Cover page of the integrated protocol

Study title: A non-randomized, open-label, multi-center, Phase I/II study of PI3K inhibitor copanlisib in pediatric patients with relapsed/refractory solid tumors or lymphoma

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

- **Original protocol,** Version 1.0, dated 03 AUG 2017
- **Amendment 01. (global amendment described in Section 15.1)**
  forming integrated protocol Version 2.0, dated 04 APR 2019
- **Amendment 02. (global amendment described in Section 15.1)**
  forming integrated protocol Version 3.0, dated 05 MAY 2020

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

1. Title page

A non-randomized, open-label, multi-center, Phase I/II study of PI3K inhibitor copanlisib in pediatric patients with relapsed/refractory solid tumors or lymphoma

Safety, tolerability, efficacy and pharmacokinetics of copanlisib in pediatric patients

Test drug:	BAY 80-6946 / Copanlisib		
Study purpose:	MTD finding, safety and activity		
Clinical study phase:	I/II	Date:	05 MAY 2020
Registration:	EudraCT: no. 2017-000383-15	Version no.:	3.0
Sponsor's study no.:	BAY 80-6946 /19176		
Sponsor:	Non-US: Bayer AG, D-51368 Leverkusen, Germany US territory: Bayer HealthCare Pharmaceuticals Inc., 100 Bayer Boulevard, P.O. Box 915, Whippany NJ 07981-0915, USA		
Sponsor's medical expert:	PPD MD 100 Bayer Boulevard, P.O. Box 915 Whippany, NJ 07981-0915 USA Telephone no.: PPD E-mail: PPD		

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

Signature of the sponsor's medically responsible person

This document is electronically signed. The eSignature is archived in the Trial Master File and can be provided upon request.

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

Name: PPD MD, Role: PPD PPD

Date: ..... Signature: .....

Signature of principal investigator

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

Name:

Affiliation:

Date: ..... Signature: .....

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

In the protocol document, this page may remain unsigned.

2. Synopsis

Title	A non-randomized, open-label, multi-center, Phase I/II study of PI3K inhibitor copanlisib in pediatric patients with relapsed/refractory solid tumors or lymphoma
Short title	Safety, tolerability, efficacy and pharmacokinetics of copanlisib in pediatric patients
Clinical study phase	**I/II**
Study objective(s)	**Phase I (dose escalation) part** The primary objective: • To establish the safety, maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of copanlisib in pediatric patients with a relapsed/refractory solid tumor or lymphoma The secondary objectives: • To characterize the pharmacokinetics (PK) of copanlisib • To assess the antitumor activity of copanlisib and to identify specific potential tumor type(s) for further development The exploratory objectives: • To evaluate pharmacodynamics of copanlisib • To evaluate biomarkers of efficacy, mode-of-action-related effect, and /or the pathomechanism of the disease **Phase II (extension) part** The primary objective: • To determine the objective response rate (ORR) of copanlisib in pediatric patients with relapsed/refractory neuroblastoma, rhabdomyosarcoma or Ewing sarcoma. • To determine the disease control rate (DCR) and progression free survival (PFS) in pediatric patients with relapsed/refractory osteosarcoma Secondary objectives: • To evaluate PFS (in indications other than osteosarcoma), overall survival (OS), and duration of response (DOR) • To evaluate safety Exploratory objectives: • To characterize population PK of copanlisib • To evaluate pharmacodynamics of copanlisib • To evaluate biomarkers of efficacy, mode-of-action-related effect, and/or the pathomechanism of the disease

Test drug(s)

Copanlisib

Name of active ingredient

Copanlisib / BAY 80-6946 / phosphatidylinositol 3-kinase (PI3K) inhibitor

Dose(s)

Phase I (dose escalation)

Copanlisib will be dosed on Day 1, Day 8, and Day 15 of every 28-day cycle.

The starting dose for the dose-escalation phase of this study will be 60% for patients < 1 year old and 80% for patients ≥ 1 year old of the dose (60 mg/weekly, 3 weeks on/1 week off) in the adult population recommended for copanlisib development. The dose levels to be explored are listed in the following tables. The step size for dose escalation and de-escalation is 20% of the adult dose. In case that a certain cohort of pediatric patients reaches the copanlisib plasma exposure of adult patients treated with the recommended dose before the pediatric MTD is defined, no higher dose level will be tested. It is estimated that 2 or 3 dose cohorts may be evaluated in this part of the study.

Copanlisib dose levels for patients < 1 year

Dose level	Copanlisib dose	
	% of adult dose	mg/m^2
-2	40	14
-1	60 [a]	21
1	80	28
2	100	35

a: Starting dose for patients < 1 year

After patients are tested at dose level 1, the population PK (popPK) analysis will determine whether the exposure has reached at least 75% of adult exposure.

Copanlisib dose levels for patients ≥ 1 year

Dose level	Copanlisib dose	
	% of adult dose	mg/m^2
-1	60	21
1	80 [a]	28
2	100	35
3 [b]	120	42

a: Starting dose for patients ≥ 1 year old

b: Dose level 3 will only be tested if the geometric mean of the copanlisib plasma exposure in the already tested cohorts is less than 75% of the adult plasma exposure of copanlisib of 60 mg. After patients are tested at dose level 2, the popPK analysis will determine whether the exposure has reached at least 75% of adult exposure.

Phase II (extension)

RP2D for copanlisib in pediatric patients, as defined in the Phase I part of the study, will be used.

Route of administration	Intravenous (IV) infusion
Duration of treatment	Patients may continue treatment with copanlisib until radiological progressive disease, unacceptable toxicity, withdrawal of consent, death or other event specified by the protocol. After completion of treatment patients will be followed for survival for at least 2 years.
Reference drug(s)	Not applicable
Indication	Phase I: relapsed or refractory solid tumors or lymphoma Phase II: relapsed or refractory solid tumors (neuroblastoma, osteosarcoma, rhabdomyosarcoma or Ewing sarcoma)
Diagnosis and main criteria for inclusion /exclusion	**Main criteria for inclusion:** • Signed informed consent form by patients and/or patients' parents/legal guardians and age appropriate assent form by the patients obtained before any study specific procedure • Male or female patients from 6 months to ≤ 21 years old at the time of study enrollment • Confirmation of diagnosis: o **Phase I:** Patients must have histologic verification of a solid tumor or lymphoma malignancy at diagnosis, with measurable or evaluable disease, for which there is no standard curative anti-cancer treatment or treatment is no longer effective and must have received ≥ 1 prior line of therapy. o **Phase II:** patients must have histologically verified tumor at initial diagnosis and radiologically or histologically confirmed status at inclusion as indicated in the following: neuroblastoma, osteosarcoma, rhabdomyosarcoma or Ewing sarcoma. In Phase II, patients with solid tumors must have measurable disease (evaluable disease is acceptable for neuroblastoma and Ewing sarcoma). Tumor assessment will be done via computed tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography-computed tomography (PET-CT). Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, may be considered measurable if there has been demonstrated progression in the lesion. Bone scans (if clinically indicated) should be obtained within ≤ 4 weeks prior to the start of treatment. • Performance level: Lansky ≥ 50% for patients ≤ 16 years of age and Karnofsky ≥ 50% for patients > 16 years of age. • Adequate bone marrow, renal and liver function. **Main criteria for exclusion:** • Active or uncontrolled infection (NCI-CTCAE Grade ≥ 2). • History or concurrent condition of interstitial lung disease of any severity and/or severely impaired lung function (as judged by the

	investigator). • Diabetes mellitus. • Uncontrolled arterial hypertension despite optimal medical management (per institutional guidelines). • Patients with central nervous system (CNS) malignancies.
Study design	Study 19176 (Children's Oncology Group [COG] study number ADVL1721) is a multicenter, open-label, non-randomized Phase I/II study of copanlisib consisting of a Phase I dose escalating part in pediatric patients with a relapsed/refractory solid tumor or lymphoma followed by a Phase II part with Simon 2-stage design to establish efficacy signal of copanlisib in pediatric patients with relapsed/refractory neuroblastoma, osteosarcoma, rhabdomyosarcoma or Ewing sarcoma. The study (applicable to Phase I and Phase II parts) is composed of the following periods: • Screening • Treatment • Active follow-up • Long-term follow-up **Phase I part** Dose escalation phase: to establish copanlisib single agent MTD and/or RP2D, PK, pharmacodynamics and safety/tolerability in the pediatric population; a Rolling-6 study design will be utilized. MTD extension phase: up to 6 patients to confirm safety at MTD. The MTD of copanlisib for patients < 1 year old will be established and analyzed separately from the patients ≥ 1 year old and the results will be provided in a descriptive statistical analysis. If in the Phase I part of the study the MTD will not be established in patients < 1 year old, the MTD determination in patients < 1 year old will continue in parallel with the Phase II part and will be stopped when the Phase II part has been closed. Patients < 1 year old may not be enrolled in the Phase II part of the study until the MTD and RP2D for that age group has been established. If in the Phase I part a certain cohort of pediatric patients reaches the copanlisib plasma exposure of adult patients treated with the recommended dose before the pediatric MTD is defined, no higher dose level will be tested. <u>Phase I dose:</u> The starting dose for the dose-escalation phase of this study will be 60% for patients < 1 year old and 80% for patients ≥ 1 year old of the dose (60 mg/weekly, 3 weeks on/1 week off) in the adult population recommended for copanlisib development. Decision about dose escalation or reduction for subsequent cohorts will be determined based on dose-limiting toxicity (DLT) evaluation according to the Rolling-6 design.

	Phase II part Separate Simon 2-stage design in up to 4 arms to establish efficacy signals in: 1) neuroblastoma; 2) osteosarcoma; 3) rhabdomyosarcoma; 4) Ewing sarcoma treated at the RP2D. Phase II dose: The RP2D in mg/m^2 will be based on findings in the Phase I portion of this study.
Methodology	Standard tumor measurement procedures will be used. Solid tumors will be evaluated based on RECIST v1.1. For neuroblastoma patients with MIBG-avid disease, the SIOPEN or Curie score will be used and for lymphoma patients, the modified Lugano Classification 2014 will be used. Tumor assessments will be performed at screening (within 28 days prior to start of treatment), during treatment period: every 8 weeks (± 7 days) until radiological tumor progression, at the end of treatment (EOT) (not needed if the patient discontinued due to PD which has been radiologically confirmed within the 4 weeks preceding EOT) and during active FU period: every 12 weeks (± 14 days) until radiological tumor progression or start of new anti-cancer therapy, whichever occurs first. Safety evaluations will be done at screening, on the first day of study drug administration (Cycle 1 Day 1), at each clinic visit during the treatment, at EOT visit and at the SFU visit. The National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 will be used to grade toxicities/AEs. Sparse blood samples for pharmacokinetic (PK) analysis will be collected in all patients to characterize the PK of copanlisib. Blood samples for pharmacodynamic and biomarker analyses will be collected from all patients (except ≤ 1 year old) at screening and at selected time points during treatment. In addition, tumor archival tissue (when available) and fresh paired tumor biopsy (when feasible) will be collected. Patients will remain on therapy with copanlisib until tumor progression, unacceptable toxicity, withdrawal of consent, death or other event specified by the protocol. Each patient will be followed for OS for at least 2 years after the last patient's last treatment (LPLT) in the study.
Type of control	Not applicable
Data Monitoring Committee	Yes (for Phase II part)
Number of patients	**Phase I**: Rolling-6 clinical study design will be utilized; up to 42 patients are expected to be enrolled. A minimum of 50% of the enrolled and treated patients will be under the age of 12. Once the MTD or recommended Phase 2 dose has been defined, up to 12 additional patients who are <12 years old with relapsed/refractory solid tumors or lymphoma may be enrolled to acquire PK data in a representative number of young patients. **Phase II**: Simon 2-stage design will be utilized per indication, up to 4 cohorts will be enrolled with up to 25 patients per cohort, up to 100 patients could be enrolled and treated. A minimum of 80% of the

	enrolled and treated patients will be under the age of 18.
Primary variable(s)	**Phase I part of the study**: • maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) **Phase II part of the study**: • objective response rate (ORR) in neuroblastoma, Ewing sarcoma and rhabdomyosarcoma • disease control rate (DCR) and progression free survival (PFS) in osteosarcoma
Time point/frame of measurement for primary variable(s)	**Phase I part** The DLT observation for the purposes of dose-escalation will be followed during the first cycle of therapy. **Phase II part** Primary variable of objective response rate (disease control rate for osteosarcoma, respectively) for each indication will be evaluated 16 weeks after the last patient will have started treatment for that indication. In case all 25 patients of osteosarcoma will be recruited, the 4 month PFS rate will also be evaluated descriptively.
Plan for statistical analysis	**Phase I part** Individual listing of DLTs will be presented by cohort. Treatment-emergent AEs, drug-related AEs, AEs leading to premature study treatment termination/ dose reduction / study drug interruptions, serious adverse events (SAEs), laboratory parameters and plasma exposure to copanlisib will be summarized by cohort using descriptive statistics for safety. **Phase II part** The primary efficacy variable ORR in neuroblastoma, rhabdomyosarcoma and Ewing sarcoma and DCR in osteosarcoma will be summarized including number of patients (N), number of responders, response rates. It will be evaluated for the full analysis set (FAS) population. If Stage 2 is reached for an indication, 85% mid-p confidence intervals as well as a conditional p-value will be calculated for this indication. Descriptive summary of the safety analyses will be performed for the age group of < 1 year old separately. If all 25 patients on osteosarcoma are recruited (i.e. if Stage 2 is reached), the survival rate of PFS at 4 months will be estimated as co-primary endpoint using the Kaplan-Meier method and its two-sided 95% CI will also be provided. Secondary efficacy variables (ORR of Phase I part, PFS (for all indications except osteosarcoma), OS and DOR for each indication reaching Stage 2 in Phase II) will be evaluated by appropriate statistical methods.

Table of contents

Table of tables

Table of figures

List of abbreviations

5PS	5 point score for the visual assessment of PET-CT
AE	Adverse event
AESI	Adverse event of special interest
AKT	Protein kinase B
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
amp	Amplification
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the curve
BCRP	Breast cancer resistance protein
BL	Baseline
BM	Biomarker
BP	Blood pressure
BSA	Body surface area
BUN	Blood urea nitrogen
C	Cycle
CBC	Complete blood count
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
C_{max}	Maximum drug concentration
CMR	Complete metabolic response
CMV	Cytomegalovirus
CNS	Central nervous system
COG	Children's Oncology Group
CR	Complete response
CRF	Case report form
CRO	Contract research organization
CRR	Complete response rate
CRu	Complete response unconfirmed
CSP	Clinical study protocol
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
CYP3A4	Cytochrome P450 isoenzyme 3A4
D	Day
DBP	Diastolic blood pressure
DCR	Disease control rate
dL	Deciliter
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting toxicity
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid
DOR	Duration of response
ECG	Electrocardiogram

ECHO	Echocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
e.g.	For example (*exempli gratia*)
EGFR	Epidermal growth factor receptor
EOT	End of treatment
EudraCT	European Union Drug Regulating Authorities Clinical Trial
EWS	Ewing sarcoma breakpoint region 1
FAS	Full analysis set
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FL	Follicular lymphoma
FLI1	Friend leukemia integration 1 transcription factor
FOXO3a	Forkhead box O3
FSH	Follicle stimulating hormone
FU	Follow-up
g	Gram
GCL	Global Clinical Leader
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GFR	Glomerular filtration rate
GMP	Good Manufacturing Practice
GPCR	G protein-coupled receptor
GPV	Global Pharmacovigilance
h	Hour
Hb	Hemoglobin
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
hCG	β-human chorionic gonadotropin
HCV	Hepatitis C Virus
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator's Brochure
IC	Informed Consent
IC50	Half maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Council for Harmonization
IDMS	Isotope dilution mass spectroscopy
i.e.	That is (*id est*)
IEC	Independent Ethics Committee
IGF2	Insulin-like growth factor 2
IHC	Immunohistochemistry
iNHL	Indolent non-Hodgkin's lymphoma
INR	International normalized ratio
IRB	Institutional review board
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
IxRS	Interactive Voice Response System /Interactive Web Response System
kg	Kilogram
LDH	Lactate dehydrogenase

LDi	Longest diameter
LDL	Low-density lipoprotein
LPFT	Last patient first treatment
LPLT	Last patient last treatment
LTFU	Long-term follow-up
MAb	Monoclonal antibody
MAPK	Mitogen-activated protein kinase
MATE2K	Multidrug and toxin extrusion protein 2
MD	Medical Doctor
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
MIBG	Iodine-123 metaiodobenzylguanidine
mL	Milliliter
mmHg	Millimeter of mercury
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
mTOR	Mammalian target of rapamycin
MUGA	Multiple gated acquisition
mut	Mutation
MYCN	v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog
MZL	Marginal-zone lymphoma
NA, N/A	Not available
NCI	National Cancer Institute
NE	Not evaluable (by investigator / oncologist)
NHL	Non-Hodgkin's lymphoma
NIP	Non-infectious pneumonitis
nM	Nanomolar
NMR	No metabolic response, equivalent with stable disease
NRU	Neutral red uptake
OI	Opportunistic infection
ORR	Objective response rate
OS	Overall survival
pAKT	Phosphorylated AKT (protein kinase B [PKB])
PAX3	Paired box gene 3
PAX7	Paired box gene 7
PCR	Polymerase chain reaction
PD	Progressive disease
PDGFR	Platelet-derived growth factor receptor
PET	Positron emission tomography
PET-CT	Positron emission tomography-computed tomography
PFS	Progression-free survival
P-gp	Permeability glycoprotein
pH	Negative log of hydrogen ion concentration
PI3K	Phosphatidylinositol-3-kinase
PID	Patient identification number
PIK3R3	Phosphatidylinositol 3-kinase regulatory subunit gamma
PIP3	Phosphatidylinositol-3,4,5-trisphosphate
PK	Pharmacokinetic(s)
PMD	Progressive metabolic disease, equivalent with progressive disease
PMR	Partial metabolic response
PO	Orally (*per os*)
PopPK	Population PK
PPD	Product of perpendicular diameters

PPS	Per protocol set
PR	Partial response
PT	Prothrombin time
PTEN	Phosphatase and tensin homolog
PTT	Partial thromboplastin time
QT	QT interval in ECG
QTc	QT interval in ECG corrected for heart rate
R2PD	Recommended Phase 2 dose
RAVE	Validated electronic data capture system used by Bayer
RBC	Red blood cell count
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RP2D	Recommended phase 2 dose
RR	Respiration rate
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical analysis system
SBP	Systolic blood pressure
SD	Stable disease
SDi	Shortest diameter
SFU	Safety follow-up
SLL	Small lymphocytic lymphoma
SmPC	Summary of Product Characteristics
SOC	Standard of care
SPD	Sum of the product of the diameters
SUSAR	Suspected, unexpected, serious adverse reaction
TEAE	Treatment-emergent adverse event
TTP	Time to progression
ULN	Upper limit normal
UMVCUE	Unbiased minimum variance unbiased conditional
US/USA	United States (of America)
vs.	Versus
WBC	White blood cell count
WHO	World Health Organization

3. Introduction

3.1 Background

PI3K pathway

Phosphatidylinositol-3-kinases (PI3Ks) play critical roles in cell proliferation and cell survival signaling. They function downstream of receptor tyrosine kinases, cytokine receptors, GPCRs and integrins, generating PIP3 second messengers that regulate multiple signal transduction pathways. The PI3K pathway is a critical regulator of multiple signal transduction pathways that promote cell survival and cell proliferation. Among the most critical of these is the PI3K-AKT axis that regulates proliferation and survival through both positive and negative regulatory mechanisms that modulate kinase and transcriptional activities.

Many components of the PI3K/AKT pathway have been shown to be mutated or otherwise dysregulated in tumors leading to diverse mechanisms of activation. This includes amplification/overexpression or mutation of receptors that are at the entry of PI3K signaling, alterations of the genes encoding the catalytic or regulatory subunits of class I PI3Ks by mutations and/or amplification/overexpression, and loss-of-function mutations of genes that encode negative regulators of the pathway. These characteristics underpinning the importance of PI3K signaling in tumors gave rise to the development of inhibitors of several components of the pathway, including the PI3K, AKT, mTOR kinases, and Rapamycin analogs that inhibit mTORC1. PI3K has been recognized as a key cancer target for PI3K/AKT pathway in the drug development. Currently multiple PI3K inhibitors including PI3Kα selective (e.g. BYL719), PI3Kβ selective (e.g. GSK2636771 and SAR260301), PI3Kδ selective (e.g. idelalisib, INCB40093, AMG319, TRG1202), PI3Kγ/δ selective (e.g. IPI-145), Pan-PI3K (e.g. BKM120) and dual PI3K/MTOR (e.g. BEZ235, GDC-0980, SAR245409, VS-5584) agents are under clinical development (1). Among these, only idelalisib, a PI3Kδ selective inhibitor has been approved for the treatment of chronic lymphocytic leukemia (CLL) in combination with rituximab, and for follicular lymphoma (FL) and small lymphocytic lymphoma (SLL).

Target pediatric indications for copanlisib

Activating mutations of PI3Ks are more common in adult cancers and associated with a more aggressive clinical course than in pediatric malignancies. In childhood malignancies, various mechanisms of the PI3K/AKT pathway activation are reported to be frequent (≥ 50%) in neuroblastoma, osteosarcoma, Ewing sarcoma and rhabdomyosarcoma (Table 3–1).

Table 3–1 Target activation and incidence of PI3K pathway alteration in potential pediatric indications (neuroblastoma, osteosarcoma, Ewing sarcoma and rhabdomyosarcoma)

Potential pediatric indications	Mechanism of PI3K pathway alteration	Preclinical activity by PI3K inhibition	Incidence of PI3K pathway alteration
Neuroblastoma	Over expression of PI3Kp85 / PI3Kp110 (IHC)-54%, ALK mut/amp-10-15%, or decrease of PTEN expression-5%; MYCN-amp-20% (2, 3).	High PI3K activity and low FOXO3a activity were each associated with poor prognosis. PI3K/AKT inhibition induced apoptosis (4, 5).	50-70%
Osteosarcoma	Massive genomic instability. EGFR expression (~80%) and genomic gains at the EGFR locus (~60%), PTEN deletion (~20%) and copy number loss (~44%) are prevalent (6).	The alternative activation pathways may be relevant to mechanisms of tumor escape following treatment with PI3K inhibitors, and warrant a rationale based combination e.g. with MAPK inhibition (7).	60-80%
Ewing sarcoma	EWS/FLI1 fusion (~85%) -> involving IGF1 (IGFR)-paracrine and autocrine-> to activate PI3K. In addition, over-expression of PIK3R3 and loss of PTEN may be associated with PI3K pathway activation and oncogenic promotion (8, 9).	PI3K inhibition may serve to decrease chemotherapy resistance, in addition to its direct anticancer effects. (10).	~85%
Rhabdomyosarcoma	PAX3 or PAX7-FOXO1-> down regulated PTEN-> PI3K/AKT; IGF2-> pAKT. PI3K pathway activation was seen in 82.5% rhabdomyosarcomas, however with co-activated MAPK in 36% and 46% of alveolar and embryonal sub-types respectively (11).	Various co-activation oncogenic alternations along with PI3K/AKT activation in rhabdomyosarcoma may limited the single agent activity by PI3K inhibitors (12).	60-80%

ALK = Anapalastic lymphoma kinase; amp = Amplification; e.g. =For example (exempli gratia); EGFR = Epidermal growth factor receptor; EWS = Ewing sarcoma breakpoint region 1; FLI1 = Friend leukemia integration 1 transcription factor; FOXO3a = Forkhead box O3; IGF2 = Insulin-like growth factor 2; IHC = Immunohistochemistry; MAPK = Mitogen-activated protein kinase; mut = Mutation; MYCN = v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog; pAKT = Phosphorylated AKT (protein kinase B [PKB]); PAX3 =Paired box gene 3; PAX7 = Paired box gene 7; PI3K =Phosphatidylinositol-3-kinase; PIK3R3 = Phosphatidylinositol 3-kinase regulatory subunit gamma; PTEN = Phosphatase and tensin homolog

Based on published data on PI3K implication in tumorigenesis and the mode of action by copanlisib to potentially block the PI3K/AKT pathway activated in high risk pediatric cancers, the following pediatric tumors were selected as target pediatric indications for copanlisib: neuroblastoma, osteosarcoma, rhabdomyosarcoma and Ewing sarcoma.

These diseases are highly heterogeneous and the overall prognosis depends on the stage of the disease and outcome of the initial therapy. Long term prognosis remains poor for children with advanced and recurrent cancers.

Neuroblastoma is a tumor of early childhood and is the most common malignancy diagnosed in the first year of life, with 25–50 cases per million individuals. 90% of tumors arise in children who are < 10 years of age, and neuroblastoma has a median age at diagnosis of 18 months. Neuroblastoma is a neuroendocrine tumor that arises in the developing sympathetic nervous system (from any neural crest element), which results in tumors in the adrenal glands and/or sympathetic ganglia (13). For patients with high risk-neuroblastoma the 5-years overall survival (OS) rate has been estimated as 29% to 50%, with better outcome observed for patients diagnosed after 2000, when consolidation with high-dose therapy and stem-cell rescue was routinely included in the treatment plan for high-risk patients (14). In patients with relapsed neuroblastoma, survival for > 1-3 years without further recurrence of disease, or without death, is rarely possible, although more recent chemotherapy combinations have been successful in eliciting a partial or complete remission.

Osteosarcoma is an aggressive bone cancer and the most common histologic form of primary bone malignancy. This disease affects mainly young adults and children, it is slightly more common in males and the incidence is about 20% of all primary bone cancers (15). Almost 70% of newly diagnosed resectable osteosarcoma will be cured with initial treatment, while prognosis for unresectable and relapsed/refractory disease remains poor with response rate up to 29% and median progression free survival (PFS) only 1.4-4 months (16).

Ewing sarcoma is a rare disease involving bones and soft tissue with the incidence reported at 1 to 3 per million people per year (17). Ewing Sarcoma is a malignancy of childhood and adolescence and here represents the second most common primary malignant tumor of bone, accounting for ~ 42% of cases in those patients who are 15 years or older. While overall 5-years OS for patients with Ewing sarcoma is 60%-70%, prognosis for patients with relapsed/refractory or metastatic disease is poor – with 5-years OS of 15%-30% (18).

