Quercetin	Weak
Rifabutin	Moderate
Rifampicin[1]	**Strong**
Rifamycin[1]	**Strong**
Rufinamide	Weak
Semagacestat	Moderate
Sulfinopyrazone	Weak
Thioridazine	Moderate
Vemurafenib	Weak

[1] Only strong CYP3A4 inducers will be forbidden.

16.9 NYHA classification

Table 16-7: NYHA classification

Class	Functional Capacity: How a patient with cardiac disease feels during physical activity
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.
Class	**Objective assessment**
A	No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
B	Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
C	Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
D	Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.

Source: *Adapted from Dolgin M, Association NYH, Fox AC, Gorlin R, Levin RI, New York Heart Association. Criteria Committee. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, MA: Lippincott Williams and Wilkins; March 1, 1994.*
Original source: *Criteria Committee, New York Heart Association , Inc. Diseases of the Heart and Blood Vessels. Nomenclature and Criteria for diagnosis, 6th edition Boston, Little, Brown and Co. 1964, p 114.*