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

Bayer study drug	BAY 80-6946 / Copanlisib		
Study purpose:	Maximum tolerated dose (MTD) finding, safety and activity		
Clinical study phase:	Phase 1/2	**Date:**	06 AUG 2019
Study No.:	19176	**Version:**	1.0
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Abbreviations

AE	Adverse event
AKT	Protein kinase B
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
BDG	Bayer drug groupings
BRM	Blinded review meeting
BSA	Body surface area
Cmax	Maximum drug concentration
CR	Complete response
CRF	Case report form
CSP	Clinical study protocol
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
day_{first}	The day of first study drug intake
day_{last}	The day of last study drug intake
DCR	Disease control rate
DLT	Dose-limiting toxicity
DOR	Duration of response
ECG	Electrocardiogram
EOT	End of treatment
FAS	Full analysis set
FU	Follow-up
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
IxRS	Interactive Voice Response System /Interactive Web Response System
kg	Kilogram
KM	Kaplan-Meier
LPLT	Last patient last treatment
LTFU	Long-term follow-up
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MTD	Maximum tolerated dose
MUGA	Multiple gated acquisition
NCI	National Cancer Institute
OEE	Overall extent of exposure
ORR	Objective response rate
OS	Overall survival
pAKT	Phosphorylated AKT (protein kinase B [PKB])
PD	Progressive disease
PFS	Progression-free survival
PI3K	Phosphatidylinositol-3-kinase
PID	Patient identification number
PK	Pharmacokinetic(s)
PopPK	Population PK
PR	Partial response
R2PD	Recommended Phase 2 dose
RECIST	Response Evaluation Criteria in Solid Tumors

SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SFU	Safety follow-up
SOC	Standard of care
TEAE	Treatment-emergent adverse event
UMVCUE	Unbiased minimum variance unbiased conditional
VRM	Validity review meeting
VRR	Validity Review Report
WHO-DD	World Health Organization Drug Dictionary

1. Introduction

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.

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.

Based on published data on phosphatidylinositol-3-kinase (PI3K) implication in tumorigenesis and the mode of action of copanlisib to potentially block the PI3K/ protein kinase B (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.

This Statistical Analysis Plan (SAP) v1.0 is based on the Integrated Clinical Study Protocol Version 2.0 (dated 04 APR 2019) for study 19176.

2. Study Objectives

The objectives of the **Phase I (dose escalation)** part of the study are provided below:

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

Secondary objectives:

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

Exploratory objectives:

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

The objectives for **Phase II (extension)** part of the study are provided below:

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

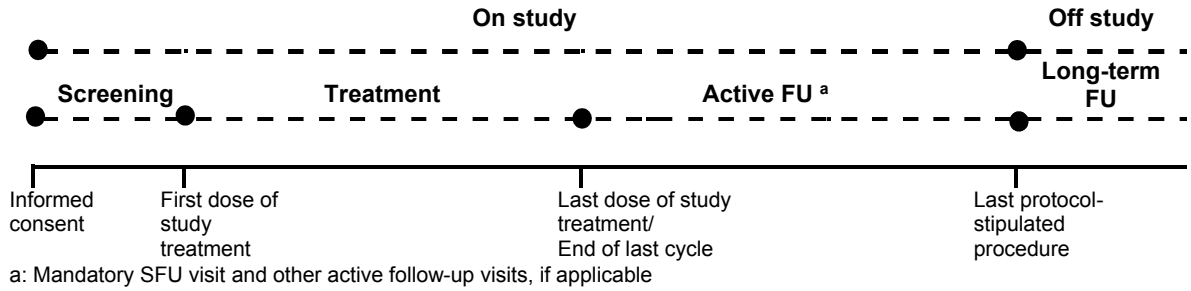
3. Study Design

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 (1). The Phase II (extension) part will use Simon 2-stage design in arms by tumor type (2).

A schematic of the study periods is presented in Figure 3-1. The following design applies to both Phase I and Phase II parts.

Figure 3-1: Study periods



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

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.

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

Active Follow–up (Active FU):

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 progressive disease (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.