Rhabdomyosarcoma is a cancer affecting connective tissues and it is derived from skeletal and muscle progenitor cells. It occurs most commonly in the area of the neck, head and genitourinary tract. Five major types are identified according to the International Classification of Rhabdomyosarcoma (19). Embryonal rhabdomyosarcoma and alveolar rhabdomyosarcoma are two most common forms, with the first diagnosed most often in younger children and the second in older children and teenagers. Overall, rhabdomyosarcoma occurs most often in children from 1 to 5 years of age. Patients with high risk rhabdomyosarcoma have a 5-years OS of 20%-40% (20).

Even though there have been noticeable improvements in the treatment in recent decades, curative therapy remains unattainable for many patients with these poor prognosis pediatric cancers. Available therapeutic options include highly toxic chemotherapeutic agents with some of them having long term toxic effect on cardiovascular system (anthracyclines) or reproductive system. Improving and providing new therapeutic options for children with recurrent disease remains a high clinical unmet need. This includes finding more efficacious and safe therapies.

3.1.1 Copanlisib (BAY 80-6946)

Copanlisib is a novel pan-class I phosphatidylinositol 3-kinase (PI3K) inhibitor with predominant activity against both PI3Kα and PI3Kδ isoforms being evaluated in adults for the treatment of a wide variety of advanced malignancies relapsed or refractory to prior therapy either as a single agent or in combination with other investigational agents. The PI3K gene product is a key component of the PI3K-AKT cell-signaling pathway. This pathway is one of the prominent pathways that promote cellular survival and is constitutively activated in many types of cancers (21, 22). Class I PI3Ks can be activated by PI3K gene mutation/amplification/overexpression and/or upstream membrane receptors, such as epidermal growth factor receptor [EGFR], human epidermal growth factor receptor 2 [HER2], insulin-like growth factor-1 receptor [IGFR], platelet-derived growth factor receptor [PDGFR], vascular endothelial growth factor, proto-oncogene c-KIT or mesenchymal epithelial transition factor receptor [Met]. In addition to mediating cancer-associated signals, activation of the PI3K/AKT pathway is also one of the major mechanisms by which tumors escape from, and become resistant to, the effects of cytotoxic chemotherapy, targeted agents such as trastuzumab (21), and radiation (21, 23). Therefore, PI3K inhibitors are expected to be effective in tumors with known or expected intrinsic PI3K activation and to overcome the resistance in combination with other chemotherapy and/or targeted agents.

3.1.2 Principal toxicology data

A comprehensive preclinical toxicology program was conducted to support clinical studies in patients with advanced cancers.

Study results confirm that the rat and dog are relevant and sensitive species for toxicological testing of copanlisib. Significant toxicities were observed in these species at doses resulting in plasma concentrations in the range of those observed in humans. Target organs based on clinical pathology or morphological findings in repeat dose studies with IV infusion of copanlisib were the lymphoid and hematopoietic system, liver, kidneys, teeth, bone/femorotibial growth plates, heart, and male and female genital systems in the rat and the lymphoid and hematopoietic system and stomach (gastric mucosa) in the dog. Effects on glucose homeostasis were seen after repeated infusion of copanlisib to both the rat and dog. Copanlisib showed no genotoxic potential *in vitro* or *in vivo*. Specific reproductive toxicity studies have not been conducted.

Copanlisib is expected to adversely affect human reproduction based on findings in the male and female reproductive system in the repeat-dose toxicity studies. Additionally, due to the mechanism of action of copanlisib as a PI3K inhibitor, adverse effects on development, including potential teratogenicity, have to be considered. Maternal toxicity of increasing severity, severe post-implantation loss, and developmental toxicity, including teratogenicity, were seen in a rat pilot developmental toxicity study beginning at a low dose.

Appropriate precautions should be taken to avoid pregnancy in female patients included in the clinical trials. Results of the local tolerance studies indicate that accurate IV injection in humans is necessary to prevent possible local incompatibility reactions due to inadvertent paravenous injection. BAY 84-1236 was identified as a non-phototoxic compound in the recommended *in vitro* 3T3 neutral red uptake (NRU) phototoxicity test.

In conclusion, the non-clinical toxicology program with copanlisib supports the conduct of clinical studies in cancer patients with IV administration.

3.1.3 Preclinical data in pediatrics

Preclinical evaluation of copanlisib in pediatric cell lines demonstrated potent activity in a subset of pediatric Ewing sarcomas, rhabdomyosarcomas and leukemia cell lines. The majority of the copanlisib combinations showed additive effects on the IC_{50}-level. However, on the IC_{80}/IC_{90}-level more than additive (synergistic) anti-proliferative efficacy was observed for the combinations with cisplatin, etoposide, SN-38, and melphlan in A-204 (rhabdomyosarcoma), SH-SY5Y (neuroblastoma) and Saos-2 (osteosarcoma) cells, as well as for the cisplatin combination in RH-30 (rhabdomyosarcoma) cells. This enhanced combination effect on IC_{80}/IC_{90} level may hint on an increased induction of cell death/apoptosis at higher compound concentrations. *In vivo* testing of copanlisib in the two rhabdomyosarcoma models A204 and RH-30 in mice showed only slight inhibition of tumor growth in monotherapy and some improvement by combination with carboplatin.

3.1.4 Clinical experience

As of 21 JUN 2018, approximately 980 patients with advanced cancer have been treated with copanlisib in different studies.

Study 12871

First–in–man study 12871 was an open-label, uncontrolled, Phase I dose-escalation study to determine the safety, tolerability, pharmacokinetics (PK) and maximum tolerated dose (MTD) of copanlisib in patients with advanced cancer. As a single agent, the MTD for copanlisib was determined to be 0.8 mg/kg. The recommended (Phase II) dose of copanlisib in adults is 60 mg given intravenously in a 3 weeks on/1 week off schedule based on an evaluation of pharmacokinetic and clinical data from ongoing single agent studies. 57 patients started copanlisib treatment: 48 patients with solid tumors (including 6 diabetic patients) and 9 patients with non-Hodgkin lymphoma (NHL) (6 FL and 3 diffuse large B-cell lymphoma [DLBCL]). Out of the 48 patients with solid tumor, complete response (CR) as best overall response was achieved in 1 patient (2.1%) with endometrial cancer, 2 patients (4%) had partial response, 15 (31%) achieved stable disease (SD), and 15 (31%) had disease progression by investigator assessment, according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Ten patients (20.8%) had disease progression by clinical judgment and 5 patients (10.4%) were not assessed. Clinical benefit (CR, partial response [PR], or SD) was observed in 18 patients (38%) overall, by investigator assessment. Among the 9 NHL patients, all 6 with follicular lymphoma (FL) responded (one CR and 5 PRs) and one patient with diffuse large B-cell lymphoma had a PR; 2 patients with FL achieved CR (per subsequent *post hoc* independent radiologic review), and 2 FL patients were on treatment > 3 years.

The most common drug-related treatment-emergent adverse events (TEAEs) by Medical Dictionary for Regulatory Activities Preferred Term (MedDRA PT) of all CTCAE (Common Terminology Criteria for Adverse Events) v3.0 grades that occurred in ≥ 20% of the

57 patients (all cohorts) were: hyperglycemia (63.2%); nausea (38.6%); and hypertension (21.1%).

Phase II Study 16349 (Part A)

In the Phase II Study 16349 (Part A) various indolent and aggressive, relapsed or refractory NHL have been treated. The data presented corresponds to an update with cut-off date of 01 OCT 2015. There were 7 patients (8.3%) still ongoing with treatment, including 4 patients in the indolent non-Hodgkin's lymphoma (iNHL)/chronic lymphocytic leukemia (CLL) cohort and 3 patients in the aggressive NHL cohort. Of the 32 indolent lymphoma patients in the per protocol set (PPS), 14 patients achieved objective tumor response (CR+CRu [complete response unconfirmed] +PR) based on independent assessment resulting in objective tumor response rate (ORR) of 43.75% (90% confidence interval: 28.73; 59.68). Of all 14 patients who achieved a response, 2 patients had CR (6.25%), 1 patient had CRu (3.13%) and 11 patients had PR (34.38%). A total of 15 patients (46.88%) achieved SD as best overall response and 1 patient (3.13%) was classified with a best response of progressive disease. Of the 48 aggressive lymphoma patients in the PPS, 13 patients achieved objective tumor response (CR+CRu+PR) based on independent assessment resulting in ORR of 27.08% (90% confidence interval: 16.83; 39.57). Of all 13 patients who achieved a response, there were 2 patients with CR (4.17%), also 2 patients with CRu (4.17%) and 9 patients had PR (18.75%). Further, 11 patients (22.92%) achieved SD as best overall response and total of 16 patients (33.33%) were classified with a best response of progressive disease.

The most commonly experienced TEAEs by MedDRA PT that occurred in ≥ 20% of the patients in Study 16349 part A (cut of date of 01 OCT 2015) were: hyperglycemia (57.1%), hypertension (54.8%), diarrhea (40.5%), fatigue (35.7%), nausea (33.3%), neutropenia (28.6%), anemia (27.4%) and pyrexia (20.2%). Of these, hyperglycemia (63.6% vs. 52.9%), fatigue (48.5% vs. 27.5%), hypertension (69.7% vs. 45.1%), anemia (33.3% vs. 23.5%) and pyrexia (30.3% vs. 13.7%) were more common in the indolent group than in the aggressive group, respectively.

3.1.5 Clinical pharmacokinetics

Copanlisib PK is linear and plasma exposure as measured by maximum drug concentration (C_{max}) and area under the curve (AUC) increased in a dose-proportional manner over an absolute dose range of 5 to 93 mg (dose range 0.1 to 1.2 mg/kg). There was no indication for time-dependency and no accumulation in the pharmacokinetics of copanlisib. The geometric mean terminal elimination half-life (CV%) of copanlisib was 39.1 h (40.8%). The geometric mean clearance (CV%) was 17.9 L/hr (45.6%). Copanlisib is excreted as unchanged compound and metabolites (about 50:50). Metabolism of copanlisib is mediated by CYP3A4 (> 90%) and to a minor extent by cytochrome P450 isoenzyme 1A1 (CYP1A1) (< 10%). Itraconazole, a strong CYP3A4 inhibitor and a P-gp and BCRP transporter inhibitor, increased the mean AUC of a single IV dose of copanlisib (60 mg) 1.53-fold with no effect on C_{max} (1.03-fold) in cancer patients. Rifampicin, a strong CYP3A4 and a /P-gp inducer, decreased the mean AUC of copanlisib by 63% with minor effect on C_{max} (15%). PK of copanlisib is not affected by age (18 to 90 years), body weight, sex, gender, race, mild and moderate renal impairment, mild hepatic impairment and smoking. Copanlisib does not prolong QT/QTc interval.

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

3.2 Rationale of the study

Based on published data on PI3K implication in tumorigenesis and the mode of action of copanlisib to potentially block the PI3K/AKT pathway activated in high risk pediatric cancers, the following pediatric tumors were selected as target pediatric indications for copanlisib: neuroblastoma, osteosarcoma, rhabdomyosarcoma and Ewing sarcoma.

Neuroblastoma, osteosarcoma, rhabdomyosarcoma and Ewing sarcoma in children have been reported to frequently harbor activated PI3K/AKT pathways (frequency of ≥ 50%). It is therefore hypothesized that inhibition of the PI3K/AKT pathway with copanlisib, a PI3K inhibitor that targets all four class I isoforms with predominant activity against α and δ isoforms, may have a positive impact on the treatment outcomes in these sub-entities and the probability of success of a development in these malignancies could be higher compared to other types of neoplasm.

Even though there have been noticeable improvements in the treatment in recent decades, curative therapy remains unattainable for many. Available therapeutic options include highly toxic chemotherapeutic agents with some of them having long term toxic effect on cardiovascular system (anthracyclines) or reproductive system. Improving and providing new therapeutic options for children with recurrent disease remains a high clinical unmet need.

Efficacy data for copanlisib administered as monotherapy in solid tumors in adults have shown clinical responses in few patients with breast and endometrial cancer. Although these are not relevant indications for the pediatric population, it is not excluded that copanlisib, through its mechanism of action, could be active also in solid tumors studied in this trial.

3.3 Benefit-risk assessment

This study will be conducted in compliance with the protocol, GCP, applicable regulatory requirements, and ICH guidelines.

Front line of treatment for mentioned childhood malignancies is well established and effective. Due to lack of available standard of care and remaining high unmet need in relapse/refractory disease, a pediatric indication in relapsed and/or refractory neuroblastoma, osteosarcoma, rhabdomyosarcoma and Ewing sarcoma is warranted.

This study is designed to investigate whether the use of copanlisib is safe, feasible and beneficial to pediatric patients with solid malignant tumors that are recurrent or refractory to standard therapy.

Copanlisib has been evaluated so far only in adults in a number of clinical studies to establish efficacy and safety of copanlisib as a single agent and in combination with other treatments in various solid and hematologic malignancies. As of 21 JUN 2018, approximately 980 patients with advanced cancer have been treated with copanlisib in different studies.

Based on PK analysis of copanlisib showing no correlation between body weight, body surface area, or other body size-related factors and copanlisib clearance, the flat dose of 60 mg copanlisib administered as a 1 hour IV infusion on days 1, 8 and 15 of a 28-day cycle (3 weeks on and 1 week off) is indicated in all ongoing or planned clinical studies in adults.

In the Phase I dose escalation part, the starting dose for the dose-escalation phase will be 60% for patients < 1 year old and 80% for patients ≥ 1 year old of the dose (60 mg/weekly, 3 weeks on/1 week off) in the adult population recommended for copanlisib development.

The safe and effective dose for the treatment of patients below the age of 22 years has not been established. Dosing in a pediatric population should only proceed in a schedule that will be defined as per this study for further development. The toxicity profile of copanlisib in adults is manageable and is expected to be better tolerated in contrast to cytotoxic agents that are currently used as the primary treatment of pediatric tumors. Hyperglycemia and hypertension were among the most common adverse events that were in general transient and manageable.

Safety will be monitored on an ongoing basis with frequent teleconferences between the investigators and the sponsor's medically responsible personnel to ensure patients' safety, wellbeing and overall integrity of the study.

During Phase I, all decisions on dose escalation, de-escalation will be made after discussion between the investigators and sponsor to ensure the safety of each patient and the study population.

The individual benefit to the participants is to provide an option to potentially prolong life expectancy and to at least maintain quality of life of patients, whose current disease state is such that there is no known effective therapy.

Since there is often no alternative for pediatric patients with advanced, recurrent or refractory cancer, the benefit-risk ratio for this Phase I/II clinical trial should be acceptable to the participants in this study. The existing positive benefit-risk assessment of copanlisib in adults

with hematological malignancies has been confirmed in solid tumors and indolent and aggressive NHL.

This clinical trial will be discontinued in the event of new findings that indicate a relevant deterioration of the benefit-risk assessment of copanlisib in either pediatric or adult patients. Based on the known safety profile of copanlisib, the potential risk of treatment in pediatric patients where no standard of care is available outweighs possible risk associated with copanlisib therapy. On the basis of the data available to date, the conduct of the clinical trial is regarded as justified.

4. Study objectives

Phase I (dose escalation) part:

The primary objective:

- To establish the safety, maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of copanlisib in pediatric patients with a relapsed/refractory solid tumor or lymphoma

The secondary objectives:

- To characterize the PK of copanlisib
- To assess the antitumor activity of copanlisib and to identify specific potential tumor type(s) for further development

The exploratory objectives:

- To evaluate pharmacodynamics of copanlisib
- To evaluate biomarkers of efficacy, mode-of-action-related effect, and / or the pathomechanism of the disease

Phase II (extension) part

The primary objective:

- To determine the objective response rate (ORR) of copanlisib in pediatric patients with relapsed/refractory neuroblastoma, rhabdomyosarcoma or Ewing sarcoma.
- To determine the disease control rate (DCR) and progression free survival (PFS) in pediatric patients with relapsed/refractory osteosarcoma

Secondary objectives:

- To evaluate PFS (in indications other than osteosarcoma), overall survival (OS), and duration of response (DOR)
- To evaluate safety

Exploratory objectives:

- To characterize population PK of copanlisib

- To evaluate pharmacodynamics of copanlisib
- To evaluate biomarkers of efficacy, mode-of-action-related effect, and/or the pathomechanism of the disease

5. Study design

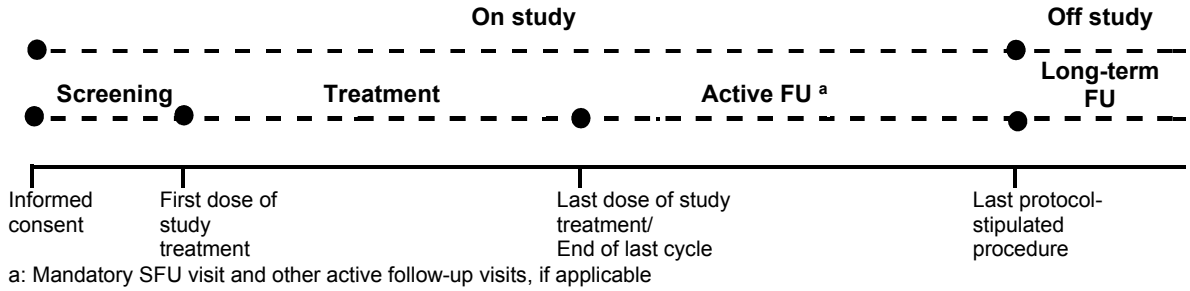
5.1 Design overview

This study 19176 (COG study number ADVL1721) is an open-label, non-controlled, dose-escalating trial to evaluate the pharmacokinetics, pharmacodynamics, safety and activity of copanlisib in pediatric patients from 6 months to ≤ 21 years of age with a relapsed or refractory solid malignant tumor or lymphoma and an extension in pediatric patients from 6 months to ≤ 21 years with a relapsed or refractory neuroblastoma, osteosarcoma, rhabdomyosarcoma or Ewing sarcoma.

The study includes two parts. The Phase I (dose escalation) part will use the Rolling-six design with expansion cohort at the maximum tolerated dose. The Phase II (extension) part will use Simon 2-stage design in arms by tumor type.

A schematic of the study periods is presented in Figure 5–1. The following design applies to both Phase I and Phase II parts.

Figure 5–1 Study periods



a: Mandatory SFU visit and other active follow-up visits, if applicable

5.1.1 Study periods

The study will comprise on the following periods: **screening**, **treatment**, **active follow-up** and **long-term follow-up**

Screening

Screening period starts after the patient and/or patient's parents (or legal guardians) have signed the informed consent form (and an assent from the patient is obtained, where applicable), and ends just before the start of treatment with copanlisib.

Treatment

The start of the treatment period is defined by first administration of study drug copanlisib. Copanlisib will be administered IV on Days 1, 8 and 15 of each 28-day treatment cycle. Treatment will be continued until radiological progressive disease, unacceptable toxicity, withdrawal of consent, death or other event specified by the protocol (see Section 6.4).

An End-of-treatment (EOT) visit will be performed within 7 days after the decision is made to discontinue study treatment.

Active Follow–up:

The active follow-up period is the interval from the end of study drug intake to the end of all clinical study protocol (CSP)-specified post-treatment interventions.

All patients who discontinue study treatment for any reason will be followed for safety at a mandatory safety follow-up visit except for patients and/or parents (or legal guardians) who refuse follow-up data collection. This safety follow-up (SFU) visit will take place 30+5 days after the last administration of study drug.

Patients who discontinue study treatment without radiological PD will be followed for radiological tumor assessments during the active FU until radiological PD is documented or until the start of first subsequent anti-cancer therapy, whichever occurs first. During this period only AEs and SAEs assessed as related to the study procedures by the investigator will be reported. AE pages of the electronic case report form (eCRF) and the SAE form should be completed in the usual manner and forwarded to the sponsor's GPV department.

Long-term follow-up (LTFU):

All patients will be followed up for survival for at least 2 years after the end of the Phase I (dose-escalation) and Phase II (extension) parts.

All patients who discontinue from study treatment or from active follow-up for any reason will enter long-term follow-up period during which survival data will be collected except for the cases when patients and/or parents (or legal guardians) refuse follow-up data collection. Patients' parents (or legal guardians) will continue to be contacted approximately every 3 months to determine survival status until death or at least 2 years after the last patient's last treatment (LPLT) in the study (See Section 9.2.1.5.2). Those patients who reached adult age during the long-term follow-up can be contacted directly or via patients' parents (or legal guardians).

Study procedures

Standard tumor measurement procedures will be used. Solid tumors will be evaluated based on RECIST v1.1. For neuroblastoma patients with MIBG-avid disease, the SIOPEN or Curie score will be used (see Appendix 16.2 and Appendix 16.3) and for lymphoma patients, the modified Lugano Classification 2014 will be used (see Appendix 16.11). Tumor assessments will be performed at screening (within 28 days prior to start of treatment), during treatment period: every 8 weeks (± 7 days) until radiological tumor progression, at EOT and during active FU period: every 12 weeks (± 14 days) until radiological tumor progression or start of new anti-cancer therapy, whichever occurs first. Tumor assessment is not required at the EOT visit if the patient discontinued due to PD which has been radiologically confirmed within the 4 weeks preceding EOT visit.

Safety evaluations will be done at screening, on the first day of study drug administration (Cycle 1 Day 1), at each clinic visit during the treatment, at EOT visit and at the SFU visit. The National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 will be used to grade toxicities/AEs.

Sparse blood samples for pharmacokinetic (PK) analysis will be collected in all patients to characterize the PK of copanlisib as outlined in Section 9.5.

Blood samples for pharmacodynamic and biomarker analyses will be collected from all patients (except ≤ 1 year old) at screening and at selected time points during treatment. In addition, tumor archival tissue (when available) and fresh paired tumor biopsy (when feasible) will be collected. See Section 9.7.1.

5.2 Phase I dose escalation design

The Phase I (dose-escalation) part of the study will determine the safety, MTD and/or RP2D of copanlisib in a pediatric population by using stepwise dose-escalation design based on Rolling-6 rule (see Table 5–1) with expansion cohort at the maximum tolerated dose.

For the dose levels of copanlisib in the Phase I part, see Section 7.4.

In the Rolling-6 study design, up to 6 patients are enrolled concurrently. Accrual to the study is suspended when 6 patients are enrolled. Accrual can be stopped earlier in any given cohort/dose level once DLTs are established and reviewed. Decisions as to whether to enroll a new patient onto the current, at next highest, or next lowest dose level will be made based on available data at the time of new patient enrollment.

Dose level assignment will be based on the number of patients enrolled in the cohort, the number of DLTs observed, and the number of patients at risk for developing a DLT (i.e., patients enrolled but who are not yet evaluable for toxicity). If the DLT criteria are amended for any reason, the next cohort under amended criteria will start at the last dose level assessed under the previous DLT criteria.

For example, when three patients to be enrolled onto a dose cohort, if toxicity data will be available for all three when the fourth patient is to be entered and the patients have no DLTs, the dose will be escalated and the fourth patient will be enrolled to the subsequent dose level.

If data are not yet available for one or more of the first three patients, or if one DLT has been observed, the new patient will enter at the same dose level. Lastly, if two or more DLTs have been observed, the dose level will be de-escalated. The process to be repeated for patients five and six. In place of suspending accrual after every three patients, accrual should only be suspended when a cohort of six will be filled.

Patients who discontinue during Cycle 1 because of any reason other than a DLT or other TEAE requiring discontinuation of treatment, and patients who were non-compliant in Cycle 1 to the extent that precludes the assessment of study objectives according to the sponsor's decision in consultation with the investigator, will be replaced to ensure the required number of evaluable patients per cohort.

Table 5–1 Decision rules for dose adjustments in Rolling-6 design

Number of patients enrolled	Number of patients with DLT	Number of patients with data pending	Decision

Table 5–1 Decision rules for dose adjustments in Rolling-6 design

Number of patients enrolled	Number of patients with DLT	Number of patients with data pending	Decision
2	2	-	De-escalate [a]
	0 or 1	-	Same dose level
3	≥ 2	-	De-escalate [a]
	0	0	Escalate [b]
	1	-	Same dose level
4	≥ 2	-	De-escalate [a]
	0	0	Escalate [b]
	1	-	Same dose level
5	≥ 2	-	De-escalate [a]
	0	0	Escalate [b]
	1	-	Same dose level
6	≥ 2	-	De-escalate [a]
	≤ 1	1	Escalate [b]
	0		Escalate [b]

DLT = Dose-limiting toxicity; MTD = Maximum tolerated dose
a: If 6 patients already entered at the next lower dose level, the MTD has been defined; if de-escalation occurs at the lowest dose level (for patients ≥ 1 year old (lowest dose level -1) and for patients < 1 year old (lowest dose level -2), please see Table 7–2 and Table 7–1, respectively), then the study is discontinued.
b: Dose escalation will take place only after comprehensive review of all collected safety data and careful evaluation by the investigators and sponsor.
Source: (24).

The recruitment will continue according to the Rolling-6 design, until the MTD is declared or copanlisib plasma exposure is assessed as being equivalent to the exposure in adult patients receiving the recommended treatment schedule. Once escalation is stopped, the last cohort will be expanded from 6 up to 12 patients in order to collect more safety and tolerability data and establish the RP2D. Intra-patient dose escalation is not permitted. Once the MTD or recommended Phase 2 dose has been defined, up to 12 additional patients who are <12 years old with relapsed/refractory solid tumors or lymphoma may be enrolled to acquire PK data in a representative number of young patients.

Assessment of **dose-limiting toxicities (DLTs)** will be performed during Cycle 1 (for the definition of DLT, please refer to Section 7.4.1.3). If ≥ 2 patients report DLTs in a cohort size of 3-6, that dose level is declared as toxic dose. If 6 patients already entered at the next lower dose level, the MTD has been defined. If de-escalation occurs at the lowest dose level, the study will be discontinued.

Maximum tolerated dose (MTD) for copanlisib will be defined as the highest dose level where 6 patients have been treated and ≤ 1 patient experiences a DLT.

- The MTD of copanlisib for patients < 1 year old will be established and analyzed separately from the patients ≥ 1 year old and the results will be provided in a descriptive statistical analysis.

If in the Phase I part of the study the MTD will not be established in patients < 1 year old, the MTD determination in patients < 1 year old will continue in parallel with the Phase II part and will be stopped when the Phase II part has been closed. Patients < 1 year old may not be enrolled in the Phase II part of the study until the MTD and RP2D for that age group has been established. However, if in the Phase I part a certain cohort of pediatric patients < 1 year old reaches the copanlisib plasma exposure of adult patients treated with the recommended dose before the pediatric MTD is defined, no higher dose level will be tested.

Equivalence to adult copanlisib plasma exposure will be defined as the geometric mean of the individual AUCs in the cohort with the highest dose level being within ± 25% of the adult exposure after dosing recommended for copanlisib development.

Recommended Phase II dose (RP2D) for copanlisib therapy will be determined by the investigators and the sponsor after having reviewed the data from all dose levels including available PK data, overall incidence and intensity of AEs and MTD.

For the detailed description of dosing and schedule, please refer to Section 7.4.

Transition from Phase I part to Phase II part

The protocol will be amended after completion of the Phase I part to update information on RP2D and other related topics (e.g. toxicities management guidance).

5.3 Phase II design

The Phase II part (extension) of the study will establish efficacy signal of copanlisib single agent treatment in pediatric patients with relapsed/refractory neuroblastoma, osteosarcoma, rhabdomyosarcoma or Ewing sarcoma.

A Simon 2-stage design will be used (30). According to Simon 2-stage design, after 10 FAS patients per indication will have been treated in Stage 1 for at least of 4 cycles, recruitment will be paused until decision for go/no-go into Stage 2 (see Section 10.5 for further information).

The RP2D as determined in the Phase I part of this study, will be used for the Phase II part of the study. This dose will be determined by the investigators and the sponsor after having reviewed the data from all evaluated dose levels in Phase I, including PK data, overall incidence and intensity of AEs and MTD.

The number of study participants in the Phase II part: planned 10 pediatric patients per opened arm in first stage and, if at least 2 responses occur, in the second stage 15 additional pediatric patients in the neuroblastoma, osteosarcoma, rhabdomyosarcoma or Ewing sarcoma arms. Up to 25 patients per arm and up to 100 patients could be enrolled and treated.

5.4 Primary variables

The primary variable of Phase I part of the study is:

- maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D)

The primary variable of Phase II part of the study is:

- objective response rate (ORR) in neuroblastoma, Ewing sarcoma and rhabdomyosarcoma
- disease control rate (DCR) and progression free survival (PFS) in osteosarcoma

5.5 Justification of the design

The study design (open-label, non-randomized, single-arm, multiple-dose administration) is a standard approach for a pediatric Phase I / dose escalation and PK study intended to investigate the pharmacokinetics and safety profile of a new compound in cancer patients or of a known compound in a new population – in this case, pediatric oncology patients. The study design for Phase I part is based on well-established and widely accepted methodologies where initially dose limiting toxicities will be established and the recommended dose will be selected for the next study.

The Rolling-6 study design is appropriate to minimize exposure of pediatric patients to ineffective treatment and to accelerate development in this setting. Age from 6 months to ≤ 21 years old and tumor types are selected based on proposed indications. Treatment duration is based on available data from adult studies and will depend on sensitivity to the treatment with copanlisib. Patients will be treated until disease progression or until another event pre-specified in the protocol is met.

The Rolling-6 design has been chosen because it allows for temporal overlap of the two cohorts of three patients used in the 3+3 design. Hence, the probability of trial suspension to further accrual is lower in the Rolling-6 design compared to the 3+3 design. Advantage of Rolling-6 design is, therefore, shortening the total trial duration without putting patient safety at risk, as the number and frequency of DLTs are similar when the two designs are compared (24). The inclusion of a placebo control or blinding of the treatment is considered not applicable for the objectives of this clinical Phase I part of the trial.

Phase II part of the study will establish efficacy signal of copanlisib in pediatric patients with relapsed/refractory neuroblastoma, osteosarcoma, rhabdomyosarcoma or Ewing sarcoma. Simon 2-stage design and sample size are considered most appropriate to minimize the exposure to ineffective treatment for pediatric patients with relapsed or refractory disease. The study primary and secondary endpoints for both phases are considered most appropriate for assessment of initial safety and efficacy signals of the investigational product. Eligibility criteria are focused on inclusion of pediatric patients with various solid malignancies after at least one line of treatment and will allow inclusion of patients with performance status and laboratory parameters appropriate for each individual clinical study. At least 2-year long term follow-up will be performed. If a certain safety signal will be observed in Phase I of the study, extended follow-up for survival may be implemented.

End of study

The end of the study as a whole will be reached as soon as the last contact of the last patient has been reached in all centers in all participating countries.

Primary completion

The primary completion event for this study is the last primary endpoint of the last patient after 4 cycles of treatment of all cohorts in the Phase II part.

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

6. Study population

Eligibility

6.1 Inclusion criteria

1. Signed informed consent form by patients and/or patients' parents/legal guardians and age appropriate assent form by the patients obtained before any study specific procedure.
2. Male or female patients from 6 months to ≤ 21 years old at the time of study enrollment.
3. Confirmation of diagnosis:
   - **Phase I:** Patients must have histologic verification of a solid tumor or lymphoma malignancy at diagnosis, with measurable or evaluable disease, for which there is no standard curative anti-cancer treatment or treatment is no longer effective and must have received ≥ 1 prior line of therapy.
   - **Phase II:** patients must have histologically verified tumor at initial diagnosis and radiologically or histologically confirmed status at inclusion as indicated in the following: neuroblastoma, osteosarcoma, rhabdomyosarcoma or Ewing sarcoma.

     In Phase II, patients with solid tumors must have measurable disease (evaluable disease is acceptable for neuroblastoma and Ewing sarcoma). Tumor assessment will be done via computed tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography-computed tomography (PET-CT) (See Section 9.4 for details). Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, may be considered measurable if there has been demonstrated progression in the lesion. Bone scans (if clinically indicated) should be obtained within ≤ 4 weeks prior to the start of treatment.
4. The following tumor type specific inclusion criteria must be met:

   <u>Lymphoma (Phase I part):</u>

   - Patients with lymphoma must have measurable disease (at least one bi-dimensionally measurable site of disease that has not been previously irradiated):

nodal disease > 1.5 cm or an extranodal lesion > 1.0 cm in longest perpendicular diameter) according to the Lugano classification 2014.

Phase I and II parts:

Neuroblastoma:

- Recurrent after treatment or refractory or progressive during initial treatment with two or more agents, including an alkylating agent and a platinum-containing agent
- Neuroblastoma patients must have measurable (MIBG non-avid disease) and/or non-measurable disease (MIBG-avid disease). Tumor evaluation will be performed within 4 weeks prior to the start of treatment.
  - Patients with measurable (MIBG non-avid) disease will have tumor assessments according to RECIST v.1.1. (See Section 16.1).
  - Patients with MIBG-avid disease will have tumor evaluation by MIBG scan according to SIOPEN or Curie score. MIBG-avid lesion that has been previously irradiated needs to have a biopsy performed at least 4 weeks post-radiation and must show viable neuroblastoma.

Osteosarcoma:

- Relapsed or refractory disease after treatment with two or more agents, including patients with pulmonary and/or osseous metastases.

Ewing sarcoma:

- Relapsed or refractory metastatic evaluable or measurable disease including single lung metastases and/or bone marrow involvement disease.

Rhabdomyosarcoma:

- Embryonal, alveolar and other histologies, recurrent after treatment or refractory or progressing during treatment with two or more agents, including cyclophosphamide or ifosfamide.

5. Life expectancy of at least 12 weeks from the time of signing informed consent/assent
6. Performance level: Lansky ≥ 50% for patients ≤ 16 years of age and Karnofsky ≥ 50% for patients > 16 years of age.
   Note: the performance level should not be considered reduced by limitations to movement or play caused by motor paresis or paralysis due to disease. Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.
7. Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements conducted within 7 days before start of study treatment:
   - Absolute neutrophil count (ANC): ≥ 1.0 x 10^9/L.

- Platelet count: ≥ 75 x 10^9/L. For patients with confirmed cancer bone marrow infiltration, platelet count ≥ 50,000 /mm^3. Platelet transfusion should not be given within 7 days before the first administration of the study drug.
- Hemoglobin: ≥ 8.0 g/ dL. Packed red blood cell transfusion or erythropoietin should not be given within 7 days before the first administration of the study drug.
- Creatinine clearance based on Schwartz Estimate ≥ 70 ml/min/1.73 m^2 or a serum creatinine based on age/gender (see Appendix 16.10).
- International normalized ratio (INR) ≤ 1.5 and partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN. Prophylactic anticoagulation of venous or arterial access devices is allowed provided that the requirements for INR and PTT or aPTT are met. Therapeutic anticoagulation is not allowed.
- Random or fasting serum glucose ≤ 126 mg/dL. If the initial glucose measurement is a random sample that is outside of this limit, then a fasting blood glucose can be obtained and must be ≤ 126 mg/dL. Note: For this protocol, fasting is defined as 8 hours elapsed since the prior meal.
- Lipase ≤ 1.5 x ULN.
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 x ULN.
- Alkaline phosphatase limit ≤ 2.5 x ULN (≤ 5 x ULN for patients with bone tumors or metastasis to bone).
- Total bilirubin ≤ 1.5 x ULN; patients with known Gilbert's syndrome or for patients with cholestasis due to compressive adenopathies of the hepatic hilum or documented liver involvement by tumor infiltration/progression - total bilirubin ≤ 5 x ULN may be enrolled.

See also Section 6.4.1 for the allowed re-screening of the laboratory tests.

8. Females of childbearing potential and males must agree to use effective contraception when sexually active. This applies for the time period between signing of the informed consent form and 1 month after the last administration of study drug. A female is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include but are not limited to hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for continuous 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in females not using hormonal contraception or hormonal replacement therapy.
   The investigator or a designated associate is requested to advise the patient how to

achieve highly effective birth control method (failure rate of less than 1%) e.g. intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner, and sexual abstinence. The use of condoms by male patients is required for one month after the last administration of study drug, unless the female partner is permanently sterile.

6.2 Exclusion criteria

Patients who meet any of the following criteria at the time of screening will be excluded

1. Previous assignment to treatment during this study. Patients permanently withdrawn from study participation will not be allowed to re-enter the study.
2. Previous anti-cancer or immunosuppressive treatment including immunotherapy and cytotoxic chemotherapy (within 28 days or less than 5 half-lives of the drug before start of study treatment whichever is less [or within 6 weeks for mitomycin C]) unless specifically mentioned in another exclusion criteria.

   Concomitant participation in another clinical study with investigational medicinal product(s).
3. 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).
4. Patients who previously received therapy with copanlisib or other PI3K inhibitors are not eligible for enrollment.
5. Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis or pulmonary embolism within 3 months before the start of study medication.
6. Patients with central nervous system (CNS) malignancies.
7. Patients with any of the following as the only site(s) of disease: palpable lymph nodes not visible on imaging studies, skin lesions, or bone marrow involvement only unless otherwise specified in the inclusion criteria (e.g. Neuroblastoma or Ewing sarcoma).
8. Active or uncontrolled infection (NCI-CTCAE Grade ≥ 2).
9. Positive cytomegalovirus (CMV) PCR test at baseline.
10. Hepatitis B (HBV) or hepatitis C (HCV). All patients must be screened for HBV and HCV up to 28 days prior to study drug start using the routine hepatitis virus laboratorial panel.
    - Patients positive for HBsAg or HBcAb will be eligible if they are negative for HBV-DNA.
    - Patients positive for anti-HCV will be eligible if they are negative for HCV-RNA.
11. Known history of human immunodeficiency virus (HIV) infection.

12. Major surgical procedure or significant traumatic injury within 28 days before start of study medication. Bone marrow biopsy, central line placement and tumor biopsy by needle or core-biopsy (with exception of excisional biopsy) will not be considered as a major surgical procedure.
13. Non-healing wound or ulcer.
14. Seizure disorder requiring treatment.
15. Diabetes mellitus.
16. Concurrent diagnosis of phaeochromocytoma.
17. Known hypersensitivity to any of the study drugs, study drug classes, or excipients in the formulation.
18. Unresolved acute toxicity higher than NCI-CTCAE v. 4.03 Grade 1 attributed to any prior antineoplastic therapy/procedure (excluding alopecia, chemotherapy-induced ototoxicity, absolute lymphocyte count (ALC) decreased, anemia, and white blood cell count (WBC) decreased). Note: Peripheral (sensory or motor) neuropathy related to limb sparing procedure or amputation is allowed.
19. Uncontrolled arterial hypertension despite optimal medical management (per institutional guidelines).
20. Cardiac abnormalities such as congestive heart failure (Modified Ross Heart Failure Classification for Children ≥ class 2, see Appendix 16.9) and cardiac arrhythmias requiring anti-arrhythmic therapy.
21. History of organ allograft (including allogeneic bone marrow transplant).
22. Patients with evidence or history of bleeding diathesis. Any hemorrhage or bleeding event within 4 weeks prior to screening.
23. History or concurrent condition of interstitial lung disease of any severity and/or severely impaired lung function (as judged by the investigator).
24. Pregnancy or breast-feeding patients. Female patients of childbearing potential must have a pregnancy test performed a maximum of 7 days before start of study treatment, and a negative result must be documented before start of study treatment.
25. Any other serious or unstable illness, or medical, psychological or social condition, that could jeopardize the safety of the patients and/or his/her compliance with study procedures or may interfere with the patient's participation in the study or evaluation of the study results.
26. For Phase II only: Any other malignancy within last 3 years except for curatively treated cervical cancer in situ, non-melanoma skin cancer and superficial bladder tumors [Ta (non-invasive tumor), Tis (carcinoma in situ) and T1(tumor invades lamina propria)].

Excluded previous therapies and medications:

27. Use of CYP3A4 strong inhibitors and/or inducers are prohibited within two weeks prior to start of study treatment.
28. Myeloid growth factors within 14 days before start of study treatment.
29. *Removed in Integrated Protocol Amendment 2.*
30. Radiopharmaceutical therapy (e.g., radiolabeled antibody, 131I-MIBG), cellular therapy (e.g. modified T cells, NK cells, dendritic cells, etc.) within 6 weeks before start of study treatment.
31. Radiation therapy:
    - ≤ 4 weeks prior to start of study treatment
    - ≥ 6 months must have elapsed if ≥ 50% radiation of pelvis

    Note: palliative radiotherapy is permitted (see Section 8.1).
32. Stem cell infusions: autologous stem cell transplant ≤ 3 months after infusion.
33. Antibodies: ≥ 3 weeks must have elapsed from infusion of last dose of antibody, and toxicity related to prior antibody therapy must be recovered to Grade ≤ 1.

6.3 Justification of selection criteria

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

6.4 Withdrawal of patients from study

6.4.1 Withdrawal

Withdrawal of patients from study treatment

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

- At their own request or at the request of their parent or legally acceptable representative. At any time during the study and without giving reasons, a patient may decline to participate further. The patient will not suffer any disadvantage as a result.
- If, in the investigator's opinion after the consultation with the sponsor, continuation of the study would be harmful to the patient's well-being.
- Occurrence of unacceptable toxicity from any study treatment.
- Severe allergic reactions to study drug ≥ CTCAE Grade 3 such as hypersensitivity reaction, exfoliate erythroderma, anaphylaxis, or vascular collapse.
- Progressive disease, as defined in the RECIST, version 1.1 (See Appendix 16.1) (or by SIOPEN or Curie score for neuroblastoma patients with MIBG-avid disease, (see

Appendix 16.2 and 16.3), or for patients with lymphoma as defined in the modified Lugano Classification, 2014 (see Appendix 16.11).

- Use of illicit drugs or other substances, which, in the opinion of the investigator or designated associate(s), may have a reasonable chance of contributing to toxicity or otherwise confound the results.
- Development of any intercurrent illness or situation, which, in the judgment of the investigator, may affect assessments of clinical status and study endpoints to a relevant degree.
- Substantial non-compliance with the requirements of the study.
- The development of a malignancy other than cancer treated in this study. New malignancy will be reported as an SAE.
- Patients with a β-human chorionic gonadotropin (hCG) test consistent with pregnancy. Pregnancy will be reported along the same timelines as an SAE.
- Start of a new anti-cancer regimen.
- Delay of more than 28 days from the last dose of study treatment due to toxicities related to copanlisib. Delays of study drug dosing due to reasons other than toxicity is not included in this definition.
- Adverse events or toxicities that are attributed to copanlisib and require discontinuation of protocol therapy as described in Section 7.4.3.
- Patient does not tolerate study drug at the protocol lowest dose level (for patients ≥ 1 year old (lowest dose level -1) and for patients < 1 year old (lowest dose level -2), please see Table 7–2 and Table 7–1, respectively).

Withdrawal of patients from study

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

- At the specific request of the sponsor and in liaison with the investigator (e.g. obvious non-compliance, safety concerns).
- Death.
- Lost to follow-up.
- Withdrawal of consent for any required observations or data submission.

A withdrawn patient is referred to “screening failure” as specified below:

Screening failure

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

Re-starting the defined set of screening procedures to enable the "screening failure" patient's participation at a later time point is not allowed – with the following exceptions:

- The patient had successfully passed the screening procedures but could not start subsequent treatment on schedule.
- The in- / exclusion criteria preventing the patient's initial attempt to participate have been changed (via protocol amendment).

In any case, the investigator has to ensure that the repeated screening procedures do not expose the patient to an unjustifiable health risk.

Re-screening of patients may only be allowed once after discussion and approval by the sponsor. Sponsor approval of re-screening for the patient who has failed screening must be documented.

The screening failure will be registered in Interactive Voice/Web Response System (IxRS) to close the patient identification number (PID), and re-screening will start again by signing a new informed consent form and being assigned a new PID.

Laboratory tests at screening

If one or more screening laboratory tests do not support eligibility, laboratory re-test is permitted only once without the need of re-consent. Only the laboratory tests which are out of range could be repeated and it should be in compliance with the requirement for blood sample volume. However, if this re-testing cannot be completed within 7 days of the Cycle 1 Day 1, the patient will be declared as a screening failure. Patients may not begin study drug treatment until the results of re-testing are available and documented to be within protocol-required range.

General procedures

Any patient removed from the study will remain under medical supervision until discharge or transfer is medically acceptable. In all cases, the reason for discontinuing study treatment and the completion of the follow-up periods must be clearly documented in the eCRF and in the patient's medical records.

All patients who discontinue due to AEs or clinical laboratory abnormalities should be followed up until they recover or stabilize, and the subsequent outcome recorded. If any patient dies during the study or within 30 days of the last dose of study drug, the investigator or his/her designated associate(s) will inform the sponsor. The cause of death should be recorded in detail within 24 h of awareness on an SAE form and transmitted to the sponsor.

The patient may object to the generation and processing of post-withdrawal data as specified in Section 13.4. For patients who withdraw consent and refuse follow-up data collection, no further study related procedures will be allowed, and no further data, including survival data, will be collected. The patients will not suffer any disadvantage as a result.

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

6.4.2 Replacement

Phase I part

Patients in the Phase I part who discontinue because of a DLT or other related toxicity that led to discontinuation of treatment during the DLT evaluation period will not be replaced.

Patients in the Phase I part who discontinue during Cycle 1 because of any reason other than a DLT or other TEAE requiring discontinuation of treatment, and patients who were non-compliant in Cycle 1 to the extent that precludes the assessment of study objectives according to the sponsor's decision in consultation with the investigator, will be replaced to ensure the required number of evaluable patients per cohort.

Phase II part

No patients will be replaced in the Phase II part.

6.5 Patient identification

At screening upon signing the ICF, each patient will be assigned a unique PID by IxRS for unambiguous identification.

The patient number is a 9-digit number consisting of:

Digits 1 to 5 = Unique center number

Digits 6 to 9 = Current patient number within the center

Patients participating in the Phase I part of study have a '1' as the 6th digit. As an example, PIDs in the Phase I part have the structure 'aabbb1ccc'. Patients participating in the Phase II part of study have a '2' as the 6th digit, e.g.'aabbb2ccc'.

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

7. Treatments

7.1 Treatments to be administered

The following treatment will be administered in this study:

- Copanlisib (BAY 80-6946) solution for IV infusion (test drug/investigational medicinal product)

Patients will receive copanlisib IV infusion as single agent on Days 1, 8 and 15 of each 28-day treatment cycle.

Phase I part: The starting dose for the dose-escalation phase of this study will be 60% for patients < 1 year old and 80% for patients ≥ 1 year old of the dose (60 mg/weekly, 3 weeks on/1 week off) in the adult population recommended for copanlisib development. See Section 7.4.1 for further details. The dosing will be based on BSA.

Phase II part: The RP2D in mg/m^2 will be based on findings in the Phase I portion of this study.

7.2 Identity of study treatment

Copanlisib (test drug)

Copanlisib is supplied as lyophilized preparation in a 6-mL injection vial. The total amount of BAY 80-6946 per vial is 60 mg. The solution for IV infusion is obtained after reconstitution of the lyophilisate with 0.9% sodium chloride solution.

Please refer to the Pharmacy Manual for detailed instructions for the reconstitution of the lyophilisate and for further dilution of the reconstituted solution.

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

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

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

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

An approved representative at the site will ensure that all received study drug is stored in a secured area on site, under recommended storage conditions and in accordance with applicable regulatory requirements.

7.3 Treatment assignment

This is an open-label study. All eligible patients will receive the same treatment, copanlisib intravenously.

After the informed consent form has been signed, the investigator will register the patient and a unique patient identification number will be assigned via IxRS.

Patients who satisfy all inclusion and exclusion criteria, will be assigned to the study drug treatment. The treatment will be assigned based on information obtained from IxRS.

The IxRS procedure is described in detail in a separate IxRS instruction manual that will be maintained in the trial master file (TMF), and in each center's investigator's trial file (ITF).

7.4 Dosage and administration

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

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

Pre-dose blood pressure will be measured twice with at least a 15 min interval between the assessments prior to start of each infusion of study drug (any time on dosing day). See Section 9.6.3.4.1 and Table 9–3 for measurement instructions and Section 7.4.3.3.4 for details on blood pressure management/dose modifications. Antihypertensive medication may be given to control the arterial hypertension.

- For patients <18 years, 2 consecutive results of the pre-dose blood pressure ≤ 95th percentile for age, height, and gender will be required start copanlisib infusion. See Table 16–5, Table 16–6, Table 16–7, and Figure 16–2.
- For patients ≥ 18 years old, 2 consecutive results of the pre-dose blood pressure <150/90 mmHg will be required to start infusion (see Section 7.4.3.3.4 for further information).

After Cycle 1 Day 1, laboratory tests prior to each infusion may be performed either the day before or on the planned day of infusion, with the exception of blood glucose, which must be performed on the day of infusion. All laboratory results must be assessed by the investigator and/or appropriate site personnel prior to administration of planned dose. Study drug will be administered only if the following laboratory test criteria are met prior to **each infusion**:

- ANC: ≥ 1.0 x 10^9/L
- Platelet count: ≥ 75 x 10^9/L. For patients with confirmed cancer bone marrow infiltration, platelet count ≥ 50,000 /mm^3. Platelet transfusion should not be given within 7 days before the administration of the study drug
- Hemoglobin: ≥ 8.0 g/ dL (transfusion permitted)
- AST and ALT ≤ 3.0 x ULN
- Lipase and Amylase ≤ 5 x ULN
- Glucose ≤ 160 mg/dL (fasting) or ≤ 200 mg/dL (non-fasting)
    - The investigator will accurately document the time of last meal intake and fasting/non-fasting status for each glucose measurement done at the site prior to drug infusion.
    - Fasting refers to a ≥ 8 h fast. Non-fasting status includes any meal intake within 8 hours prior to infusion.
    - From Cycle 1 Day 1 onwards, glucose measurements at the site may be done either by laboratory analysis or in capillary blood.

A delay due to adverse events of more than 7 days for the scheduled dose within a cycle will be considered a missed dose. Missed doses due to AEs will not be replaced and will be considered DLT during cycle 1. The minimum interval needed between two infusions of study drugs is 5 days. Patients that do not meet criteria to initiate a subsequent cycle within 28 days from the last dose of study treatment will permanently discontinue protocol therapy.

Recommendations on meal timing on infusion days

Because of inhibitory effect on PI3K α-isoform, which is implicated in insulin metabolism, copanlisib infusions could be associated with temporarily increase in blood glucose. Addition of meal in close proximity to study drug infusion may exacerbate glucose increase. It is recommended that timing of meal intake on infusion days is managed and monitored by the investigators. Consultation with treating physician or pediatric endocrinologist is advised.

All glucose measurements pre-dose, during and post the study drug infusions, administration of insulin or other glucose lowering medications, if applicable, fasting/non-fasting status and timing of meal intake on infusion days will be collected as part of the clinical source documentation and reviewed by the investigator.

7.4.1 Dosage – Phase I part

Copanlisib treatment will be administered on Day 1, Day 8 and Day 15 of every 28-day cycle. Patients who meet the eligibility criteria will receive copanlisib IV infusion with intermittent (3 weeks on / 1 week off) dosing schedule at the assigned dose level.

7.4.1.1 Selection of starting dose

The starting dose for the dose-escalation phase of this study will be 60% for patients < 1 year old and 80% for patients ≥ 1 year old of the dose (60 mg/weekly, 3 weeks on/1 week off) in the adult population recommended for copanlisib development.

The first cohort of patients in this trial will be treated with a dose of 21 mg/m^2/week for patients < 1 year old and 28 mg/m^2/week for patients ≥ 1 year old by taking in consideration the average adult BSA of 1.73 m^2. It is estimated that 2 or 3 dose cohorts may be evaluated in this part of the study. Please refer to Table 7–1 and Table 7–2 for dose levels of copanlisib for patients < 1 year old and ≥ 1 year old, respectively.

Table 7–1 Copanlisib dose levels for patients < 1 year

Dose level	Copanlisib dose	
	% of adult dose	mg/m^2
-2	40	14
-1	60 [a]	21
1	80	28
2	100	35

a: Starting dose for patients < 1 year
After patients are tested at dose level 1, the population PK (popPK) analysis will determine whether the exposure has reached at least 75% of adult exposure.

Table 7–2 Copanlisib dose levels for patients ≥ 1 year

Dose level	Copanlisib dose	
	% of adult dose	mg/m²
-1	60	21
1	80 [a]	28
2	100	35
3 [b]	120	42

a: Starting dose for patients ≥ 1 year old
b: Dose level 3 will only be tested if the geometric mean of the copanlisib plasma exposure in the already tested cohorts is less than 75% of the adult plasma exposure of copanlisib of 60 mg. After patients are tested at dose level 2, the popPK analysis will determine whether the exposure has reached at least 75% of adult exposure.

7.4.1.2 Dose escalation schedule

In the Phase I part, decision about dose escalation or reduction for subsequent cohorts will be determined based on DLT evaluation according to the Rolling-6 design, see Section 5.2. If in the Phase I part a certain cohort of pediatric patients reaches the copanlisib plasma exposure of adult patients treated with the recommended dose (60 mg/weekly, 3 weeks on/1 week off) before the pediatric MTD is defined, no higher dose level will be tested.

For patients < 1 year old, if dose level -1 (starting dose) is not tolerable, copanlisib dose will be reduced to 40% of the dose in adult (60 mg/weekly, 3 weeks on/1 week off) (dose level -2). If dose level -1 is tolerable, copanlisib dose will be escalated to 80% of the dose in adult (dose level 1). If dose level 1 is tolerable, copanlisib dose can be escalated further to achieve 100% of total copanlisib adult dose (dose level 2) (please refer to Table 7–1).

For patients ≥ 1 year old, if dose level 1 (starting dose) is not tolerable, copanlisib dose will be reduced to 60% of the dose in adult (dose level -1). If dose level 1 is tolerable, copanlisib dose will be escalated to achieve 100% of total copanlisib adult dose (dose level 2). If dose level 2 is tolerable, copanlisib dose can be escalated further to 120% of the dose in adult (dose level 3) (please refer to Table 7–2).

All safety and PK data will be reviewed at the completion of the first cycle of treatment at each dose level. The sponsor and investigators will review the data to determine if further dose escalation is warranted.

7.4.1.3 Definition of dose-limiting toxicities (DLTs)

DLT is defined as any of the following adverse reactions observed during first cycle of treatment, and assessed as possibly, probably or definitely related to treatment with copanlisib. The DLT observation period for the purposes of dose-escalation will be the first cycle of therapy.

NCI-CTCAE Version 4.03 will be used to assess toxicities/adverse events (AEs).

DLTs will include:

- **Non-hematological AEs:**
  - Grade ≥ 2 non-infectious pneumonitis
  - Grade ≥ 2 rash which despite maximal supportive care persists for more than 7 days duration will be considered a DLT.
  - Grade 2 blood pressure elevation that does not return to ≤ 95th percentile for age, height, and gender and results in a missed dose as per Table 7–8.
  - Any ≥ Grade 3 AE attributable to protocol therapy with the specific exclusion of:
    - Grade 3 fatigue lasting < 3 days
    - Grade 3 nausea and vomiting lasting < 3 days
    - Grade 3 or 4 fever < 5 days duration.
    - Grade 3 infection < 5 days duration.
    - Grade 3 rash (papulopustular, maculopapular, or acneiform or NOS) that returns to baseline or grade ≤ 1 within 7 days with or without supportive care. NOTE: **Any grade 3 rash** that requires radiologic or operative intervention will be considered a DLT.
    - Grade 3 liver enzyme elevation, including ALT/AST/GGT that returns to levels that meet infusion criteria in Section 7.4 within 7 days.
    - Grade 3 electrolyte laboratory abnormalities including, but not limited to, hypophosphatemia, hypokalemia, hypocalcemia, or hypomagnesemia responsive to supplementation
    - Grade 3 asymptomatic elevated lipase or amylase that returns to grade ≤ 2 within 7 days
    - Grade 3 or 4 elevated alkaline phosphatase will not be considered a DLT
    - Hyperglycemia: hyperglycemia **will not be considered** as a DLT except in the following conditions:

      - Hyperglycemia of any grade that results in delay of start of Cycle 2 by >7 days, missed dose during Cycle 1, or reduction of dose in Cycle 1 as per Table 7–7 will be considered a DLT

      - Grade 4 hyperglycemia (>500 mg/dL) with life-threatening consequences will be considered a DLT

Note: Allergic reactions leading to discontinuation of study drug will not be considered as DLT.

- **Hematological AEs:**
  - Grade 4 neutropenia lasting ≥ 3 days
  - Grade 3 thrombocytopenia with bleeding

- Grade 4 thrombocytopenia lasting ≥ 3 days
- Grade 4 anemia (in the absence of marrow disease progression)
- Grade ≥ 3 INR increase or PTT increase with bleeding

Notes:

- See Section 7.4.3.2 for management of hematologic toxicity.
- Hematological AEs listed above will not be considered as DLT in patients with proven bone marrow involvement at baseline.
- Grade 3 or 4 febrile neutropenia will not be considered as DLT (unless neutropenia criteria above are fulfilled).
- Lymphopenia will not be considered a DLT.

Generally, any AE during cycle 1 that is attributed to copanlisib and results in a missed dose or results in delayed start of cycle 2 by >7 days will be considered a DLT.

7.4.2 Dosage – Phase II

The protocol will be amended after completion of the Phase I part to update information on the recommended dose of copanlisib for the Phase II part (RP2D).

7.4.3 Dose modifications

Copanlisib dose modifications must be done according to the guidelines given in Section 7.4.3.2 and Section 7.4.3.3. If the dose is reduced or interrupted, the investigator's decision is to be clearly documented in the patient's records and in the eCRF. If a patient experiences several toxicities and there are conflicting recommendations, the recommended dose adjustment which reduces the dose to the lowest level should be used.

Please refer to Table 7–1 and Table 7–2 for the dose levels of copanlisib for patients < 1 year old and ≥ 1 year old, respectively.

7.4.3.1 Dose-limiting hematological and non-hematological toxicity

Section was removed by amendment 1.

7.4.3.2 Hematological toxicity

The guidelines for dose modifications in case of hematological toxicity which occurred during study treatment are given in Table 7–3.

Table 7–3 Dose modification of study treatment for hematological toxicity

Hematological toxicity of CTCAE Grade (any of the following) which occurred during study treatment	Study drug action
• Grade 4 thrombocytopenia lasting ≥ 3 days (platelet < 25,000/mm^3) or Grade 3 (platelet < 50,000/mm^3) with bleeding • Grade 4 neutropenia (ANC < 500/mm^3) [a] lasting ≥ 3 days • Grade ≥ 3 INR or PTT with bleeding • Grade 4 anemia	Delay infusion until return to laboratory criteria displayed in dosing criteria (see Section 7.4) [c]. Patient should be treated at one dose level lower [b]. If more dose reductions are required than allowed per protocol or infusion delayed more than 28 days from last dose, discontinue study treatment permanently. For the lowest dose level for patients ≥ 1 year old (dose level -1) and for patients < 1 year old (dose level -2), please see Table 7–2 and Table 7–1, respectively.

ANC = Absolute neutrophil count; CBC = Complete blood count; CTCAE = Common Terminology Criteria of Adverse Events; Hb = Hemoglobin; INR = International normalized ratio, PTT = Partial thromboplastin time.

a: For patients who develop CTCAE Grade 4 neutropenia or febrile neutropenia, repeat of ANC every 3 days is recommended until patient meets dosing criteria in Section 7.4.

Note: G-CSF may be administered as outlined in Section 8.1 Permitted Concomitant Therapy

b: After having recovered from toxicity to CTCAE Grade ≤ 1 and in the absence of any criteria for further dose reduction or study drug discontinuation for at least one full cycle, a dose re-escalation at the following cycle will be allowed.

c: Treatment with pRBC or platelet transfusion is allowed, however dosing criteria for platelets in Section 7.4 must be transfusion independent (criteria met at least 7 days after most recent transfusion).

7.4.3.3 Non-hematological toxicity

Dose modifications for non-hematological toxicities except glucose increases, dermatologic toxicity, NIP and arterial hypertension are outlined in Table 7–4.

Table 7–4 Dose modification of study treatment for non-hematological toxicity (except glucose increases, dermatologic toxicity, non-infectious pneumonitis and arterial hypertension)

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

CTCAE = Common Terminology Criteria of Adverse Events.

a: Despite maximum supportive therapy. Laboratory-based toxicities including but not limited to elevated lipase, amylase, ALT/AST/GGT that are not considered clinically significant do not require dose reduction by one level. Grade 3 toxicities that are excluded as a DLT in Section 7.4.1.3 do not require a dose reduction.

b: Not applicable for the lowest dose level, see Table 7–1and Table 7–2.

c: Including infusion reactions.

A delay > 28 days from the last dose of study treatment due to toxicities requires permanent discontinuation of study treatment.

Study treatment must be discontinued if the lowest dose level of is not tolerated (for patients ≥ 1 year old [lowest dose level -1] and for patients < 1 year old [lowest dose level -2], please see Table 7–2 and Table 7–1, respectively).

After having fully recovered from toxicity and in the absence of any criteria for further dose reduction or study drug discontinuation, a dose re-escalation will be allowed at the investigator's discretion.

Management and treatment of non-hematological toxicity will be performed by the investigator per local standard of care (SOC).

7.4.3.3.1 Dermatologic toxicity

The guidelines for dose modifications in case of dermatologic toxicity are given in Table 7–5.

Table 7–5 Dose modification of study treatment for dermatologic toxicity

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

CTCAE = Common Terminology Criteria of Adverse Events. Toxicities according to CTCAE version 4.03.
a: Despite maximum supportive therapy.
b: Not applicable for lowest dose level (for patients ≥ 1 year old [lowest dose level -1] and for patients < 1 year old [lowest dose level -2], please see Table 7–2 and Table 7–1, respectively).
If a patient is already on the lowest dose level and meets criteria for further dose decrease, study treatment will be discontinued permanently.
In case of dose reductions due to dermatologic toxicity, no re-escalation is allowed after the dose reduction.

7.4.3.3.2 Non-infectious pneumonitis

In the event of NIP, an adjustment as described in Table 7–6 must be applied.

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

	Study drug action	
Suspected or confirmed NIP of CTCAE	**For current course of therapy**	**For next course of therapy**
Grade 1	No change	Not applicable
Grade 2	Interruption until recovery to ≤ Grade 1	Decrease by one dose level [a]
Grade 2 re-occurrence	Permanent discontinuation	No
Grade ≥ 3	Permanent discontinuation	No

NIP = Non-infectious pneumonitis; CTCAE = Common Terminology Criteria for Adverse Events.
a: Not applicable for lowest dose level (for patients ≥ 1 year old [lowest dose level -1] and for patients < 1 year old [lowest dose level -2], please see Table 7–2 and Table 7–1, respectively). No re-escalation is allowed after the dose reduction. If a patient is already on the lowest dose level and meets criteria for further dose decrease, study treatment will be discontinued permanently.

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

The investigator is requested to differentiate between NIP and infectious pneumonitis (viral, bacterial, fungal), aspiration pneumonitis, or other pneumonitis clearly not due to a potential hypersensitivity reaction to the copanlisib infusion; and provide the basis for his/her assessment that it is infectious or other, as appropriate. The investigator is requested to report with the most specific clinical terms to describe the condition, not simple “pneumonitis”.

7.4.3.3.3 Glucose increases

Mild to moderate asymptomatic increases of blood glucose may occur with copanlisib infusion, and with larger increases potentially occurring post-prandially.

Hyperglycemia of any grade that results in delay of cycle 2 by more than 7 days, missed dose during cycle 1, or reduction of dose in cycle 1 as per Table 7–7 will be considered a DLT.

For the guidelines for the management of transient post-infusion glucose increases and dose modification of copanlisib, refer to the following Table 7–7.

Table 7–7 Dose Modification of Study Treatment and Management of Glucose Increase

Criteria	Glucose increase management	Copanlisib dose modification
Blood Glucose ≤ 160 mg/dL (fasting) or ≤ 200 mg/dL (non-fasting)	Monitor glucose per Table 9–1 (Study Flow Chart) and Table 9–4 (Monitoring on infusion days)	Continue copanlisib at current dose level
Blood Glucose > 160 mg/dL (fasting) or > 200 mg/dL (non-fasting) up to 499 mg/dL (fasting or non-fasting)	-Hydration if appropriate -Repeat laboratory glucose determination approximately every 1 hour until glucose level decreases on at least 2 consecutive measurements, then monitor glucose as clinically indicated and at least as outlined in Table 9–1 (Study Flow Chart) and Table 9–4 (Monitoring on infusion days) -If the repeated glucose value is decreasing, the glucose may be followed without glucose lowering treatment if hydration status is normal as clinically assessed -Consultation with pediatric endocrinologist is recommended, initiate glucose lowering agent as indicated per local standard of care as indicated. -The patient may continue to receive concomitant insulin or an oral glucose lowering agent for the management of hyperglycemia while receiving copanlisib.	Hold copanlisib until fasting glucose is 160 mg/dL or less, or a random/non-fasting blood glucose of 200 mg/dL or less. Subsequent dosing can maintain at current dose level.
Blood Glucose ≥ 500 mg/dL (fasting or non-fasting)	-Hydration -Repeat laboratory glucose determination approximately every 1 hour until glucose level decreases on at least 2 consecutive measurements, then monitor glucose as clinically indicated and at least as outlined in Table 9–1 (Study Flow Chart) and Table 9–4 (Monitoring on infusion days) -Consultation with pediatric endocrinologist is recommended, initiate glucose lowering agent (e.g. insulin or oral agent) as indicated per local standard of care. - The patient may continue to receive concomitant insulin or an oral glucose lowering agent for the management of hyperglycemia when copanlisib is restarted	**On first occurrence**: Hold copanlisib until fasting blood glucose ≤ 160 mg/dL or random/non-fasting blood glucose of ≤ 200 mg/dL. Then reduce copanlisib by one dose level. **On subsequent occurrences**: Hold copanlisib until fasting blood glucose is ≤ 160 mg/dL or random/non-fasting blood glucose of ≤ 200 mg/dL. Then reduce copanlisib by an additional dose level. If patient is at the lowest dose level, permanently discontinue copanlisib. - Permanently discontinue copanlisib in case of symptoms or life threatening consequences.

7.4.3.3.4 Arterial hypertension

Pre-dose blood pressure will be measured twice with at least a 15 min interval between the assessments prior to start of infusion of study drug (any time on dosing day).

- For patients < 18 years, 2 consecutive results of the pre-dose blood pressure ≤ 95th percentile for age, height, and gender will be required to start copanlisib infusion.
- For patients ≥ 18 years old, 2 consecutive results of the pre-dose blood pressure < 150/90 mmHg will be required to start infusion.

The guidelines for dose modifications for hypertension are provided in Table 7–8.

The recommendations for the treatment of blood pressure increases are given in Section 7.4.4.2.

Patients with a blood pressure of CTCAE Grade 4 must permanently discontinue the study drug (see Section 6.4.1).

Table 7–8 Dose modifications for hypertension

Toxicity (hypertension) CTCAE modified for age, height, and gender [c, d]	Study drug action	Recommendation
Grade 1 SBP or DBP 90th percentile to ≤ 95th percentile for age, height, and gender	• Continue copanlisib	• Consider increased BP monitoring
Grade 2 SBP and/or DBP > 95th percentile for age, height, and gender to the ≤ 99th percentile for age, height, and gender plus 5 mmHg	• Infusion should be interrupted and may be resumed when BP has returned to ≤ 95th percentile for age, height, and gender or skipped otherwise • Continue subsequent study drug administrations at the same dose level and infusion rate	• Intensify BP monitoring [a] until BP returns to ≤ 95th percentile
During infusion: Grade 3 SBP and/or DBP > 99th percentile for age, height, and gender plus 5 mmHg	• Infusion should be interrupted and may be resumed when BP has returned to ≤ 95th percentile for age, height, and gender or skipped otherwise • Subsequent study drug administrations should be reduced by 1 dose level and continued at the same infusion rate [b]	• Intensify BP monitoring [a] until BP returns to ≤ 95th percentile
Post-dose: Drug-related Grade 3 SBP and/or DBP > 99th percentile for age, height, and gender plus 5 mmHg	• Subsequent study drug administrations should be reduced by 1 dose level and continued at the same infusion rate [b]	• Treat with the aim to achieve BP ≤ 95th percentile: o Start antihypertensive medication AND / OR o Increase current antihypertensive medication AND / OR o Add additional antihypertensive medications
CTCAE hypertension of grade 4 Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis)	• Permanent discontinuation	-

Table 7–8 Dose modifications for hypertension

CTCAE = Common Terminology Criteria for Adverse Events; BP = Blood pressure; DBP = Diastolic blood pressure; HR = Heart rate; RR = Respiration rate; SBP = Systolic blood pressure.
a: BP, HR and RR assessments every 15 min (± 5 min).
b: If a patient is already on the lowest dose level (for patients ≥ 1 year old [lowest dose level -1] and for patients < 1 year old [lowest dose level -2], please see Table 7–2 and Table 7–1, respectively) and experiences post-dose hypertension of CTCAE Grade 3 or SBP and/or DBP > 99th percentile for age, height, and gender plus 5 mmHg, consider more intensive therapy than previously used.
c: CTCAE modified will be utilized to determine the grade of hypertension in patients < 18 years old. The upper limit of normal (ULN) is defined as a BP equal to the 95th percentile for age, height, and gender.
d: CTCAE v.4.03 will be utilized to determine the grade of hypertension in patients ≥ 18 years old. For study drug action and recommendations, use SBP/DBP of > 150/90 for > 95th percentile for age, height, gender and use SBP/DBP of > 160/100 for > 99th percentile for age, height, gender in patients ≥ 18 years old.
In case of dose reductions due to arterial hypertension, no re-escalation is allowed after the dose reduction.

The selection of anti-hypertensive medication used in this setting should be performed at the investigator's discretion, considering possible site-specific treatment guidelines. All medication should be recorded in the patient's eCRF and the patient's medical record.

7.4.4 Treatment of toxicities

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

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

Mild to moderate asymptomatic increases of blood glucose may occur with copanlisib infusion, and with larger increases potentially occurring post-prandially.

The guidelines for the management of transient post-infusion glucose increases are given in Table 7–7.

The need for further glucose monitoring at home should be determined by the investigator based on post-infusion glucose profile and clinical status of the patient.

7.4.4.2 Treatment of blood pressure increases associated with study treatment

It is important that patients with pre-existing arterial hypertension adhere to their regular medication schedule and take their usual doses on the days of study drug infusion. The management of acute arterial hypertension following study treatment will need to be individualized for each adult/pediatric patient per local SOC.

The guidelines for dose modifications for hypertension are provided in Section 7.4.3.3.4.

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

7.4.4.3.1 Monitoring guidelines for Opportunistic Infections

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

- Evaluation of any new onset or worsening of pulmonary symptoms (i.e. cough, dyspnea or fever) that includes a lung examination at each visit prior to infusion.

Enhanced monitoring when prior medical history or laboratory parameters could be associated with one of the following risk factors:

- History of CMV, herpes.
- History of lower respiratory tract infection, history of immunodeficiency in the last 12 months.
- Lymphocytes count < 500/mm^3 while on treatment in clinical study.

For patients with identified risk factors and those who presented with new onset or worsening of pulmonary symptoms or developed OI on study treatment, any additional laboratory and diagnostic methods will be strongly recommended and performed per local SOC and reported as unscheduled laboratory and diagnostic methods of assessment in the eCRF.

Note: Treatment of opportunistic infections should be based on local SOC.

7.4.4.3.2 Prophylaxis of Opportunistic Infections

OI prophylaxis may be initiated at the discretion of the treating investigator's judgment of the benefit/risk ratio in any patient, irrespective of whether a high-risk feature is present, per local SOC. If so, drug name, indication, dosage and route of administration must be reported on the concomitant medication page of the eCRF.

Prophylactic treatment of OI should be based on local SOC.

7.5 Blinding

Not applicable; this is an open-label study.

7.6 Drug logistics and accountability

The study drug will be stored at the investigational site in accordance with GCP and GMP requirements and the instructions given by the clinical supplies department of the sponsor (or its affiliate) 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. On the day of receipt, the responsible site personnel will confirm receipt of study drug via IxRS. The personnel will use the study drug only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return, administration and destruction (if any) of the study drug must be properly documented according to the sponsor's agreed and specified procedures.

Vial number and other relevant information per treatment will be recorded on the eCRF and the appropriate drug dispensing form. Reason(s) for dose delay and reduction will also be recorded in the eCRF.

Drug accountability on patient level must be done every cycle, starting on Day 1 of Cycle 1.

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 intravenous copanlisib will be performed in the clinic on a weekly basis on Days 1, 8, and 15 of each 28-day cycle, and must be recorded in the eCRF.

8. Non-study therapy

8.1 Prior and concomitant therapy

All medications taken by the patients in addition to the study medication are defined as concomitant medication. Medication other than the study drug must not be taken during the study without consulting the investigator. All therapies that are considered necessary for the patient's welfare and that are not expected to interfere with the evaluation of the study drug may be given at the discretion of the investigator. Where the use of drugs is medically indicated (e.g. in case of emergency), the pediatric patient/parent/legal guardian must inform the investigator within a reasonable time period after intake of concomitant medication.

All concomitant medications (including start / stop dates, dose and dose frequency, route of administration, and indication) must be recorded in the patient's source documentation as well as in the appropriate pages of the eCRF.

Administration of contrast media for protocol-specified radiological procedures does not need to be reported, unless there is an AE related to the contrast medium administration (e.g. allergic reaction).

For prohibited prior therapy please refer to Section 6.2.

Prohibited concomitant therapy

- Strong CYP3A4 inhibitors and inducers (see Appendix 16.12). Copanlisib is primarily metabolized by CYP3A4. Therefore, concomitant use of strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, clarithromycin, ritonavir, indinavir, nelfinavir and saquinavir), and inducers of CYP3A4 (e.g., rifampicin, phenytoin, carbamazepine, phenobarbital, St. John Wort) are not permitted within two weeks prior to start of study treatment until the SFU visit.
- Grapefruit and grapefruit juice, Seville oranges, and star fruit (CYP3A4 inhibitor) consumption is not permitted during the study.
- Concomitant therapy with any other anticancer agent than copanlisib, immunosuppressive agents, other investigational therapies until the SFU visit.
- Anti-arrhythmic therapy other than beta blockers or digoxin until the SFU visit.
- Prophylactic myeloid growth factor in the first cycle of therapy in Phase I part of the study.
- Since high levels of biotin (vitamin B7) can interfere with the results of the immune assay tests including biomarker analysis, HBc-Ab, HBe-Ag, HBs-Ag, HCV-Ab, HIV-Ag/Ab combo, and HIV combo, patients should refrain from taking biotin supplements for at least 72 hours prior to immunoassay test collection.

Permitted concomitant therapy

- Standard therapies for concurrent medical conditions.
- Treatment with non-conventional therapies (for example herbs or acupuncture), and vitamin/mineral supplements is acceptable provided that they do not interfere with the study endpoints, in the opinion of the Investigator.
- Bisphosphonates per investigator's discretion.
- Prophylactic anticoagulation of venous or arterial access devices is allowed provided that the requirements for INR and PTT or aPTT are met. Close monitoring is recommended according to standard of care. If either of these values is above the therapeutic range, the doses should be modified and the assessments should be repeated weekly until it is stable. Low-dose aspirin and low-dose heparin are permitted.
- Therapeutic anti-coagulation with monitoring of coagulation parameters according to standard of care will be permitted based on medical judgement of the local investigator and on the benefit-risk assessment. Localized anti-coagulation for central line (e.g. tissue plasminogen activator [TPA], urokinase, heparin etc.) is permitted.
- Antiemetics: prophylactic anti-emetics may be administered according to standard practice. The routine use of standard antiemetics, including 5-HT3 blockers, such as granisetron, ondansetron, or an equivalent agent, is allowed as needed. The use of corticosteroids as antiemetics prior to study drug administration will be not allowed.

- Palliative and supportive care for the other disease-related symptoms and for toxicity associated with treatment will be offered to all patients in this trial.
- Palliative irradiation shall be permitted provided that:
  - In the opinion of the investigator, the patient does not have PD.
  - The radiation field does not encompass a target lesion
  - The radiation field does not encompass a lung field (to reduce the risk for pneumonitis).
- Patients taking narrow therapeutic index medications should be monitored proactively, if these medications cannot be avoided.
- Substrates of the renal drug transporter MATE2K (e.g. cimetidine, procainamide and N-methylnicotinamide) need to be used with caution.
- G-CSF may be administered if ANC< 500/mm^3 for 3 days or if experienced febrile neutropenia or grade 4 CTCAE v.4.03 neutropenia in previous cycle and should be administered as per label and local SOC. Long acting G-CSF should not be administered.
- The maximum allowed dose of corticosteroids will be 0.5 mg/kg or 10 mg/day of prednisone whichever is less. Note: Topical or inhaled corticosteroids are permitted.

8.2 Post-study therapy

During the active follow-up, after the end of study treatment period is completed, patients will not be restricted with regard to pursuing available treatments for their disease. All patients enrolled should be followed for overall survival for at least two years after end of treatment.

9. Procedures and variables

9.1 Tabular schedule of evaluations

Table 9–1 Study flow chart

	Screening [a] maximum days before C1D1		**Treatment**						**Active FU**			**Long Term FU** [x]
									EOT	**Safety FU** [v]	**Other active FU visits**	
			Cycle 1			**Cycle 2 and higher**			Within (days) after decision to stop	Within (days) after last dose		
Days	**-28**	**-7**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**7**	**30**	**every 3 months**	**every 3 months**
Acceptable time window (unless otherwise specified) (in days)				-1 to + 2 days			-1 to + 2 days		-7 days	+ 5 days	± 14 days	± 14 days
Screening and enrollment												
Patient informed consent (including consent for both genetic and non-genetic test using plasma and tumor tissues) [b]	Written informed consent must be obtained prior to any study-specific procedures.											
Check in- and exclusion criteria	X	X	X									
Medical and surgical history	X											
Disease confirmation	X											
Demographics	X											
Height (length for infants), weight, body surface area calculation [c]			X	X	X	X	X	X	X [c]			
IxRS transaction	X		X	X	X	X	X	X	X			
Serum pregnancy test for females of childbearing potential [d]		X				X			X			
HBsAg, HBcAb, anti-HCV [f]	X											
CMV PCR	X											
ECHO or MUGA [g]	X								X			
Safety												
Toxicity / AE assessment [h]	X	X	X	X	X	X	X	X	X	X		
Concomitant medication	X	X	X	X	X	X	X	X	X	X		
Physical examination and vital signs (including performance status) [i]		X	X	X	X	X	X	X	X	X		

Table 9–1 Study flow chart

	Screening [a] maximum days before C1D1		**Treatment**						**Active FU**			**Long Term FU** [x]
									EOT	**Safety FU** [v]	**Other active FU visits**	
			Cycle 1			**Cycle 2 and higher**			Within (days) after			
									decision to stop	last dose		
Days	**-28**	**-7**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**7**	**30**	**every 3 months**	**every 3 months**
Acceptable time window (unless otherwise specified) (in days)				-1 to + 2 days			-1 to + 2 days		-7 days	+ 5 days	± 14 days	± 14 days
Heart rate and respiration rate [i]			X	X	X	X	X	X				
12 or 15 -lead ECG [j]		X	X			X			X			
Complete blood count with differential and platelet count [k]		X	X [k]	X	X	X	X	X	X	X		
Chemistry panel [l]		X	X[l]	X	X	X	X (C2)	X(C2)	X	X		
Coagulation panel [m]		X				X			X			
Urinalysis (dipstick or local lab)		X				X			X			
Glucose			X [n]	X [o]	X [o]	X [o]	X [o]	X [o]				
Blood pressure		X	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]	X			
Creatinine clearance or serum creatinine [q]		X				X			X			
Biomarkers												
Tumor archival tissue (when available) [r]	X											
Fresh paired tumor biopsy (when feasible) [r]	X				X				X			
Blood (platelet rich plasma) sampling for pAKT (2.5mL) for patients > 1 year old [s]	X	X			X							
Blood sample for plasma biomarker analysis (3mL) for patients > 1 year old [s]	X	X			X				X			

Table 9–1 Study flow chart

	Screening [a] maximum days before C1D1		Treatment						Active FU			Long Term FU [x]
									EOT	Safety FU [v]	Other active FU visits	
			Cycle 1			Cycle 2 and higher			Within (days) after			
									decision to stop	last dose		
Days	**-28**	**-7**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**7**	**30**	**every 3 months**	**every 3 months**
Acceptable time window (unless otherwise specified) (in days)				-1 to + 2 days			-1 to + 2 days		-7 days	+ 5 days	± 14 days	± 14 days
Efficacy												
Tumor evaluation (CT or MRI scan or PET-CT, or MIBG scan) [t]	X		Every 8 weeks (± 7 days) until radiological tumor progression						X [t]		X [t]	
Bilateral bone marrow biopsy and/or bone marrow aspiration (patients with lymphomas or neuroblastoma) [e]	X		Will be done at the discretion of the local investigator and to confirm first CR for patients with bone marrow involvement at baseline.									
Study treatment administration												
Copanlisib infusion			X	X	X	X	X	X				
Pharmacokinetic sample [u]			X		X							
Long-term follow-up												
Survival status (for at least 2 years after last patient's last treatment)												X
Document other anticancer therapies												X

AE = Adverse event; ANC = Absolute neutrophil count; aPTT = Activated partial thromboplastin time; BM = Biomarker; C = Cycle; CBC = Complete blood count; CMV = Cytomegalovirus; CR = Complete response; CT = Computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; D = Day; ECG = Electrocardiogram; ECHO = Echocardiogram; EOT = End of Treatment; FU = Follow-up; HBcAb = Hepatitis B core antibody; HBsAg = Hepatitis B surface antigen; HCV = Hepatitis C Virus; INR = International normalized ratio; IxRS = Interactive Voice Response System /Interactive Web Response System; LDL = Low-density lipoprotein; MIBG = Iodine-123 metaiodobenzylguanidine; MRI = Magnetic resonance imaging; MUGA = Multiple gated acquisition; NCI = National Cancer Institute; PCR = Polymerase chain reaction; pAKT = Phosphorylated AKT (protein kinase B [PKB]); PD = Progressive disease; PET-CT = Positron emission tomography-computed tomography; PK = Pharmacokinetics; PTT = Partial thromboplastin time; SFU = Safety follow-up visit; SOC = Standard of care.

a Screening procedures may be completed during multiple visits but must be completed within specified timeframes before the first dose of study drug.

b Informed consent/assent form must be signed before any study-related procedures are performed (including screening procedures). The Informed

consent/assent form includes consent for plasma sample and archival and fresh biopsy tumor tissue collection for the analysis of non-genetic and genetic biomarkers, these samples should be collected where feasible/available.

c Height (length for infants) and weight will be measured at Cycle 1 Day1 and every dosing visit thereafter. At EOT, only weight will be checked as part of safety assessment. See Section 9.6.3.2.

d Female patients of childbearing potential must have a negative pregnancy test result ≤ 7 days prior to start of study treatment. After Cycle 1 serum pregnancy test is mandatory at every cycle and at the EOT visit for countries where it is required by local regulations. More frequent evaluation for pregnancy may be required in certain countries; all local regulations regarding pregnancy testing in clinical study patients must be followed.

e Bilateral bone marrow biopsy and/or bone marrow aspiration will be performed within 28 days before first study drug infusion in patients with lymphomas or neuroblastoma and in any tumor with marrow disease involvement at baseline or if suspicion for involvement at study entry. During the study period, bilateral bone marrow biopsy and/or bone marrow aspiration will be done at the discretion of the local investigator and to confirm first CR for patients with bone marrow involvement at baseline. Bone marrow biopsy/aspiration will be performed as per local standard of care.

f For patients of ≤1 year old, HBsAg, HBcAb, anti-HCV measurements to be done prior to -7 day visit. For other ages, measurements can be done any time within 28 days prior to the first study drug administration.

g ECHO or MUGA: to be done at screening, end of treatment and as clinically indicated.

h AE assessment is to be started from signing of informed consent until 30 days after the last dose of study drug. In addition, during the Active follow-up period, AEs considered to be related to study drug or study-related procedures will be reported. Any new findings or worsening of any ongoing medical history conditions after the patient has signed the informed consent are to be listed as adverse events (See Section 9.6.1.3).

i Physical examination including vital signs (heart rate, pulse oximetry, respiration rate and temperature), blood pressure measurement and performance status(Lansky / Karnofsky performance) (See Section 9.6.3.1). On infusion days, heart rate and respiration rate will be assessed at pre-dose and every 15 min (± 5 min) during the study drug infusion. In addition, at each visit prior to infusion, evaluation of any new onset or worsening of pulmonary symptoms (i.e. cough, dyspnea or fever) that includes a lung examination (see Section 7.4.4.3 for further information). Dentition examination per local SOC should be performed as part of the physical exam at screening.

j 12-lead (or 15-lead) ECG will be performed at Screening, on Cycle 1 Day 1 prior to infusion and at the end of infusion. In subsequent cycles: D1 of every cycle at the end of infusion and at the EOT visit.

k Complete blood count (CBC) with differential and platelet count: see Section 9.6.3.8. In case of cytopenias NCI-CTCAE Grade ≥ 3 (e.g. platelet < 50,000/mm^3, hemoglobin < 8 g/dl, ANC< 1000/mm^3), CBC may be performed more frequently as per investigator discretion and per local SOC. If done within 7 days, it may not be repeated.

l Chemistry panel: See Section 9.6.3.8. Total cholesterol, LDL and triglycerides will be tested only at screening, on Day 1 of every 2^{nd} cycle starting from Cycle 2, and at the EOT visit. If done within 7 days it may not be repeated.

m Coagulation panel: aPTT or PTT and INR.

n On C1D1 glucose will be measured at pre-dose <1 h prior to start of study drug infusion and post-dose after the end of study drug infusion according to instructions in Table 9–4. Additional measurements to be performed at the clinic as clinically indicated.

o Glucose test <1 h prior to study drug infusion and post-dose after the end of study drug infusion according to instructions in Table 9–4. Additional measurements to be performed at the clinic as clinically indicated.

p Pre-dose blood pressure will be measured twice with at least a 15 min interval between the assessments prior to start of infusion of study drug (any time on dosing day) See Section 7.4 for the required pre-dose blood pressure values before infusion can be started. After start of infusion, a single blood pressure measurement is conducted at 4 time points according to instructions given in Table 9–3 (mid-dose and post-dose blood pressure measurements). See also

guidance in Table 7–8. The patient should rest for at least 10 min before blood pressure is recorded. For blood pressure levels for children by age, height and gender percentile, see Appendix 16.6. For recommended dimensions for blood pressure cuff bladders, see Appendix 16.7.

q Creatinine clearance based on Schwartz Estimate ≥ 70 ml/min/1.73 m^2 or a serum creatinine based on age/gender (see Appendix 16.10).

r Collection of fresh biopsy is optional and encouraged to be performed when it is feasible. Samples can be collected at baseline (screening), on C1D15 or C1D16 within 24 hours after start of infusion or EOT. Available archival tumor samples must be submitted with date of material collection to investigate or identify biomarkers that may be predictive of copanlisib effects/efficacy and to contribute to better understanding the disease.

s BM plasma and platelet rich plasma samples. At screening: for patients > 1 year and < 6 years old BM samples should be collected any time within screening but prior to -7 day visit. For patients ≥ 6 years old BM samples should be taken within 7 days prior to the first study drug administration.

At C1D15: for patients > 1 year and < 6 years old, BM plasma samples will be collected at C1D15 only at 3 hours (± 30 min) after start of infusion. For patients ≥ 6 years old, BM samples will be collected before infusion (up to 30 min prior to start of infusion) and 3 hours (± 30 min) after start of infusion. Patients ≤ 1 year old will be excluded from blood sample collection.

t Tumor evaluation will be performed at screening (within 28 days prior to start of treatment), during treatment period: every 8 weeks (± 7 days) until radiological tumor progression, at EOT visit, and during active FU period every 12 weeks (± 14 days) until radiological tumor progression or start of new anti-cancer therapy, whichever occurs first. Please note: Tumor assessment is not required at the EOT visit if the patient discontinues due to PD which has been radiologically confirmed within the 4 weeks preceding EOT.

u PK sampling will be performed in all patients for copanlisib. The samples will be obtained during Cycle 1 on Days 1 and 15 according to Table 9–2.
PK sampling for copanlisib: Pre-dose PK: pre-infusion (< 30 min prior to start of infusion).Post-dose PK: 1-1.25 hour, 1.5-3 hour (patients ≥ 6 years only) and 22-24 hours after start of the infusion. If sampling is not feasible at Cycle 1, samples may be collected at Cycle 2 (see Section 9.5).

v Patients discontinuing the study treatment for any reason will enter active follow-up. The mandatory safety follow-up (SFU) visit will take place 30+5 days after the last administration of study drug.

x After active follow-up period patients will continue to be followed for overall survival for at least 2 years after the LPLT until death or unless consent is withdrawn.

9.2 Visit description

9.2.1 Timing of assessments

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

All procedures during the treatment period should be done according to the relative days mentioned in this CSP. For assessments during the treatment period, deviations of -1 day and +2 days are acceptable unless otherwise specified in the protocol.

The assessments apply to both Phase I and Phase II parts unless otherwise specified.

9.2.1.1 Screening period

Procedures performed prior to informed consent as standard of care may be used as screening assessments, if performed within the specified window (relative to start of dosing) and according to the protocol requirements.

Up to 28 days prior to the first study drug administration:

- Obtain written informed consent/assent. The Informed Consent/Assent Form includes consent for plasma sample, archival tumor tissue and optional fresh paired tumor biopsy collection for the analysis of genetic and non-genetic biomarkers.
- Check inclusion/exclusion criteria (see Section 6.1 and 6.2).
- Complete medical and surgical history including demographics (See Section 9.3.1), relevant medical history findings, concomitant illnesses, allergy history, prior surgeries, most recent histology of tumor, most recent staging and grading of tumor, history of anticancer treatments (including type of treatment, type of response, date and duration of response and date of subsequent relapse), assessment of baseline toxicity
- Disease confirmation
- IxRS transaction to register the patient in the system.
- Bilateral bone marrow biopsy and/or bone marrow aspiration will be performed within 28 days before first study drug infusion in patients with lymphomas or neuroblastoma and in any tumor with marrow disease involvement at baseline or if suspicion for involvement at study entry (see Section 9.4).
- Blood test for HBV and HCV: HBsAg, HBcAb and anti-HCV antibody. (If HBsAg or HBcAb positive also HBV DNA; if HCV IgG positive also HCV RNA). For patients of ≤ 1 year old, HBsAg, HBcAb, anti-HCV measurements to be done prior to -7 day visit. For other ages, measurements can be done any time within 28 days prior to the first study drug administration.
- Blood test for CMV infection per local SOC. Patients who are CMV test positive at baseline will not be eligible.

Care should be taken to minimize the amount of blood taken, and consideration given regarding the timing and volumes of blood required for other assessments at screening, such that the recommended limits for blood loss in children is not exceeded (see Appendix 16.5).

- MUGA or echocardiogram (see Section 9.6.3.6).
- Toxicity and assessment of adverse events. Any new findings or worsening of any ongoing medical history conditions after the patient has signed the informed consent are to be listed as adverse events (see Section 9.6.1.3).
- Concomitant medications
  - Note: contrast media does not need to be recorded as concomitant medication unless there is an AE related to its administration (e.g. allergic reaction).
- Fresh tumor tissue samples (optional) will be collected when feasible, and available archival tumor samples must be submitted with date of material collection to investigate or identify biomarkers that may be predictive of copanlisib effects/efficacy and to contribute better understanding of the disease.
- Radiological tumor evaluations (IV [and oral, if indicated, as per institutional standards] contrast enhanced CT, MRI or PET-CT as per local standards, of the primary tumor location area, and all other areas which could be targeted and/or suspected in the malignancy the patient has (see Section 9.4.1).
- Plasma sample for biomarker analyses (for patients > 1 year and < 6 years old).
- Platelet rich plasma samples for pAKT biomarker analysis (for patients > 1 year and < 6 years old).

Within 7 days prior to the first study drug administration:

- Review of inclusion/exclusion criteria (See Section 6.1 and 6.2).
- Pregnancy test (for females of childbearing potential only) (See Section 9.6.3.8.)
- Toxicity and assessment of adverse events (See Section 9.6.1.3).
- Concomitant medications
  - Note: contrast media does not need to be recorded as concomitant medication unless there is an AE related to its administration (e.g. allergic reaction).
- Physical examination including vital signs, and performance status (see Section 9.6.3.1 and 9.6.3.4). Dentition examination per local SOC should be performed as part of the physical exam at screening. Recommendation for blood pressure cuff sizes is provided in Appendix 16.7.
- 12 or 15-lead ECGs (see Section 9.6.3.5).
- Creatinine clearance based on Schwartz Estimate ≥ 70 ml/min/1.73 m^2 or a serum creatinine based on age/gender (See Section 9.6.3 and Appendix 16.10).

- Blood tests for CBC with differential and platelet count, chemistry, and coagulation panels (see Section 9.6.3.8).

  Care should be taken to minimize the amount of blood taken, and consideration given regarding the timing and volumes of blood required for other assessments at screening, such that the recommended limits for blood loss in children is not exceeded (see Appendix 16.5).

- Urinalysis (e.g. dipstick or local lab). Microscopy as clinically indicated (see Section 9.6.3.8).
- Plasma sample for biomarker analyses (for patients ≥ 6 years old).
- Platelet rich plasma samples for pAKT biomarker analysis (for patients ≥ 6 years old).

Based on the information obtained from the above assessments, the patient's eligibility will be decided upon eligibility check; no patient will be assigned to treatment unless all selection criteria are met.

9.2.1.2 Treatment period

After all screening assessments have been completed and the patient's eligibility has been confirmed and documented, the patient will be registered for treatment via IxRS.

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

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

- Evaluation of any new onset or worsening of pulmonary symptoms (i.e. cough, dyspnea or fever) that includes a lung examination at each visit prior to infusion (see Section 7.4.4.3 for further information).

9.2.1.2.1 Treatment – Cycle 1

Cycle 1 Day 1

- Review of inclusion/exclusion criteria
- IxRS treatment assignment
- Height (length), weight measurement, BSA calculation (see Section 9.6.3.2).
- Toxicity and AE assessment (see Section 9.6.1.3).
- Complete physical examination including performance status, vital signs, and complete review of body systems (see Sections 9.6.3.1 and 9.6.3.4).
- Heart rate and respiration rate. On infusion days, heart rate and respiration rate will be assessed at pre-dose and every 15 min (± 5 min) during the study drug infusion (see Section 9.6.3.4).

- 12 or 15-lead ECGs will be performed prior to infusion and at the end of infusion.
- Concomitant medication review.
- Pre-dose blood pressure will be measured twice with at least a 15 min interval between the assessments prior to start of infusion of study drug (any time on dosing day). See Section 7.4 for the required pre-dose blood pressure values before infusion can be started.

  After start of infusion, a single blood pressure measure is conducted at 4 timepoints according to instructions in Table 9–3 (mid-dose and post-dose blood pressure measurements).

  The patient should rest for at least 10 min before blood pressure is recorded. See Section 9.6.3.4.1 for further information.
- Glucose will be measured at pre-dose <1 h prior to start of study drug infusion and post-dose after the end of study drug infusion according to instructions in Table 9–4. Additional measurements to be performed at the clinic as clinically indicated.
- Complete blood count with differential and platelet count (see Section 9.6.3.8).
- Chemistry panel. If done within 7 days prior to C1D1 does no need to be repeated (see Section 9.6.3.8).
- PK sampling for copanlisib:

  Pre-dose PK: pre-infusion (< 30 min prior to start of infusion)

  Post-dose PK: 1-1.25 hour, 1.5-3 hour (patients ≥ 6 years only) and 22-24 hours after start of the infusion.

  If sampling is not feasible at Cycle 1, samples may be collected at Cycle 2. A separate IV line should be used for PK draws (see Section 9.5).
- Study drug IV infusion.

Cycle 1 Day 8

- Height (length), weight measurement (see Section 9.6.3.2).
- Toxicity and AE assessment (see Section 9.6.1.3).
- Concomitant medication review.
- Complete physical examination including performance status, vital signs and complete review of body systems (see Sections 9.6.3.1 and 9.6.3.4).
- Heart rate and respiration rate. On infusion days, heart rate and respiration rate will be assessed at pre-dose and every 15 min (± 5 min) during the study drug infusion (see Section 9.6.3.4).
- Complete blood count differential and platelet count (see Section 9.6.3.8).
- Chemistry panel (see Section 9.6.3.8).

- Glucose test <1 h prior to study drug infusion and post-dose 1 h after the end of study drug infusion according to instructions in Table 9–4. Additional measurements to be performed at the clinic as clinically indicated.
- Pre-dose blood pressure will be measured twice with at least a 15 min interval between the assessments prior to start of infusion of study drug (any time on dosing day). See Section 7.4 for the required pre-dose blood pressure values before infusion can be started.

  After start of infusion, a single blood pressure measure is conducted at 4 timepoints according to instructions in Table 9–3 (mid-dose and post-dose blood pressure measurements).

  The patient should rest for at least 10 min before blood pressure is recorded. See Section 9.6.3.4.1 for further information.
- IxRS transaction for medication dispensing.
- Study drug IV infusion.

Cycle 1 Day 15

- Height (length), weight measurement (see Section 9.6.3.2).
- IxRS transaction for medication dispensing.
- Toxicity and AE assessment (see Section 9.6.1.3).
- Concomitant medication review.
- Complete physical examination including performance status, weight, vital signs, pressure, and complete review of body systems and complete review of body systems (see Sections 9.6.3.1 and 9.6.3.4).
- Heart rate and respiration rate. On infusion days, heart rate and respiration rate will be assessed at pre-dose and every 15 min (± 5 min) during the study drug infusion (see Section 9.6.3.4).
- Complete blood count with differential and platelet count (see Section 9.6.3.8).
- Chemistry panel (see Section 9.6.3.8).
- Glucose test <1 h prior to study drug infusion and 1 h after the end of study drug infusion according to instructions in Table 9–4. Additional measurements to be performed at the clinic as clinically indicated.
- Pre-dose blood pressure will be measured twice with at least a 15 min interval between the assessments prior to start of infusion of study drug (any time on dosing day). See Section 7.4 for the required pre-dose blood pressure values before infusion can be started.

After start of infusion, a single blood pressure measure is conducted at 4 timepoints according to instructions in Table 9–3 (mid-dose and post-dose blood pressure measurements).

The patient should rest for at least 10 min before blood pressure is recorded. See Section 9.6.3.4.1 for further information.

- Plasma sample for biomarker analyses: for patients > 1 year and < 6 years old, plasma samples will be collected at C1D15 only at 3 hours (± 30 min) after start of infusion. For patients ≥ 6 years old, BM samples will be collected up to 30 min prior to start of infusion and 3 hours (± 30 min) after start of infusion. Patients ≤ 1 year old will be excluded from blood sample collection.
- Platelet rich plasma samples for pAKT biomarker analysis: for patients > 1 year and < 6 years old, plasma samples will be collected at C1D15 only at 3 hours (± 30min) after start of infusion. For patients ≥ 6 years old, BM samples will be collected up to 30 min prior to start of infusion and 3 hours (± 30 min) after start of infusion. Patients ≤ 1 year old will be excluded from blood sample collection.
- Fresh tumor tissue samples when consent provided and when feasible.
- PK sampling for copanlisib:

  Post-dose PK: 1-1.25 hour, 1.5-3 hour (patients ≥ 6 years only) and 22-24 hours after start of the infusion.
- Study drug IV infusion.

9.2.1.2.2 Treatment – Cycle 2 and higher

Cycle 2 and higher, Day 1

- Height (length for infants) and weight measurement (see Section 9.6.3.2).
- IxRS transaction for medication dispensing.
- Serum pregnancy test (if applicable): after Cycle 1 serum pregnancy test is mandatory at every cycle for countries where it is required by local regulations.
- Toxicity and AE assessment (see Section 9.6.1.3).
- Concomitant medication review.
- Complete physical examination including performance status, vital signs, blood pressure, and complete review of body systems (see Sections 9.6.3.1 and 9.6.3.4).
- Heart rate and respiration rate. On infusion days, heart rate and respiration rate will be assessed at pre-dose and every 15 min (± 5 min) during the study drug infusion (see Section 9.6.3.4).
- 12 or 15 -lead ECG will be performed on D1 of Cycle 2 and every subsequent cycle at the end of infusion (see Section 9.6.3.5).

- Complete blood count with differential and platelet count (see Section 9.6.3.8).
- Chemistry panel. Total cholesterol, LDL and triglycerides will be tested only at screening, on Day 1 of every 2nd cycle starting from Cycle 2, and at the EOT visit. If done within 7 days it may not be repeated (see Section 9.6.3.8).
- Coagulation panel: INR and PTT or aPTT
- Urinalysis (e.g. dipstick or local lab). Microscopy as clinically indicated (see Section 9.6.3.8).
- Glucose test <1 h prior to study drug infusion and post-dose 1 h after the end of study drug infusion according to instructions in Table 9–4. Additional measurements to be performed at the clinic as clinically indicated.
- Pre-dose blood pressure will be measured twice with at least a 15 min interval between the assessments prior to start of infusion of study drug (any time on dosing day). See Section 7.4 for the required pre-dose blood pressure values before infusion can be started.

  After start of infusion, a single blood pressure measure is conducted at 4 timepoints according to instructions in Table 9–3 (mid-dose and post-dose blood pressure measurements). The patient should rest for at least 10 min before blood pressure is recorded. See Section 9.6.3.4.1 for further details.
- Creatinine clearance based on Schwartz Estimate ≥ 70 ml/min/1.73 m^2 or a serum creatinine based on age/gender (See Section 9.6.3.8 and Appendix 16.10).
- Study drug IV infusion.

Cycle 2 and higher, Day 8

- Height (length for infants) and weight measurement (see Section 9.6.3.2).
- IxRS transaction for medication dispensing.
- Toxicity and AE assessment (see Section 9.6.1.3).
- Concomitant medication review.
- Complete physical examination including performance status, vital signs, blood pressure, and complete review of body systems (see Sections 9.6.3.1 and 9.6.3.4).
- Heart rate and respiration rate. On infusion days, heart rate and respiration rate will be assessed at pre-dose and every 15 min (± 5 min) during the study drug infusion (see Section 9.6.3.4).
- Complete blood count with differential and platelet count (see Section 9.6.3.8).
- Cycle 2 only: Complete chemistry panel (See Section 9.6.3.8).

- Pre-dose blood pressure will be measured twice with at least a 15 min interval between the assessments prior to start of infusion of study drug (any time on dosing day). See Section 7.4 for the required pre-dose blood pressure values before infusion can be started.

  After start of infusion, a single blood pressure measure is conducted at 4 timepoints according to instructions given in Table 9–3 (mid-dose and post-dose blood pressure measurements). The patient should rest for at least 10 min before blood pressure is recorded. See Section 9.6.3.4.1
- Glucose test <1 h prior to start of study drug infusion and 1 h after the end of study drug infusion according to instructions in Table 9–4. Patients are not required to be fasting prior to pre-dose glucose measurement.
- Study drug IV infusion.

Cycle 2 and higher, Day 15

- Height (length for infants) and weight measurement (see Section 9.6.3.2).
- IxRS transaction for medication dispensing.
- Toxicity and AE assessment (see Section 9.6.1.3).
- Concomitant medication review.
- Complete physical examination including performance status, vital signs, blood pressure, and complete review of body systems (see Sections 9.6.3.1 and 9.6.3.4).
- Heart rate and respiration rate. On infusion days, heart rate and respiration rate will be assessed at pre-dose and every 15 min (± 5 min) during the study drug infusion (see Section 9.6.3.4).
- Complete blood count with differential and platelet count (see Section 9.6.3.8).
- Cycle 2 only: Complete chemistry panel (see Section 9.6.3.8).
- Glucose test <1 h prior to study drug infusion and post-dose 1 h after the end of study drug infusion according to instructions in Table 9–4. Patients are not required to be fasting prior to pre-dose glucose measurement.
- Pre-dose blood pressure will be measured twice with at least a 15 min interval between the assessments prior to start of infusion of study drug (any time on dosing day). See Section 7.4 for the required pre-dose blood pressure values before infusion can be started.

  After start of infusion, a single blood pressure measure is conducted at 4 timepoints according to instructions given in Table 9–3 (mid-dose and post-dose blood pressure measurements).

  The patient should rest for at least 10 min before blood pressure is recorded. See Section 9.6.3.4.1.

- Study drug IV infusion.

9.2.1.3 Tumor assessments

Please refer to Section 9.4 for the schedule of radiological tumor assessments and bilateral bone marrow biopsy and/or bone marrow aspiration.

9.2.1.4 End-of-treatment visit

The procedures to be performed at the EOT visit will take place **not later than 7 days** after the decision is made to discontinue the study treatment. They will comprise the following:

- Only weight will be checked as part of safety assessment. See Section 9.6.3.2.
- IxRS transaction to register end of treatment.
- Serum pregnancy test (if applicable): mandatory for countries where it is required by local regulations (see Section 9.6.3.8).
- Toxicity and AE assessment (see Section 9.6.1.3).
- Concomitant medication review
- Complete physical examination including performance status, vital signs, and complete review of body systems (see Sections 9.6.3.1 and 9.6.3.4).
- A 12 or 15-lead ECG: necessary only if not recorded within the previous 4 weeks.
- Complete blood count with differential and platelet count (see Section 9.6.3.8).
- Chemistry panel (see Section 9.6.3.8). Total, conjugated and unconjugated bilirubin, alkaline phosphatase, ALT, AST. Total cholesterol, LDL and triglycerides. If a patient can't adhere to fasting requirements, the evaluation of lipid-panels including triglycerides is considered not feasible (lipid panels will be omitted).
- Coagulation panel: INR and PTT or aPTT
- MUGA or echocardiogram.
- Urinalysis (e.g. dipstick or local lab). Microscopy as clinically indicated (see Section 9.6.3.8).
- Creatinine clearance based on Schwartz Estimate $\geq$ 70 ml/min/1.73 m^2 or a serum creatinine based on age/gender (see Section 9.6.3.8 and Appendix 16.10).
- Fresh tumor tissue samples when consent provided and when feasible.
- Plasma sample for biomarker analysis (except patients $\leq$ 1 year old).

9.2.1.5 Follow-up periods

An additional contact with the patient may be required before the next scheduled visit or telephone call if the most recent data on survival is needed at a specific time point during Active follow-up or Long-term follow-up (e.g. for a DMC meeting or data analysis).

9.2.1.5.1 Active follow-up

The active follow-up period is the interval from the end of study drug intake to the end of all CSP-specified post-treatment interventions. All patients who discontinue study treatment for any reason will be followed for safety at a mandatory safety follow-up visit except for the cases when patients and/or parents (or legal guardians) refuse follow-up data collection. Safety follow-up (SFU) visit will take place 30 + 5 days after the last administration of study drug.

Patients who discontinue study treatment for reasons other than radiological PD will have radiological assessments as outlined in this CSP from the time of discontinuation of treatment of until PD is documented or new anti-tumor treatment is administered.

Safety follow-up visit:

If a patient discontinues study treatment at any time during the study for any reason (except death or lost to follow-up) a safety follow-up evaluation should be performed 30 days (window of + 5 days is allowed) after the last dose of study medication. Please note that adverse events should be reported up to 30 days after the last dose of study drug

- Toxicity/AE assessment (see Section 9.6.1.3).
- Concomitant medication review.

If clinically indicated:

- Physical examination including performance status, weight, vital signs, blood pressure, and review of body systems (see Section 9.6.3.1).
- Complete blood count with differential and platelet count and chemistry (see Section 9.6.3.8).
- If a patient has begun treatment with another anticancer agent and is no longer being seen in the clinic, the post-treatment safety assessment can be conducted via telephone.

Other active follow-up visits

Patients who discontinue study treatment for reasons other than radiological PD will enter the active follow-up period, except for patients and/or parents (or legal guardians) who object to follow-up data collection. The patients in the active follow-up will have radiological assessments as outlined in this CSP from the time of discontinuation of treatment until radiological PD for this patient is observed or until the start of first subsequent anti-cancer therapy, whichever occurs first.

During this period only AEs and SAEs assessed as related to the study procedures by the investigator will be reported. AE pages of the eCRF and the SAE form should be completed in the usual manner and forwarded to the applicable sponsor's GPV department.

During the study for up to 2 years after the last patient first treatment (LPFT), routine growth and dentition examinations will be performed for patients on study until the end of active FU per local SOC. A hand-wrist and dental imaging studies may be performed per local SOC and per investigator's discretion, if any abnormality is observed.

9.2.1.5.2 Long-term follow-up

All patients will be followed-up for survival for at least 2 years after the end of the phase I (dose-escalation) and phase II (extension) parts. Following completion of the active follow-up study period, patients' parents (or legal guardians) will continue to be contacted approximately every 3 months (± 14 days) to determine survival status until death or for at least 2 years after the LPLT in the study, independent of the reason for study termination, except for patients who object to follow-up data collection. Patients or their parents or legal guardians or their healthcare providers will be contacted either in person or by telephone. Those patients who reached adult age during the long-term follow-up can be contacted directly or via patients' parents (or legal guardians).

Information to be recorded at these contacts:

- Survival status, including date of contact.
- Documentation of the first new anti-cancer treatment regimen including response, if given.
- Date and cause of death, if applicable.

9.3 Population characteristics

9.3.1 Demographic

For demographic assessment the following parameters will be recorded: age, sex/gender, race/ethnicity.

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 patient'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

- Date of diagnosis and stage of disease
- Tumor site and size, site(s) and date(s) of metastases, type of surgery conducted

- Karnofsky / Lansky performance status
- Prior anti-neoplastic therapies, including the response to the therapies
- All medications and significant non-drug therapies taken before study entry, including the following
  - Medication trade name and dose
  - Reason for medication
  - Start date and end date, or if continuing at the time of study entry

9.4 Efficacy

9.4.1 Radiological tumor assessments

Standard tumor measurement procedures will be used. Radiological tumor evaluations will be performed based on IV [and oral, if indicated, as per institutional standards] contrast enhanced CT, MRI or PET-CT as per local standards, of the primary tumor location area and all other areas which could be targeted and/or suspected in the malignancy the patient has. The method chosen at the baseline should be the same throughout the study. If at baseline IV (or oral) contrast-enhanced CT is medically contraindicated, sites may acquire MRI (contrast-enhanced) of the primary tumor location area and all other areas which could be targeted and/or suspected in the malignancy the patient has. Only if a patient develops contra-indication to both CT and MRI contrast medium during the study, the case examinations could be continued without contrast medium.

Tumor assessments will be performed at screening (within 28 days prior to start of treatment), during treatment period every 8 weeks (± 7 days) until radiological tumor progression, at EOT visit and during active FU period every 12 weeks (± 14 days) until radiological tumor progression or start of new anti-cancer therapy, whichever occurs first. Scans done up to 28 days prior to first dose can be used as baseline studies. Please note: tumor assessment is not required at the EOT visit if the patient discontinues study treatment due to PD which has been radiologically confirmed within the 4 weeks preceding EOT visit.

NOTE: post-base line imaging performed within 7 weeks after the date of baseline tumor evaluation will not be evaluable for DCR analysis of stable disease (SD) in patients with osteosarcoma.

For neuroblastoma patients with MIBG-avid disease, MIBG scan will be used and assessment will be done according to SIOPEN or Curie score (see Appendix 16.2 and 16.3). Bone scan will be done if bone metastases are suspected (not applicable for neuroblastoma patients). Modified Lugano Classification 2014 will be used for evaluation of lymphoma (see Appendix 16.11) and RECIST v1.1 (see Appendix 16.1) will be used for solid tumors evaluation.

MRI/CT/PET-CT/MIBG scans must meet the standard of care for the imaging of lesions in the respective organ system(s) and preferably evaluated by the same investigator/radiologist. However, CT scans of PET-CT images used for lesion assessments must be of diagnostic CT quality (CT is required for lesion assessments). Copies of all imaging performed for tumor

assessment in all enrolled patients will be stored electronically at the site. Copies of the imaging studies may be requested for an optional retrospective review.

Bilateral bone marrow biopsy and/or bone marrow aspiration will be performed within 28 days before first study drug infusion in patients with lymphomas, or neuroblastoma and in any tumor with marrow disease involvement at baseline or if suspicion for involvement at study entry.

During the study period, bilateral bone marrow biopsy and/or bone marrow aspiration will be done at the discretion of the local investigator and to confirm first CR for patients with bone marrow involvement at baseline. Bone marrow biopsy/aspiration will be performed as per local standard of care.

9.5 Pharmacokinetics / pharmacodynamics

For PK: Each patient will provide blood samples during Cycle 1 (or, optionally, during Cycle 2 if it was not done on Cycle 1) on Days 1 and 15 according to Table 9–2. PK sampling will be performed in all patients for copanlisib.

Table 9–2 Blood sample collection for copanlisib PK assessment

Age ≥ 6 years			
Cycle	**Study Day**	**Time window**	**Volume of blood (mL)**
		Pre-dose PK	
1	Day 1	pre-infusion (< 30 min prior to start of infusion	1.0
		Post-dose PK (after start of infusion)	
1	Day 1	1 – 1.25 h	1.0
1	Day 1	1.5 – 3 h	1.0
1	Day 1/2	22 – 24 h	1.0
1	Day 15	1 – 1.25 h	1.0
1	Day 15	1.5 – 3 h	1.0
1	Day 15/16	22 – 24 h	1.0
		Total blood volume to be collected per patient	7 mL
Age < 6 years			
Cycle	**Study Day**	**Time window**	**Volume of blood (mL)**
		Pre-dose PK	
1	Day 1	pre-infusion (< 30 min prior to start of infusion	1.0
		Post-dose PK (after start of infusion)	
1	Day 1	1 – 1.25 h	1.0
1	Day 1/2	22 – 24 h	1.0
1	Day 15	1 – 1.25 h	1.0
1	Day 15/16	22 – 24 h	1.0
		Total blood volume to be collected per patient	5 mL

H = hour; PK = Pharmacokinetic

PK samples taken outside of protocol specified planned sampling time will be recorded but will not be considered as protocol deviations. The date and clock time of each sample as well as dates and times of the doses will be recorded in the electronic Case Report Form (eCRF) as PK calculations will be based on the sampling times relative to dosing times Samples may be collected irrespective of any dose modifications during the treatment cycle.

A separate IV line must be used for PK blood draws. This line must not be used for IV infusion of the drug.

The PK will be evaluated using population PK (popPK) model.

Details about the collection, processing, storage and shipment of samples will be provided separately (please refer to Laboratory Manual).

Concentration data of copanlisib from this study will be analyzed to estimate the individual maximum drug concentration (C_{max}) and area under the curve (AUC), and to measure the variability of copanlisib PK in this population and to compare the mean exposure of the all cohorts to the adult exposure. A popPK model will be used for the analysis.
A separate data evaluation plan, providing details of the evaluation will be provided prior to the beginning of the population PK analysis. Evaluation of the data will be presented in a separate report. Individual PK parameters derived from the population PK model will be statistically summarized for each cohort.

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 patient or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

A surgical procedure that was planned prior to the start of the study by any physician treating the patient should not be recorded as 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 patient was at risk of death at the time of the event, it does not refer to an event which hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

   - The admission results in a hospital stay of less than 12 hours
   - The admission is pre-planned
     (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 AEs should be documented using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI-CTCAE, v. 4.03). For events not listed in the NCI-CTCAE version 4.03, the following scale will be used:

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe
- Grade 4: Life-threatening
- Grade 5: Fatal

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.

Causality should be assessed separately for each study treatment as detailed in the CRF. If the investigator feels that the event cannot be firmly attributed to one of the study treatments (e.g. owing to a suspected underlying interaction), the same assessment will be documented for each study treatment.

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 patient is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration.

An assessment of "yes" indicates that 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 (re-challenge): Patient'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 patient may have.
  - Concomitant medication or treatment:
    The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them 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 patient's pharmacodynamics should be considered.
- The assessment is not possible

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
- Drug interrupted
- Dose reduced
- Dose not changed

- 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

All patients who discontinue due to AEs or clinical laboratory abnormalities should be followed up until they recover or stabilize, and the subsequent outcome recorded. If any patient dies during the study or within 30 days of the last dose of study drug, the investigator or his/her designated associate(s) will inform the sponsor. The cause of death should be recorded in detail within 24 h of awareness on an SAE form and transmitted to the sponsor.

A laboratory test abnormality considered clinically significant, e.g., causing the patient to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged significant by the investigator, should be reported as an AE. Each event should be described in detail along with start and stop dates, intensity, relationship to investigational product, action taken and outcome.

AEs observed or mentioned upon open questioning by a member of the investigator team or spontaneously reported by the patients or their parents/legal guardians will be documented. Parents/legal guardians will be encouraged and carefully instructed to report adverse reactions and events to the investigator in a timely manner, particularly in young children, who may not be able to identify adverse reactions. AEs will be documented in an event-based manner, using NCI-CTCAE v.4.03 guidelines.

The observation phase for AEs will start after signing of informed consent/assent and will end in general at the safety follow-up visit. During the active follow-up period, after the SFU visit, AEs and SAEs considered related to the study drug or study-related procedures will be reported and documented.

The investigator has to record on the respective CRF pages all adverse events occurring in the period that starts with the signing of the informed consent and will end 30 days after the last dose of study drug. The safety follow-up will occur 30 days (window of +5 days is allowed) after the last dose of study drug. AE pages of the eCRF and the SAE form should be completed in the usual manner and forwarded to the applicable sponsor's GPV department.

After the end of the follow-up phase there is no requirement to actively collect AEs including deaths. 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 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 an SAE only if the underlying event which resulted in death is unknown.

For all serious adverse events (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 serious adverse events (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.

If disease progression leads to signs and symptoms that meet the criteria for seriousness (see Section 9.6.1.1), the associated signs and symptoms should be reported as SAEs, not the underlying cause (i.e. "progressive disease" should not be reported as SAE). In this case, disease progression should be mentioned on the SAE form as "alternative explanation".

Investigator's notification of the sponsor

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

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

For all SAEs, the investigator is required to document in full the course of the SAE and any therapy given, including any relevant findings/records in the report. For documentation of laboratory findings as SAE, please refer to Section 9.6.3.8.

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 hours 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.

If the investigator becomes aware of bone or teeth alterations after the end of long-term follow-up for safety, he/she should report this as an SAE

Notification of the IECs / IRBs

Notification of the IECs / 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 investigator's brochure (IB)

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

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

9.6.1.6 Adverse events of special safety interest

Copanlisib is an investigational drug and current knowledge of the AEs associated with this compound is limited. As with any new chemical entity, there is always potential for AEs that may be class related. Non-infectious pneumonitis (NIP) has been observed with copanlisib, as with other PI3K drugs, and since the sponsor wishes to be aware of any such reports rapidly, NIP has been designated as an AE of special interest (AESI). Regardless of whether an AE consistent with NIP is assessed as causally related/not related to study drug, or as serious/non-serious, the investigator should notify the sponsor within 24 hours as outlined in Section 9.6.1.4. The AESI should be entered in the SAE form, and if the event is assessed as

non-serious, the non-serious assessment should be noted in the form. The AESI will be also entered in the eCRF.

9.6.2 Pregnancies

The investigator must report to the sponsor any pregnancy occurring in a female study patient 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 patient, 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 Further safety

9.6.3.1 Physical examination

Physical examination includes performance status assessment (see grading definitions in Appendix 16.4), vital signs (see Section 9.6.3.4), and complete review of body systems.

The physical examination (by means of inspection, palpation, auscultation) will be performed by a physician at the investigational site.

For this examination, the investigator will assess / examine the following:

- General appearances
- Skin
- Eyes
- Ears, nose and throat
- Head and neck
- Lungs
- Heart
- Abdomen
- Lymph nodes
- Musculoskeletal system (including extremities and spine)
- Neurological findings

If indicated by the patient's history, the following will be examined by specialists, if applicable:

- Genito-urinary system
- Gynecological organs
- Rectum

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

9.6.3.2 Body weight, height and BSA calculation

Body weight and height (length for infants) will be measured upon arrival by a member of the investigator's team:

BSA will be calculated at Cycle 1 Day 1 based on either the Mosteller formula or the DuBois formula. Mosteller formula is recommended as it combines accurate BSA calculation with ease of use. However, the formula that is chosen at Cycle 1 Day 1 must be used throughout the study.

Mosteller: BSA (m^2) = ([Height(cm) x Weight(kg)]/ 3600)^{½}

DuBois: BSA (m^2) = 0.20247 x Height(m)$^{0.725}$ x Weight(kg)$^{0.425}$

9.6.3.3 Growth and dental exams

During the study for up to 2 years after the LPFT routine growth and dentition examinations may be performed for patients on study until the end of active FU per local SOC. A hand-wrist and dental imaging studies may be performed per local SOC and per investigator's discretion, if any abnormality is observed.

9.6.3.4 Vital signs

Heart rate, pulse oximetry, respiration rate, blood pressure and temperature will be assessed according to the schedule summarized in the flow chart of Section 9.1. If clinically indicated, it is at the investigator's discretion to perform these measurements more frequently.

On infusion days, heart rate and respiration rate will be assessed at pre-dose and every 15 min (± 5 min) during the study drug infusion.

9.6.3.4.1 Blood pressure measurement on infusion days

Pre-dose blood pressure will be measured twice with at least a 15 min interval between the measurements prior to infusion of study drug (any time on dosing day). After start of infusion, a single measurement is conducted at 4 time points after start of infusion (see Table 9–3).

The patient should rest for at least 10 min before blood pressure is recorded. For blood pressure levels for children by age and height percentile, see Appendix 16.6. For recommended dimensions for blood pressure cuff bladders, see Appendix 16.7

Table 9–3 Blood pressure measurement on copanlisib infusion days

Pre-dose BP measurement [a]	Mid-dose BP measurement	Post-dose BP measurement
2 measures with least a 15 min interval between assessments	30 min (+/-10 min) after start of infusion (mid-infusion)	0h (+10 min) after end of infusion *(equivalent to 1h post start of infusion)* 1h (+/-10 min) after end of infusion *(equivalent to 2h post start of infusion)* 2h (+/-10 min) after end of infusion *(equivalent to 3h post start of infusion)*

BP = Blood pressure; H = Hour; Min = Minute.
a: Any time on dosing day

9.6.3.5 Electrocardiogram

12 or 15-lead ECG at screening (within 28 days of Cycle 1 Day 1), on Cycle 1 Day 1 prior to and at the end of copanlisib infusion and on Day 1 of every cycle at the end of copanlisib infusion. At EOT visit, a 12 or 15-lead ECG is necessary only if not recorded within the previous 4 weeks.

9.6.3.6 Cardiac function

Cardiac function test: echocardiogram or MUGA scan at screening (within 28 days of Cycle 1 Day 1), and at EOT visit, and as clinically indicated. At EOT, a test is necessary only if not recorded within the previous 4 weeks.

The method chosen at baseline (i.e. either echocardiogram or MUGA scan) must be used throughout the whole study period. Additional cardiac function tests are required if any signs or symptoms of cardiac dysfunction occur.

The study number, patient number, visit and the date of the echocardiogram/MUGA scan are noted on every echocardiogram/MUGA scan. The overall interpretation of the echocardiogram/MUGA scan and findings will be recorded in the source documentation and in the eCRF.

9.6.3.7 Lansky-Karnofsky Performance status

Patients' ability to manage activities of daily living will be appraised utilizing the performance status scale by Lansky/Karnofsky (see Appendix 16.4). The patient's performance score will be estimated according to the schedule summarized in Section 9.1. The same scale will be used throughout the study which was used at the baseline.

9.6.3.8 Laboratory examinations

Local laboratory will be used for the analysis of blood and urine samples collected to address safety parameters. The following blood and urine samples will be collected by a member of the investigator's team:

- Complete blood count: Hemoglobin, hematocrit, RBC, WBC (with differential to include absolute neutrophil, lymphocyte, monocyte, basophil and eosinophil counts) and platelet count.
- Chemistry panel: Creatinine, urea/BUN, lipase, amylase, total protein, albumin, uric acid, LDH, calcium, sodium, potassium, chloride, phosphorus, magnesium, bicarbonate (or carbon dioxide if bicarbonate is not routinely measured at the site) and serum glucose. Total, conjugated and unconjugated bilirubin, alkaline phosphatase, ALT, AST. Total cholesterol, LDL and triglycerides will be tested only at screening, on Day 1 of every 2nd cycle starting from Cycle 2, and at the EOT visit. On these dates patients must be fasting prior to sampling according to local standards. If a patient can't adhere to fasting requirements, the evaluation of lipid-panels including triglycerides is considered not feasible (lipid panels will be omitted).
- Coagulation panel: aPTT (activated partial thromboplastin time) or PTT (partial thromboplastin time) and INR (international normalized ratio)
- Urinalysis (dipstick): blood cells, glucose, ketones, bilirubin, protein, and pH (dipstick). Additional microscopic examinations will be performed if clinically indicated. If dipstick use is not permitted at site, local lab may be used for sample analysis.

- Creatinine clearance based on Schwartz Estimate ≥ 70 ml/min/1.73 m^2 or a serum creatinine based on age/gender (see Appendix 16.10).
- Pregnancy test (for females of childbearing potential only).

Care should be taken to minimize the amount of blood taken, and consideration given regarding the timing and volumes of blood required for other assessments at each visit, such that the recommended limits for blood loss in children is not exceeded (see Appendix 16.5).

For patients with identified risk factors and those who presented with new onset or worsening of pulmonary symptoms or developed OI on study treatment, any additional laboratory and diagnostic methods according to local SOC reported as unscheduled laboratory and diagnostic methods of assessment.

An isolated laboratory abnormality that meets the criteria for a CTCAE Grade 4 classification is not reportable as an SAE, unless the investigator assesses that the event meets standard ICH criteria for an SAE (SAE definition in Section 9.6.1.1).

Baseline laboratory abnormalities that are part of the disease profile should not be reported as an AE, specifically when they are allowed or not excluded by the protocol inclusion/exclusion criteria. If an investigator is in doubt about the applicable reporting obligations, he / she should consult with the study monitor of the sponsor.

9.6.3.9 Glucose measurement on infusion days

On Cycle 1 Day 1 and on subsequent infusion days glucose will be measured according to instructions given in Table 9–4.

Table 9–4 Glucose measurement on copanlisib infusion days

	Pre-dose glucose measurement	Post-dose glucose measurement
Cycle 1 Day 1 [a]	<1 h prior to start of copanlisib infusion	0 h (+ 5 min) after end of infusion (*equivalent to 1h post start of infusion*) 1h (+/- 5 min) after end of infusion (*equivalent to 2h post start of infusion*) 2h (+/- 5 min) after end of infusion (*equivalent to 3h post start of infusion*)
Subsequent infusion days [a] (Cycle 1 Day 8 onwards)	<1 h prior to start of copanlisib infusion	1h (+/- 5 min) after end of infusion (*equivalent to 2h post start of infusion*)

H = Hour; Min = Minute.
a: Additional measurements to be performed at the clinic as clinically indicated.

9.7 Other procedures and variables

9.7.1 Biomarker investigations

Biomarker investigations in the current study will include both PD biomarker assessments to examine the effect of copanlisib on signaling pathway activity and downstream tumor cell processes, as well as potentially predictive biomarkers to determine which molecular subsets may respond to treatment. The biomarker results may be reported separately from the main clinical study report (CSR).

9.7.1.1 PD biomarker assessment

PD biomarkers reflecting the effect of copanlisib on signaling pathway activity will be evaluated. For example, pharmacodynamic biomarker assessments may include analysis of changes in tumor cell signaling (e.g. pAKT, pS6), downstream tumor effects (e.g. Ki67, reflecting cell proliferation, and cleaved caspase 3, reflecting apoptosis), and tumor gene expression; changes in pAKT in platelet rich plasma as a surrogate tissue; and changes in plasma protein levels.

Collection and use of biomarker specimens for pharmacodynamic biomarker assessment:

- **Blood (plasma) sampling for biomarker evaluation:** Blood samples will be obtained and used for plasma preparation at screening (baseline) and at C1D15 before infusion (up to 30 min prior to start of infusion) and 3 hours (± 30 min) after start of infusion. For patients > 1 year and < 6 year old BM plasma samples will be collected at C1D15 only at 3 hours (± 30min) after start of infusion. Patients of ≤ 1 year old will be excluded from blood sample collection. Plasma may be used to quantify the circulating levels of various proteins via enzyme linked immunosorbent assay or other immunoassay (e.g. multiplex).
- **Blood (platelet rich plasma) sampling for pAKT assay:** Blood samples will be obtained and used for platelet rich plasma preparation at screening (baseline) and C1D15 before infusion (up to 30 min prior to start of infusion) and 3 hours (± 30 min) after start of infusion. For patients > 1 year and < 6 year old BM plasma samples will be collected at C1D15 only at 3 hours (± 30min) after start of infusion. Patients of ≤ 1 year old will be excluded from blood sample collection.
- **Tumor tissue samples (optional if feasible):** Fresh biopsy tissue will be collected from patients during screening and treatment (C1D15 or C1D16) or at EOT when feasible. Tumor tissue may be a source of nucleic acids (e.g. DNA or RNA) or protein, used to study, for example, gene expression and protein levels / signaling status (e.g. pAKT, Ki67) for target engagement and resistance mechanism evaluation.

All samples will be collected and processed as per instruction in the Laboratory Manual.

9.7.1.2 Molecular tumor characterization / potentially predictive biomarkers

Baseline candidate biomarkers will be evaluated for correlation with the response to treatment ("predictive biomarkers"). Baseline candidate predictive biomarkers may include, for example, tumor genetics, tumor proteins, RNA profiles, and plasma proteins. Many of the pharmacodynamic biomarkers will also be evaluated for predictive ability by analyzing baseline levels only.

Use of biomarker specimens for predictive biomarker assessment (using the same baseline samples described above for pharmacodynamic biomarkers):

- Archival tumor samples (as well as the fresh tumor biopsy, if available) may be used as a source of DNA for evaluating tumor associated alterations in genes of interest (e.g. PI3K, KRAS, PTEN, and other genes associated with the pathomechanism of the disease). Protein signaling status and levels at baseline (e.g. pAKT, PTEN) and baseline RNA profiles may also be assessed for predictive ability.
- The plasma samples collected at baseline, during treatment and EOT may also be used to identify potentially predictive biomarkers, for example through examination of plasma protein levels and/or genetic mutations from circulated tumor DNA.
- In addition to the proteins and genes listed above, other biomarkers deemed relevant to gain further knowledge about the pathomechanism of the disease or about the drug (i.e. mode of action or safety of the drug) may be measured, based on newly emerging data from other ongoing studies of these investigational drugs and / or literature data.

9.8 Appropriateness of procedures / measurements

All parameters, as well as the methods to measure them, are standard variables/methods in studies and clinical practice. They are widely used and generally recognized as reliable, accurate, and relevant. Parameters and methods not considered standard procedure should be validated appropriately before their use in this study.

10. Statistical methods and determination of sample size

10.1 General considerations

Statistical analysis will be performed using SAS version 9.2 or later; the version used will be specified in the statistical analysis plan (SAP). In general, continuous variables will be summarized using number of non-missing values (n), number of missing values, means, standard deviations, medians, maximum, minimum, and interquartile range.

Ordinal variables will be summarized using n, number of missing values, medians, maximum, minimum, and interquartile range.

Categorical variables will be summarized using n, number of missing values, and percentages.

Time-to-event variables will be summarized using Kaplan-Meier estimates.

Further details on the statistical analyses will be provided in the SAP.

10.2 Analysis sets

The statistical analysis sets are defined as follows:

Safety analysis set (SAF): All patients with at least one intake of study drug. The SAF will be used for safety evaluations for both Phase I and Phase II.

Full analysis set (FAS): All patients with at least one intake of study drug. This set will be used for patient characteristics, demographic, and efficacy evaluations for both Phase I and Phase II.

The efficacy variables in Phase I and Phase II will be analyzed in the FAS.

PK analysis set: All patients with at least one intake of study drug and with at least one valid measurement for copanlisib after first dosing will be included in the copanlisib PK analysis.

Additional analysis sets, and additional details on analysis sets, may be defined in the SAP.

10.3 Variables and planned statistical analyses

10.3.1 Primary variables

10.3.1.1 Primary safety variable for Phase I

The maximum tolerated dose (MTD): the highest dose level of copanlisib that can be given so that not more than 1 out of 6 patients experience a DLT during the DLT evaluation period.

Other primary safety variables also include DLTs, treatment-emergent AEs, SAEs, treatment-related AEs.

10.3.1.2 Primary efficacy variable for Phase II

Objective response rate (ORR): A patient is a responder if the patient has a tumor response on-study of CR or PR, based on radiological assessments utilizing RECIST 1.1 (see Appendix 16.1) for solid tumor patients except for neuroblastoma patients with MIBG-avid disease in which SIOPEN or Curie score will be used (see Appendix 16.2 and 16.3). The ORR is defined separately in each indication, as the number of responders divided by the number of patients in FAS in the indication.

ORR is the primary efficacy variable in neuroblastoma, Ewing sarcoma and rhabdomyosarcoma.

Disease control rate (DCR): A patient has disease control if the patient has a confirmed tumor response of CR or PR or a tumor response of SD (post-base line imaging performed within 7 weeks after the date of baseline tumor evaluation date will not be evaluable for DCR analysis of SD in patients with osteosarcoma) as determined per RECIST 1.1 criteria for solid tumor patients. The DCR is defined as the number of patients with disease control divided by the number of patients in FAS in the indication.

DCR is the primary efficacy variable in osteosarcoma.

For Stage 1 evaluation (in exactly 10 FAS patients per indication), solely the absolute number of responders in neuroblastoma, Ewing sarcoma and rhabdomyosarcoma, or number of patients with disease control in osteosarcoma will be determined, to make a decision for Stage 2.

ORR or DCR will be determined in their respective indication from Stage 1 and (potentially) Stage 2 results in FAS patients as unbiased minimum variance unbiased conditional (UMVCUE) estimate, using methodology as described in Porcher and Desseaux, 2012 (29).

Progression-free survival (PFS) is defined as the time from first dose of study drug to disease progression according to RECIST1.1 for osteosarcoma patients, or death (if death occurs before progression is documented). Patients alive without progression will be censored at the last tumor assessment.

PFS is considered as co-primary (descriptively evaluated) variable in patients with osteosarcoma.

10.3.2 Secondary variables

10.3.2.1 Efficacy variables

Anti-tumor efficacy of copanlisib in Phase I part, measured as ORR by dose cohort is defined as the number of responders divided by the number of patients in FAS in the indication. Appropriate response criteria will be used (i.e. either RECIST 1.1 for solid tumors (Appendix 16.1) or modified Lugano Classification 2014 for lymphoma (Appendix 16.11), or SIOPEN or Curie score for neuroblastoma patients with MIBG-avid disease (see Appendix 16.2 and 16.3).

The following efficacy endpoints will be measured for Phase II part only, separately for each indication reaching Stage 2.

Duration of response (DOR) is defined as the time from the date of first observed tumor response (CR or PR) until first subsequent disease progression or until death (if death occurs before progression is documented) due to any cause. Patients surviving without disease progression will be censored at the last tumor assessment. Duration of response will be defined for responders only (i.e. patients with CR or PR)).

PFS in each indication except for osteosarcoma is defined as the time from first dose of study drug to disease progression according to RECIST1.1 for solid tumor patients (except osteosarcoma) and SIOPEN or Curie score for neuroblastoma patients with MIBG-avid disease, or death (if death occurs before progression is documented). Patients alive without progression will be censored at the last tumor assessment.

Overall survival (OS) is defined as the time from first dose of study drug until death from any cause or until the last date the patient is known to be alive.

10.3.2.2 Safety variables

Safety variables will include treatment-emergent AEs, SAEs, laboratory parameters, ECGs and vital signs. The severity of AEs will be graded using the NCI CTCAE v 4.03 dictionary. AEs will be classified as related or not related to test drug by the investigator. A treatment-emergent AE is defined as any event arising or worsening after start of test drug administration until 30 days after the last dose of the study drug intake (end of safety follow-up).

Patients' ability to manage activities of daily living will be appraised utilizing the performance status scale by Lansky/Karnofsky. The patients' performance score will be estimated according to the schedule summarized in Section 9.1.

10.3.2.3 PK variables

Copanlisib maximum drug concentration (C_{max}) and area under the curve ($AUC_{(0-168)}$) on Cycle 1 Day 1 and Day 15.

10.3.3 Exploratory variables

10.3.3.1 Biomarker/ pharmacodynamics (PD) variables

- pAKT from surrogate tissue (platelet rich plasma)
- Glucose metabolism markers (plasma glucose, insulin, and C-peptide)
- Plasma protein panel
- Molecular status (genetic alterations, protein expression and / or activation) of biomarkers related to PI3K signaling in tumor tissue.

10.3.4 Statistical and analytical plans

A complete description of the planned statistical analyses will be provided in SAPs.

The primary analysis of the primary efficacy variable for Phase II will be performed on the data collected up to the last patient of that indication having had the chance to complete 4 cycles of treatment. The analysis set to be used will be the FAS. Patients who have progressive disease prior to 4 cycles will be considered fully evaluable for response and included in the efficacy analyses. At that time point, an exploratory analysis of all other variables will be performed, as reasonable. The final analyses of all secondary efficacy and safety variables and exploratory variables will be performed approximately 2 years after last patient completes the treatment (LPLT).

10.3.4.1 Demographic and other baseline characteristics

Demographics and baseline characteristics will be summarized for FAS population by means of descriptive statistics and/or frequency tables as appropriate, separately for Phase I and Phase II. In Phase II, the results will additionally be split by indication.

10.3.4.2 Primary efficacy (Phase II only)

The primary efficacy variable ORR (DCR for osteosarcoma, respectively) for Phase II will be summarized including number of patients (N), number of responders, response rate estimate (using UMVCUE method), for FAS as primary analysis set. ORR (DCR for osteosarcoma) will be reported by each indication independently. For the co-primary endpoint PFS rate at 4 months (for osteosarcoma), an analyses will be performed only after Stage 2 (see end of this section for details). For all indications (except osteosarcoma) reaching Stage 2, the respective statistical hypotheses per indication will be:

H_0: ORR $\leq$ 10% vs H_1: ORR > 10% will be evaluated based on data cut-off at the day the last patient of the respective indication has had the chance to complete 4 cycles of treatment, i.e. being part of FAS.

Per indication, ORR $\leq$ 10% will be statistically rejected for a specific indication in case at least 5 responses were measured from the 25 recruited patients.

For osteosarcoma (if Stage 2 is reached), DCR will be tested, with the hypotheses being:

H_0: DCR $\leq$ 10% vs H_1: DCR > 10% will be evaluated based on data cut-off at the day the last patient with osteosarcoma has completed 4 cycles of treatment, i.e. being part of FAS.

DCR $\leq$ 10% will be statistically rejected in case at least 5 responses were measured from the 25 FAS patients with osteosarcoma. In case Stage 2 is reached, per indication, 85% confidence intervals as well as p-values according to Porcher & Dessaux, 2012 (29) will be provided for ORR (DCR, respectively). Conditional statistical methods should be preferred, as applicable. Details will be provided in the SAP.

If Stage 2 is reached for patients in osteosarcoma, the survival rate of PFS at 4 months in osteosarcoma will be estimated as co-primary endpoint using the Kaplan-Meier method and its two-sided 85% CI will be provided. This analysis will be done for FAS.

10.3.4.3 Secondary efficacy

In the Phase I part, ORR (DCR for osteosarcoma, respectively) will be summarized by cohort in the FAS only.

In the Phase II part, for indications reaching Stage 2, Time-to-event variables (PFS, DOR and OS) will be evaluated by Kaplan-Meier estimates and plots by indication. Medians with Brookmeyer-Crowley confidence intervals using LOGLOG transformation will be provided. The efficacy variables will be analyzed in the FAS. Number of patients at risk over time will also be provided. Further details will be described in the SAP. For the indication osteosarcoma, PFS evaluation will be a co-primary analysis as described in section 10.3.4.2, if stage 2 is reached.

10.3.4.4 Safety

The overall incidences of treatment-emergent AEs will be presented by MedDRA system organ class, preferred term, and by the CTCAE v. 4.03 worst grade. Listings of adverse events and laboratory toxicities by NCI CTCAE grade will be provided. The incidences of treatment-emergent AEs will be presented also separately by drug relationship. The number (%) of patients who discontinued study drug due to an AE or required a dose reduction or interruption caused by an AE will be summarized. Similarily, serious adverse events will be evaluated.

Descriptive summary tables will be presented for other safety variables including laboratory changes, abnormal findings in physical examination, changes in performance level by Lansky/Karnofsky, changes in vital signs (weight, blood pressure, heart rate and body temperature), changes in ECG.

All hematological/biochemical toxicities based on laboratory measurements will be graded by CTCAE v4.03 and categorized by MedDRA and will be summarized.

Patient performance level will be evaluated descriptively, through summary statistics and listings.

All safety analyses will be done separately for Phase I by cohort and for Phase II by indication. Patients enrolled in the PK group (< 12 years old) will be evaluated with the Phase I cohorts.

Individual listing of DLTs will be presented for Phase I by cohort.

Descriptive summary of safety analyses will be performed for the age group of < 1 year old separately.

Additional details will be described in the SAP.

10.3.4.5 Pharmacodynamics

The change in pAKT relative to total AKT in surrogate tissue (platelet rich plasma) will be summarized by cohort for Phase I part and by indication for Phase II part using descriptive statistics. The maximum change from baseline of insulin and C-peptide during copanlisib treatment will be reported.

10.3.4.6 Biomarkers

The following variables will be summarized by cohort for Phase I part and by indication for Phase II part using descriptive statistics.

- Exploration of change from baseline in pAKT from surrogate tissue (platelet rich plasma) during copanlisib treatment
- Exploration of the time course of glucose metabolism markers (plasma glucose, insulin, and C-peptide) during copanlisib treatment
- Exploration of change from baseline in plasma protein panel

- Molecular status (genetic alterations, protein expression and / or activation) of biomarkers related to PI3K signaling in tumor tissue. Molecular status at progression may be assessed if a fresh tumor is collected at progression (optional).

Further exploratory statistical analyses may be performed and relationships between biomarker data and clinical outcome will be evaluated in a separate report. Biomarker variables and analyses will be further described in the SAP and/or in a separate document.

10.3.4.7 Pharmacokinetics (PK)

All copanlisib concentration-time data collected during the study will be listed only.

10.4 Determination of sample size

Phase I part

The purpose of the Phase I part is to determine copanlisib single agent MTD in the pediatric population. No formal sample size calculation will be performed. Number of patients will depend on observed safety signal with 3-6 patients enrolled per cohort in the Rolling-6 study design. Approximately up to 42 patients will be enrolled and treated. A minimum of 50% of the enrolled and treated patients will be under the age of 12.

Phase II part

Simon's two-stage optimal design (30) will be used, for each of the four indications for Phase II separately. For all the indications, the null hypothesis that the true response rate (disease control rate for osteosarcoma) is 10% will be tested against a one-sided alternative. Per indication, the first stage will include 10 patients. After these no patients are accrued in that indication until decision for Stage 2 in that indication is made. If there is only one or no response (for osteosarcoma: one or no response/stable disease) in these 10 patients, the respective indication will be stopped (no start of respective Stage 2). Otherwise, 15 additional patients will be accrued into Stage 2 for a total of 25. The null hypothesis will be rejected if 5 or more responses (disease controlled patients for sarcoma, respectively) are observed in 25 patients. This design yields a per-indication type I error rate of 7.5% and power of 80% when the true response rate (disease control rate, respectively) is 30%.

In case of Stage 2 being reached for all four indications, the number of patients across all indications is 100 patients. Any over-recruitment, i.e. to more than 25 patients per indication, has to be avoided. A minimum of 80% of the enrolled and treated patients will be under the age of 18.

10.5 Planned interim analyses

Phase I part

Individual patient’s safety data will be reviewed without formal statistical analysis on an ongoing basis and before the dose escalation decision during the dose escalation phase. The DLTs, escalation or MTD status, and decision will be documented in a monitoring report.

Phase II part

According to Simon 2-stage design, after 10 FAS patients per indication (neuroblastoma; osteosarcoma; rhabdomyosarcoma; Ewing sarcoma) will have been treated in Stage 1 for at least of 4 cycles, recruitment will be paused until decision for go/no-go into Stage 2. To support the go/no-go decision into Stage 2, Stage 1 data will be evaluated for ORR or DCR for respective indication. The evaluation will be based on a clean database of Stage 1 with cut-off date if the last patient of the respective indication has had the chance to complete 4 cycles of treatment.

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. Patient data necessary for analysis and reporting will be entered/transmitted into a validated database or data system (CIE/TOSCA; SAS).

Data required according to this protocol will be recorded by investigational site personnel via data entry into the internet based EDC software system RAVE, which Bayer has licensed from Medidata Solutions Worldwide. RAVE has been validated by Medidata Solutions Worldwide and Bayer for use in its clinical studies. RAVE allows for the 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. Bayer extensively applies the logic 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 and transferred on a periodic basis to Bayer's internal computer system via a secure Virtual Private Network.

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 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.

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 patients 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 (patient 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 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 pressure readings to support a diagnosis of hypertension).
- Safety and rights of patients are being protected
- Study is conducted in accordance with the currently approved protocol (including study treatment being used in accordance with the protocol)
- Any other study agreements, GCP, and all applicable regulatory requirements are met.

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

11.3 Data processing

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

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: e.g. pharmacokinetic data, antibody data.

11.4 Missing data

It should be underlined that the discontinuation of study treatment is not the equivalent to withdrawal of informed consent. Additionally, withdrawal of consent does not withdraw permission to collect vital status. Withdrawal of this consent must be made separately.
In general, missing data will not be imputed in this study. Every effort should be made to collect all data. All missing or partial data will be presented in the patient data listing as they are recorded on the Case Report Form (CRF).

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.

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

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

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

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

12. Premature termination of the study

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

- If risk-benefit ratio becomes unacceptable owing to, for example,
  - Safety findings from this study (e.g. SAEs)
  - Results of 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 patients, including those in post study follow-up, must be taken care of in an ethical manner.

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

13. Ethical and legal aspects

13.1 Investigator(s) and other study personnel

Sponsor's Medical Expert

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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 principal investigator of each center must sign the protocol signature page and must receive all required external approvals (e.g. health authority, ethics committee, sponsor) before patient recruitment may start at the respective center. Likewise, all amendments to the protocol must be signed by the principal 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.

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

External data evaluation bodies

Data Monitoring Committee

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

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 patients 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 Good Clinical Practice (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 patients without prior IEC/IRB/sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IEC/IRB/head of medical institution/sponsor. Any deviations from the protocol must be explained and documented by the investigator.

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

13.4 Patient information and consent

All relevant information on the study will be summarized in an integrated patient information sheet and informed consent form provided by the sponsor or the study center. Separate patient information sheets and assent forms for pediatric patients of different age groups will be created, taking into consideration local requirements for patient information sheet and informed consent/assent. When an adolescent is legally emancipated, i.e. ceases to be a minor, or reaches the legal age of consent, informed consent will be sought directly from him/her as soon as possible. In addition, patient's development stage, intellectual capacities and life/disease experience will be taken into consideration when obtaining oral or written assent. A sample patient information and informed consent form and assent forms are provided as a document separate to this protocol.

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

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

Each patient and/or parents / legal guardians will be informed about the following aspects of premature withdrawal:

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

Each patient and/or parents / legal guardians will have ample time and opportunity to ask questions.

Only if the patient and/or parents / legal guardians voluntarily agrees to sign the informed consent form (and assent form, where applicable) and have done so, may the patient enter the study. Additionally, the investigator will personally sign and date the form. The patient and/or parents / legal guardians will receive a copy of the signed and dated form (and assent form, where applicable).

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

In the event that informed consent and assent form are obtained on the date that baseline study procedures are performed, the study record or patient´s clinical record must clearly show that informed consent and assent form were obtained prior to these procedures.

For minors or adults under legal protection, consent shall be given by the parents / legal guardian(s). The assent form of a minor or adult under legal protection shall also be requested where such a person is able to express his/her own will. His/her refusal or the withdrawal of his/her consent may not be disregarded.

The informed consent form and assent form and any other written information provided to patients and/or parents / legal guardians will be revised whenever important new information becomes available that may be relevant to the patient's or parent's / legal guardian's consent, or there is an amendment to the protocol that necessitates a change to the content of the patient information and / or the written informed consent form and assent form. The investigator will inform the patient and/or parents / legal guardian of changes in a timely manner and will ask the patient and/or parents (or legal guardians) to confirm patient's participation in the study by signing the revised informed consent form (and assent form, where applicable). Any revised written informed consent form, assent 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 patients / insurance

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

13.7 Confidentiality

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

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

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

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

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15. Protocol amendments

15.1 Amendment 1

Amendment 1 is a global amendment dated 04 APR 2019.

15.1.1 Overview of changes

Overall Rationale for the Amendment

The primary driver of this protocol amendment is the amendment to DLT criteria. Under the previous version of the protocol, DLTs were not graded based on clinical significance of the AE but rather on numerical values (e.g. lab values that were not considered clinically significant enough to be considered truly dose-limiting) and both Sponsor and investigators considered that it was not reflective of the true safety profile of the study drug. Therefore, this amendment revises the DLT criteria to reflect what would be considered truly dose-limiting maintaining the safety of the patients but allowing for more flexibility to dose patients in this population of high unmet medical need. Additional changes were made to make the dose modification consistent with the updated DLT criteria.

Protocol Amendment Summary of Changes Table

Section # and Name	Description of Changes	Brief Rationale
5.2 Phase I dose escalation design 7.4.1.3 Definition of dose-limiting toxicities	Clarified which dose level of study drug should be used if DLT criteria are changed. Multiple modifications to criteria to more accurately classify DLTs	When DLT criteria change, it is logical to enroll at the previous dose level prior to the change since safety profile and number of DLTs may be significantly different under the new criteria. To avoid inconsistencies with dose modification guidance, to avoid rapidly reversible and manageable toxicities be categorized as DLTs, and to assure consistency with dose criteria and amended time window allowed before mandating omission of study drug dose.
7.4.3.1 Dose-limiting hematological and non-hematological toxicity 6.4.1 Withdrawal	The dose modification tables for dose-limiting hematological and non-hematological toxicity were removed.	To make dose modifications for AEs consistent regardless of whether the AEs are DLTs or non-DLTs.
6.1 Inclusion criteria 6.2 Exclusion criteria	Changed inclusion criterion for duration of agreement to use contraception after last administration of study drug. Addition of sub-heading in inclusion criterion #4.	Alignment with updated product label. For additional clarity on which parts of the study this applies to.

Section # and Name	Description of Changes	Brief Rationale
	Inclusion criterion #7: Addition of maximum glucose threshold Modifications to AST/ALT and ALP criteria Addition of neuroblastoma to exclusion criterion #7 and anemia to exclusion criterion #18.	 Maximum serum glucose threshold (based on a generalized ULN for the normal population) set to prevent patients who are predisposed to hyperglycemia issues (e.g. glucose intolerance). To avoid inconsistencies with the DLT criteria and to clarify that bone metastasis can also elevate ALP levels. For consistency with the inclusion criteria.
6.4.1 Withdrawal	The withdrawal criteria were edited. Changed the time window of 30+5 days for reporting deaths in the study.	Text was edited to be consistent with dose modification guidelines in treatment sections and to simplify the protocol. The safety data is collected up to 30 days after the last dose (not 30 +5 days) although the safety FU visit occurs during a window of 30+5 days to provide flexibility in scheduling a visit.
7.4 Dosage and administration	Dosing criteria (lab-based) were edited. Time window for dose delay before mandating discontinuation of study drug was expanded. Removal of INR from the list of laboratory assessments to be performed prior to each dose.	To avoid inconsistencies with dose modification guidelines and DLT criteria (primarily serum glucose, lipase, and amylase) and to clarify. To add flexibility to deliver doses within a cycle in a safe manner while still providing a maximum delay in dosing (28 days) and to avoid rapidly reversible and manageable toxicities to be categorized as DLTs since omission of a dose is technically dose-limiting. For consistency with existing text as INR will be performed on Day 1 of each cycle.

Section # and Name	Description of Changes	Brief Rationale
7.4.3.2 Hematological toxicity 7.4.3.3 Non-Hematological toxicity 7.4.3.3.3 Glucose increases 7.4.4.1 Management of transient post-infusion glucose increases that can occur with study treatment	Various minor edits to dose modification tables.	To assure consistency with amended dosing criteria and amended time window allowed before mandating omission of study drug dose. Most notably, the hyperglycemia management table was modified to be based on the approved FDA label guidance with some modifications to reduce inconsistencies with the rest of the protocol (dosing criteria, DLT criteria).
8.1 Prior and concomitant therapy	Added criterion to refrain the use of biotin to prohibited concomitant therapy. Clarified when therapeutic anti-coagulation is permitted	This addition is in line with FDA Safety communication/recommendations on the use of biotin. High levels of biotin can interfere with the result of the immunoassay test. There is no known interaction with any of the anticoagulant medications and copanlisib. However, any concurrent anticoagulant use should be based on medical judgement of the treating physician considering thrombocytopenia has been reported with copanlisib.
9.1 Tabular schedule of evaluations, Table 9-1 9.2.1.1 Screening period 9.4.1 Radiological tumor assessments 9.2.1.3 Tumor assessments 9.2.1.4 End-of-treatment visit 9.4.1 Radiological tumor assessments.	Ewing sarcoma patients are not mandated to have a bilateral bone marrow biopsy and/or bone marrow aspiration. Clarified the schedule of bone marrow biopsy and/or bone marrow aspiration during the study treatment.	Agreement with investigators and following standard of care in this patient population. For additional clarity.
7.4 Dosage and administration 7.4.3.3.4 Arterial hypertension 9.1 Tabular schedule of evaluations, Table 9-1 9.2.1.2.1 Treatment –	Updated blood pressure measurement language to be in line with new copanlisib hypertension guidance. Added guidance for patients $\geq$ 18 years old.	Changes were made to reflect updated copanlisib safety information pertaining to potential drug-related transient blood pressure increases and feedback from investigators/lymphoma specialists regarding hypertension monitoring and management to make the process more feasible without compromising patient safety.

Section # and Name	Description of Changes	Brief Rationale
Cycle 1 9.2.1.2.2 Treatment – Cycle 2 and higher 9.6.3.9 Glucose measurement on infusion days 9.6.3.4.1 Blood pressure measurement on infusion days	Clarified glucose measurement language and added a time-window for the pre-dose glucose measurement.	For clarity and based on feedback from the investigators.
9.1 Tabular schedule of evaluations, Table 9-1 9.2.1.1 Screening period 9.2.1.2.1 Treatment – Cycle 1 9.2.1.2.2 Treatment – Cycle 2 and higher 9.2.1.4 End-of-treatment visit 9.6.3.5 Electrocardiogram	Added an option to use 15-lead ECG.	Addition to reflect standard of care procedure in this population.
9.1 Tabular schedule of evaluations, Table 9-1 9.2.1.1 Screening period 9.2.1.5.1 Active follow-up 9.6.3.3 Growth and dental exams	Correction of naming of procedure which reflects that a dentition examination does not need to be performed by a dentist. Changed the timing of this procedure at screening.	To reflect standard of care in this population.
9.1 Tabular schedule of evaluations, Table 9-1 9.2.1.1 Screening period 9.2.1.4 End-of-treatment visit	Clarified that, for patients > 1 year and < 6 years old, blood for biomarker analysis should be collected at -28 day visit. Corrected inconsistency in the plasma sampling at EOT.	For consistency with body protocol text.
9.2.1.1 Screening period 9.4.1. Radiological tumor assessments	Removal of the requirement to assess all anatomical areas specified in all patients.	As per investigator feedback, radiological assessment should be performed only of the primary tumor location area, thus minimizing radiation exposure to a vulnerable patient population.
9.2.1.1 Screening period	Modified text regarding the procedures performed pre-informed consent in the screening period section for	To allow for results of any procedure performed pre-consent as part of standard of care patient assessment to be used for study screening purposes, if performed within the required window /

Section # and Name	Description of Changes	Brief Rationale
	clarification.	to the required standards. Also to minimize unnecessary blood draws from this vulnerable patient population.
9.6.3.8 Laboratory examinations	Addition of BUN as alternative to urea in chemistry panel.	To allow more flexibility for sites assessing at local laboratory facilities.
9.1 Tabular schedule of evaluations, Table 9-1 9.2.1.2.1 Treatment – Cycle 1 9.2.1.2.2 Treatment – Cycle 2 and higher 9.6.3.2 Body weight, height and BSA calculation	Removal of BSA calculation from visits other than C1D1	Dosing not typical to change mid-cycle, so BSA calculation is unnecessary.
2 Synopsis 10.2 Analysis sets 10.3.1.2 Primary efficacy variable for Phase II 10.3.4 Statistical and analytical plans 10.3.4.1 Demographic and other baseline characteristics 10.3.4.2 Primary efficacy (Phase II only) 10.3.4.3 Secondary efficacy 10.3.4 Statistical and analytical plans	Removal of the per protocol set (PPS) from planned statistical analysis for Phase II efficacy endpoints. Clarification of the primary efficacy analysis. Correction of timing of final analysis.	The reason to not use PPS in this study from a statistical perspective is that PPS is intended to identify a treatment effect which would occur under optimal conditions without any major protocol deviation and non-availability of primary endpoint. After the adult study, it is unlikely that there will be a major difference between the two populations. In addition, the data following the more conservative FAS/ITT concept are considered more useful for further clinical development. Patients who have progressive disease prior to 4 cycles will be considered fully evaluable for response and included in the efficacy analyses. Consistency with related protocol sections.
1. Title page Signature of the sponsor's medically responsible person 13.1 Investigator(s) and other study personnel	Changes regarding the sponsor's medical expert and sponsor's medically responsible person.	Due to personnel change and reorganization of sponsor's medical team information was updated.
3.1.4 Clinical experience 3.3 Benefit-risk assessment	Updated the number of patients treated with copanlisib.	Updated information.

Section # and Name	Description of Changes	Brief Rationale
16.1 Pregnancy information form 6.2 Exclusion criteria	Removal of the pregnancy information form.	Incorrect version included in error.
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

15.1.2 Changes to the protocol text

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

15.2 Amendment 2

Amendment 2 is a global amendment dated 05 MAY 2020.

15.2.1 Overview of changes

Overall Rationale for the Amendment

The primary driver of this protocol amendment is to allow for additional enrollment of younger patients (<12 years old), if needed, after MTD and RP2D determination in order to assure that there is adequate data to characterize safety and pharmacokinetics in younger patients before moving onto phase II. In addition, this will further help to ensure that the requirement outlined under Section 10.4 that at least 50% of patients enrolled and treated will be under 12 years of age is fulfilled for the Phase I part. Additional changes in this amendment include clarifications in the eligibility criteria and allowable washout periods of prior therapies, resolution of inconsistencies and technical errors, and editorial updates.

Protocol Amendment Summary of Changes Table

Section # and Name	Description of Changes	Brief Rationale
5.2 Phase I dose escalation design 10.4 Determination of sample size Synopsis	Added description for enrollment of additional patients (< 12 years old) to acquire PK data once the MTD or recommended Phase 2 dose has been defined and updated the number of patients.	To ensure that at least 50% of dose escalation patients are <12 years old per FDA requirement.
6.1 inclusion criteria	Modification of description of measurable vs. evaluable	Clarification of the acceptance of measurable vs. evaluable disease in Part I

Section # and Name	Description of Changes	Brief Rationale
Synopsis	disease.	and Part II.
6.2 Exclusion criteria	Previous anti-cancer immunosuppressive treatment defined more specifically as exclusion criteria and immunotherapy and/or chemotherapy removed from "Excluded previous therapies".	To remove the discrepancy that chemotherapy washout was listed as "28 days or 5 half-lives" in one exclusion criteria, but as "4 weeks" in another exclusion criteria, and to consolidate the description of allowable washout periods of prior therapies.
7.4.1 Dosage – Phase I part 7.4.3 Dose modifications 8.1 Prior and concomitant therapy	Consistency ensured throughout the protocol that G-CSF can be used when ANC < 500 + sepsis or culture-negative sepsis.	Clarification of the use of G-CSF when ANC<500.
10.5 Planned interim analyses	Removal of language regarding the treatment of overrun patients.	Language was considered unnecessary in regard to conduct of the study and can be dealt with in the context of supportive documents such as the Statistical Analysis Plan (SAP).
10.3.1.2 Primary efficacy variable for Phase II 10.3.2.1 Efficacy variables	The survival time was defined to begin from the first intake of study drug instead of enrollment.	Correction of the definitions of endpoints (PFS and OS) for statistical analysis to align with SAP v1.0.
10.3.4.4 Safety	Specified the safety analysis of patients enrolled in the PK group.	To clarify that the patients enrolled in the PK group are evaluated with Phase I cohorts.
9.5 Pharmacokinetics / pharmacodynamics Table 9-2	Corrected a technical error.	Technical error, table continued on the next page with a wrong table heading for the patients Age < 6 years. Should not have stated "≥ 6 years", but < 6 years.
Throughout the protocol.	Changed "patients enrolled" into "patients enrolled and treated" where applicable.	To avoid the misinterpretation that enrolled would represent only patients who signed informed consent but did not go on to be treated. This would support the intent of several regulatory documents that use the term "enrolled" with the assumption that the vast majority, if not all, of enrolled patients were treated and had evaluable safety and efficacy data.
Signature of the sponsor's medically responsible person	Added a statement about the eSignature process.	Administrative change to describe the electronic signing of the document.

15.2.2 Changes to the protocol text

Changes to the protocol text are provided in a separate track changes version. In addition to the changes above, other changes were made to update administrative details, and correct typographical errors.

16. Appendices

16.1 RECIST v.1.1

Response and progression will be evaluated in this study using the RECIST, version 1.1. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used.

Measurable disease:
Tumor lesions: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) with a minimum size of:
10 mm by CT scan (CT scan slice thickness no greater than 5 mm) or MRI. If scans with slice thicknesses greater than 5 mm are used, the minimum size should be twice the slice thickness.
10 mm caliper measurement by clinical examination (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.
Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components that can be evaluated by CT or MRI, can be considered as measurable lesions if the soft tissue component meets the definition of measurability.
All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Tumor lesions situated in a previously irradiated area are not considered measurable unless there has been demonstrated progression in the lesion.
Non-measurable disease:
All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) are considered non-measurable disease. Leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitic involvement of skin or lung, abdominal masses/ abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques and blastic bone lesions are all non-measurable.
Target lesions:
All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as *target lesions* and be recorded and measured at baseline. These 5 lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs and should be suitable for

reproducible repeated measurements. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for *all target lesions* will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression of the measurable dimension of the disease. If there are > 5 measurable lesions, those not selected as *target lesions* will be considered together with non-measurable disease as *non-target lesions*.

Non-target lesions:

All non-measurable lesions (or sites of disease) plus any measurable lesions over and above the 5 listed as *target lesions*. Measurements are not required but these lesions should be noted at baseline and should be followed as "present", "absent" or in rare cases "unequivocal progression".

Best Response

All patients will have their BEST RESPONSE on study classified as outlined below:

Complete Response (CR): Disappearance of all clinical and radiological evidence of tumor (both *target* and *non-target*). Any pathological lymph nodes (whether target or non target) must have a reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum, no unequivocal progression of existing non target lesions and no appearance of new lesions.

Stable Disease: Steady state of disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD), no unequivocal progression of existing non target lesions and no appearance of new lesions.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Unequivocal progression of existing non target lesions or the appearance of one or more new lesions will also constitute progressive disease.

Table 16–1 Response for patients with target and non-target lesions

Target lesions	Non-target lesions	New lesions	Overall response	Best response for this category also requires
CR	CR	No	CR	Two objective status determinations of CR (not less than 4 weeks apart) before progression
CR	Non-CR/Non-PD	No	PR	
CR	Not evaluated	No	PR	
PR	Non-PD or not all evaluated	No	PR	Two determinations of PR or better (not less than 4 weeks apart) before progression, but not qualifying for CR
Stable disease	Non-PD or not all evaluated	No	Stable disease	Documented at least > 6 weeks from baseline
Not all evaluated	Non-PD	No	NE	
PD	Any	Yes or No	PD	
Any	PD	Yes or No	PD	
Any	Any	Yes	PD	

CR=complete response, NE=not evaluable, PR=partial response, PD=progressive disease
Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration*". Every effort should be made to document the objective progression even after discontinuation of treatment

Table 16–2 Response for patients with non-target lesions only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/Non-PD [a]
Not evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR=complete response, NE = not evaluable, PD=progressive disease
[a] Non-CR/non-PD is preferred over "stable disease" for non-target disease.

Method of measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Clinical Lesions - Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules, palpable lymph nodes) and ≥ 10mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.

CT/MRI - CT is the best currently available and reproducible methods to measure target lesions selected for response assessment. CT scans should be performed with cuts of 5 mm or less in slice thickness. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable. This applies to the chest, abdomen and pelvis. Head & neck and extremities usually require specific protocols.

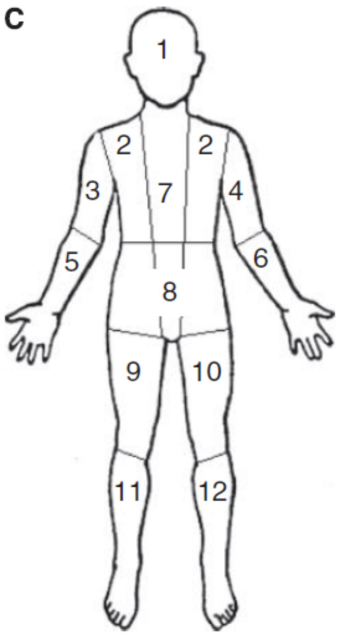
16.2 SIOPEN scoring method

SIOPEN scoring method for neuroblastoma patients with osteomedullary disease is based on the Criteria for Evaluation of Disease Extent by (123)I-metaiodobenzylguanidine Scans in Neuroblastoma (27).

Owing to the high specificity and sensitivity in neuroblastoma, 123I-MIBG imaging has superseded the use of 99mTc -technetium bone scans for the detection of skeletal metastases in the majority of children with neuroblastoma, which take up the tracer in 90% of cases, and has been recommended by the last international consensus conference as a standard element of staging and response evaluation The SIOPEN score is the current method being used in Europe under prospective evaluation in a phase III trial.

In this method, the skeletal distribution of MIBG was recorded in 12 anatomical body segments as follows: skull, thoracic cage, proximal right upper limb, distal right upper limb, proximal left upper limb, distal left upper limb, spine, pelvis, proximal right lower limb, distal right lower limb, proximal left lower limb and distal left lower limb (Figure 16–1).

Figure 16–1 123-MIBG scoring SIOPEN-method



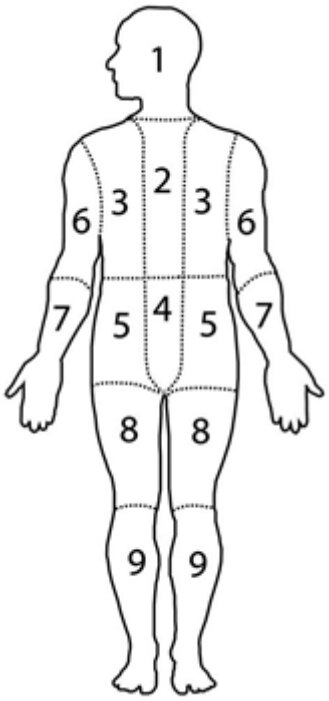
(C) 123I-MIBG scoring SIOPEN-method 3: method 3 divides the skeleton into 12 anatomic segments. The extension score for method 3 is graded as: 0, no sites per segment, 1, one discrete site per segment; 2, two discrete lesions; 3, three discrete lesions; 4, > 3 discrete foci or a single diffuse lesions involving < 50% of a bone; 5, diffuse involvement of > 50–95% whole bone; 6, diffuse involvement of the entire bone.

The extent and pattern of skeletal MIBG involvement was scored using a 0–6 scale to discriminate between focal discrete lesions and patterns of more diffuse infiltration. Each segment is scored as 0, no involvement; 1, one discrete lesion; 2, two discrete lesions; 3, three discrete lesions; 4, > 3 discrete foci or a single diffuse lesion involving < 50% of a bone; 5, diffuse involvement of > 50 to 95% whole bone; 6, diffuse involvement of the entire bone, with a maximum score of 72. This method showed 95% concordance in a blinded review by six nuclear medicine physicians.

Response criteria according to the SIOPEN score:
The absolute score is obtained by adding the scores of all the segments. The relative score is calculated by dividing the absolute score at each time by the corresponding pretreatment overall score. The relative score will be considered for response evaluation:

- **Complete response:** relative score of 0
- **Partial response:** relative score of ≤ 0.5
- **Stable disease:** relative score > 0.5 to ≤ 1
- **Progressive disease:** relative score > 1 (appearance of new lesions)

16.3 Curie scoring method



CURIE score is based on the presence of MIBG uptake in multiple anatomic regions.

Ten different sites are scored, including 9 skeletal sites as follows: the head and the face (area 1) the neck and back vertebral column (area 2), the ribs and the sternum (area 3), the lumbar and sacral column (area 4), the pelvis (area 5), the arms (area 6), the fore-arms and the hands (area 7), the thighs (area 8), the legs and the feet (area 9). The tenth site is related to any kind of soft-tissue lesions.

- Skeletal sites are individually scored from 0 to 3 as follows:

  0, no MIBG involvement;

  1, one MIBG-avid lesion present;

  2, more than one MIBG-avid lesion present;

  3, MIBG avidity present in > 50% of an individual site.

- Soft-tissue lesions are scored as follows:

  0, no MIBG involvement;

  1, one MIBG-avid soft-tissue lesion present;

  2, more than one MIBG-avid soft-tissue lesion present;

  3, MIBG avidity in a soft-tissue lesion that occupied > 50% of the chest or abdomen.

A patient's Curie score at each time point is calculated as the sum of scores over all individual sites, with a maximum score of 30.

MIBG based Response Criteria:

- **Complete response (CR):** MIBG score = 0
- **Partial response (PR):** relative score of ≤ 0.5 - >= 50% reduction in MIBG score
- **Stable disease (SD):** relative score > 0.5 to ≤ 1 – (≤ 50% reduction in score)
- **Progressive disease (PD):** relative score > 1 (appearance of new lesions) – increase in score

16.4 Performance status scales/scores

Table 16–3 Lansky-Play Scale conversion to Karnofsky

Lansky Play Performance Scale		Karnofsky Performance Status	
100	Fully active, normal	100	Normal, no complaints; no evidence of disease
90	Minor restrictions in physically strenuous activity	90	Able to carry on normal activity; minor signs or symptoms of disease
80	Active, but tires more quickly	80	Normal activity with effort, some signs or symptoms of disease
70	Both greater restriction of, and less time spent in, active play	70	Cares for self but unable to carry on normal activity or to do work
60	Up and around, but minimal active play; keeps busy with quieter activities	60	Requires occasional assistance but is able to care for most of personal needs
50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities	50	Requires frequent assistance and medical care
40	Mostly in bed; participates in quiet activities	40	Disabled; requires special care and assistance
30	In bed; needs assistance even for quiet play	30	Severely disabled; hospitalization is indicated although death not imminent
20	Often sleeping; play entirely limited to very passive activities	20	Very ill; hospitalization and active supportive care necessary
10	No play; does not get out of bed. Moribund	10	Moribund, fatal processes progressing rapidly
0	Unresponsive. Dead.	0	Unresponsive. Dead.

16.5 Blood sampling in pediatric patients

According to the European guideline (28), blood loss should not exceed 3% of total blood volume over four weeks, and it should not exceed 1% of total blood volume at any single time. The total volume of blood is estimated at 80 to 90 mL/kg body weight; 3% is 2.4 mL blood per kg body weight. Table 16–4 shows the acceptable blood volumes for different age ranges.

Table 16–4 Age ranges and corresponding volume limits for blood sampling

	Whole blood volume (mL/kg)	Mean body weight (kg)	Whole blood volume (mL)	3% (mL)	1% (mL)
Infant, 6 months	86	7.85	675	20.3	6.7
Infant, 12 months	80	10.1	808	24.2	8.1
Children, 6 years	80	20.6	1648	49.4	16.5
Children, 10 years	75	32.6	2445	73.4	24.5
Adolescent, 15 years	71	54.3	3855	115.7	38.6

16.6 Blood pressure levels for children by age and height percentile

Table 16–5 Blood pressure levels for boys by age and height percentile

Age, y	BP Percentile	SBP, mm Hg							DBP, mm Hg						
		Percentile of Height							Percentile of Height						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	50th	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	50th	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	50th	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	50th	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	50th	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	50th	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	50th	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	50th	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	50th	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90
11	50th	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	50th	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50th	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	50th	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	50th	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	50th	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50th	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

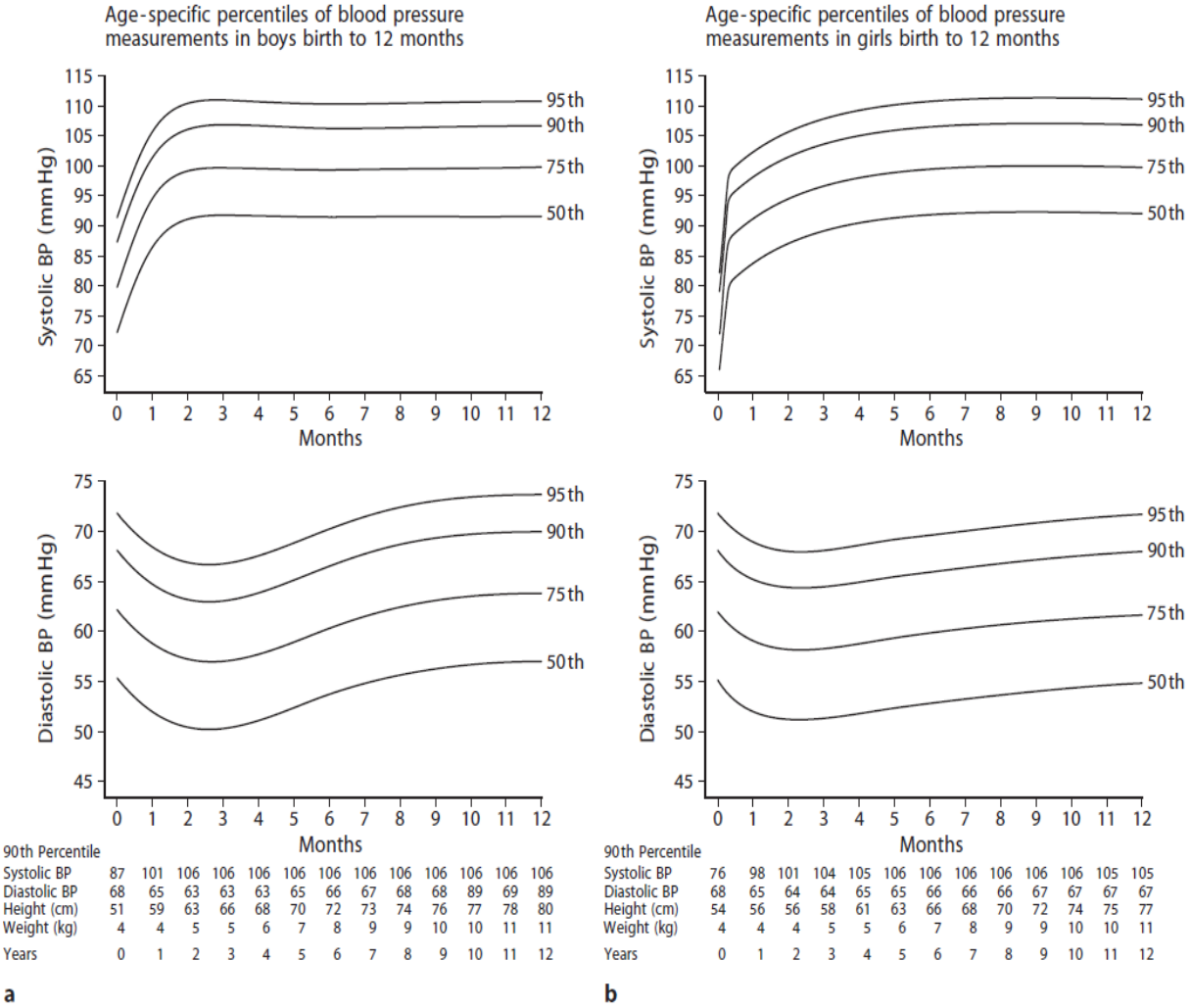
The 90th percentile is 1.28 SD, the 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.

Table 16–6 Blood pressure levels for girls by age and height percentile

Age, y	BP Percentile	SBP, mm Hg							DBP, mm Hg						
		Percentile of Height							Percentile of Height						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	50th	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	50th	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	50th	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	50th	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	50th	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	50th	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	50th	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	50th	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87
10	50th	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	50th	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	50th	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	50th	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	50th	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	50th	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	50th	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

* The 90th percentile is 1.28 SD, the 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.

Figure 16–2 Age-specific percentiles for blood pressure in boys (a) and girls (b) from birth to 12 months of age



90th Percentile

Systolic BP	87	101	106	106	106	106	106	106	106	106	106	106	106
Diastolic BP	68	65	63	63	63	65	66	67	68	68	89	69	89
Height (cm)	51	59	63	66	68	70	72	73	74	76	77	78	80
Weight (kg)	4	4	5	5	6	7	8	9	9	10	10	11	11
Years	0	1	2	3	4	5	6	7	8	9	10	11	12

a

90th Percentile

Systolic BP	76	98	101	104	105	106	106	106	106	106	106	105	105
Diastolic BP	68	65	64	64	65	65	66	66	66	67	67	67	67
Height (cm)	54	56	56	58	61	63	66	68	70	72	74	75	77
Weight (kg)	4	4	4	5	5	6	7	8	9	9	10	10	11
Years	0	1	2	3	4	5	6	7	8	9	10	11	12

b

16.7 Hypertension

Hypertension is defined as average systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) that is greater than or equal to the 95th percentile for sex, age, and height on three or more occasions (please refer to Table 16–5 and Table 16–6) for children from 1 to 17 years old, and Figure 16–2 for infants from birth to 12 months old).

Prehypertension in children is defined as average SBP or DBP levels that are greater than or equal to the 90th percentile, but less than the 95th percentile. Any adolescent (≥ 12 years) whose blood pressure is greater than 120/80 mmHg is also given this diagnosis, even if the blood pressure is below the 90th percentile.

Table 16–7 Recommended dimensions for blood pressure cuff bladders

Age range	Width (cm)	Length (cm)	Max. arm circumference (cm) [a]
Newborn	4	8	10
Infant	6	12	15
Child	9	18	22
Small adult	10	24	26
Adult	13	30	34
Large adult	16	38	44
Thigh	20	42	52

[a] Calculated so that the largest arm would still allow the bladder to encircle arm at least 80%

16.8 NCI-CTCAE

This study will use the NCI-CTCAE version 4.03 for toxicity and AE reporting. A copy can be downloaded from the Cancer Therapy Evaluation Program home page (http:ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)
All appropriate treatment areas should have access to a copy of the NCI-CTCAE version 4.03.

16.9 Modified Ross Heart Failure Classification for Children

Table 16–8 Modified Ross Heart Failure Classification for Children

Class I	Asymptomatic
Class II	Mild tachypnea or diaphoresis with feeding in infants Dyspnea on exertion in older children
Class III	Marked tachypnea or diaphoresis with feeding in infants Marked dyspnea on exertion Prolonged feeding times with growth failure
Class IV	Symptoms such as tachypnea, retractions, grunting, or diaphoresis at rest

Source: (31)

16.10 Serum creatinine based on age/gender

A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
6 months to < 1 year	0.5	0.5
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimated GFR (32) utilizing child health and stature data published by the CDC.

16.11 Evaluation of tumor response in lymphomas (Phase I part)

In patients with lymphoma, tumor response will be evaluated according to modified Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification (25).

	Target lesions (nodal)	Target lesions (extranodal)	Non-target lesions	Spleen	New lesion	Bone marrow
CR	All normal (LDi ≤ 1.5 cm)	All disappeared	All normal	Normal size for age	No	Normal by morphology If not assessable: IHC and/or PCR negative
PR	Decrease ≥ 50% in the SPD from baseline		All normal or stable	Spleen must have regressed by 50% in extent beyond normal at baseline	No	Not relevant
SD	• Decrease < 50% in the SPD from baseline • No criteria for PD		All normal or stable	Normal size for age or stable size (not meeting criteria for PR or PD)	No	Not relevant
PD	Individual node/lesion: • LDi > 1.5 cm AND • Increase ≥ 50% in the PPD from nadir AND • Increase in LDi or SDi from nadir * ≥ 0.5 cm for lesions ≤ 2 cm ≥ 1.0 cm for lesions > 2 cm		New or increased	• New splenomegaly: the splenic length must increase ≥ 2 cm from baseline length • Recurrent splenomegaly: the splenic length must increase ≥ 2 cm from nadir length • Progressive splenomegaly: the splenic length must increase by > 50% of the extent beyond normal at baseline and must increase ≥ 1 cm in total vertical length	Yes: • New node > 1.5 cm in any axis • New extranodal site > 1.0 cm in any axis (if < 1.0 cm in any axis its presence must be unequivocal and must be attributable to lymphoma)	New or recurrent involvement

CR = complete response; IHC = Immunohistochemistry; LDi = longest diameter; PD = progressive disease; PPD = product of perpendicular diameters; PR = partial response; SD =stable disease; SDi = shortest diameter; SPD = sum of the product of the diameters

* If* LDi ≤ 2 cm at nadir, absolute increase required for any diameter (LDi or SDi) will be 0.5 cm; if LDi > 2 cm at nadir, absolute increase required for any diameter (LDi or SDi) will be 1.0 cm.

Note: In case the patient has only diffuse spleen involvement with splenomegaly careful evaluation of the spleen should be performed as the overall response will be driven by the response for splenomegaly, unless any non-target lesion(s) or a target lesion shows progression or a new lesion/new or recurrent involvement of bone marrow is present.

Criteria for PET-CT response assessment (for lymphomas)

	Target Lesions (Nodal)	Target lesions (Extranodal)	Non target lesions	Spleen	New lesions	Bone marrow
CMR	Score 1, 2, or 3 with or without a residual mass on 5PS*		N/A	N/A	None	No evidence of FDG-avid disease in marrow
PMR	Score 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease; at end of treatment, these findings indicate residual disease		N/A	N/A	None	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed)
NMR	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment		N/A	N/A	None	No change from baseline
PMD	Individual target nodes/nodal masses Score 4 or 5 with an increase in intensity of uptake from baseline **and/or** Extranodal lesions new FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment		None	N/A	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g. infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	New or recurrent FDG-avid foci

CMR= complete metabolic response; FDG = Fluorodeoxyglucose; N/A = not applicable; PMR= partial metabolic response; NMR= no metabolic response, equivalent with stable disease; PMD= progressive metabolic disease, equivalent with progressive disease

Note:

- Most avid lesion will determine final score whereas volume/overall uptake and/or intensity of uptake of lesions should also be considered for response assessments.
- PET-avid lesions must have a minimum score of 4 at baseline in order to be called “PET positive”.
- Only lesions with a score ≥ 4 can be considered a valid measurable target lesion if CT scan is available.
- Lesions with score 1, 2 or 3 are considered “PET negative” and do not qualify for target lesion at baseline
- PET negative patients at BL with a positive histology must be followed-up with CT scan only.

For further details refer to the Imaging Manual.

* 5PS= 5 point score for the visual assessment of PET-CT:
Score 1 = no uptake above background
Score 2=uptake ≤ mediastinum
Score 3 =uptake > mediastinum but ≤ liver
Score 4 = uptake moderately > liver
Score 5=uptake markedly higher than liver and/or new lesions
Score X= new areas of uptake unlikely to be related to NHL

Response assessment based on CT/MRI and PET-CT scans.

Note: a PET-CT response overrides in most cases the response by CT and/or MRI alone: e.g. if PET-CT response = CMR and CT/MRI response = PR, overall response is CR (for further details refer to the Imaging Manual).

16.12 CYP3A4 inhibitors and inducers

A list of strong inhibitors and inducers of CYP3A4 (prohibited) is shown below.

Strong CYP3A4 inhibitors	Boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole, atazanavir, tipranavir, troleoandomycin, elvitegravir, danoprevir, conivaptan, boceprevir, suboxone and cobicistat
Strong CYP3A4 inducers	Avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort (hypericum perforatum) and enzalutamide

CYP3A4 = Cytochrome P450 isoenzyme 3A4
Source: 33, 34, 35 and 36.