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 in the study. Those patients who reached adult age during the long-term follow-up can be contacted directly or via patients' parents (or legal guardians).

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 3–1) with expansion cohort at the maximum tolerated dose. The sample size was based on feasibility, not formal statistical calculation. 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 30 patients will be enrolled and treated. A minimum of 50% of the enrolled patients will be under the age of 12.

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 dose-limiting toxicities (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.

Table 3–1 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 3–2 and Table 3–3, 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.

Copanlisib will be dosed 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.

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 dosing will be based on body surface area (BSA).

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)$^{0.425}$

The dose levels to be explored are listed in the following tables. 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.

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 3–2 and Table 3–3 for dose levels of copanlisib for patients < 1 year old and ≥ 1 year old, respectively.

Table 3–2 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 3–3 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.

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.

Phase II extension 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. 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 4.4 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. A minimum of 80% of the enrolled patients will be under the age of 18.

4. General Statistical Considerations

4.1 General Principles

The statistical evaluation will be performed by using the software package SAS release 9.2 or higher (SAS Institute Inc., Cary, NC, USA). All variables will be analyzed by descriptive statistical methods. The number of data available and missing data, mean, standard deviation, minimum, quartiles, median, and maximum will be calculated for continuous data. Ordinal data will be summarized using n, number of missing values, median, minimum, maximum and quartiles. Frequency tables will be generated for categorical data. Time-to-event variables (in days) will be summarized using Kaplan-Meier (KM) estimates.

4.2 Handling of Dropouts

A patient who discontinues study participation prematurely for any reason is defined as a “dropout” if the patient has already been administered at least 1 dose of the study drug (copanlisib).

Patients must be withdrawn from the study treatment or the study if any of the pre-specified withdrawn criteria is met. See protocol Section 6.4.1 for the pre-specified withdrawn criteria.

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).

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.

The number of patients who prematurely discontinue the study and study treatment for any reason, as well as the reasons for premature discontinuation of study treatment and the completion of the follow-up periods, will be reported.

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 treatment-emergent adverse event (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.

4.3 Handling of Missing Data

In general, missing data, except for partially missing dates, will not be imputed in this study. In order to achieve the goal of a well conducted clinical trial according to Good Clinical Practice (GCP), every effort should be made to resolve incomplete or missing dates during the course of the study (i.e. edit checks, data cleaning / monitoring etc.). When only partial dates are available, the following replacement rules will be used: if the start date is partially missing, the first day of that month will be used when only the day is missing; if the stop date is partially missing, the last day of the month will be used when only the day is missing; if both the day and the month are missing, the date will be missing. All missing or partial data will be presented in the patient data listing as they are recorded on the Case Report Form (CRF).

4.4 Interim Analyses and Data Monitoring

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

Simon's two-stage optimal design will be used for each of the four indications (neuroblastoma; osteosarcoma; rhabdomyosarcoma; Ewing sarcoma) of the Phase II part separately. For each indication, the null hypothesis is that the background response rate (disease control rate for osteosarcoma) of 10% will be tested against a one-sided alternative. With type I error rate of 7.5%, power of 80% and the success response rate of 30%, Stage 1 will include 10 patients. After 10 patients per indication have been treated in Stage 1 for at least 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. If an indication that is not stopped at Stage 1, 15 additional patients will be accrued into Stage 2 for a total of 25.

In case of recruitment overrun of Stage 1 (despite plans to pause recruitment), the 10 patients for Stage 1 will be determined based on the date/time of signing the informed consent. Overrun patients will only stop their treatment in case Stage 2 is not reached and might contribute as patients to Stage 2.

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. 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 last treatment (LPLT).

4.5 Data Rules

4.5.1 Time intervals

If time intervals are to be displayed other than days in statistical evaluations, then one year is considered to have 365.24 days (average length of a year, including leap years), one month is considered to have 30.44 days (average length of a month, including leap years), one week is considered to have 7 days, and one cycle is considered to have 28 days (i.e. 4 weeks).

4.5.2 Baseline

Baseline is defined as the last measurements performed prior to the first study drug administration in Cycle 1, unless otherwise specified.

4.5.3 Repeated measures

If there are repeated measurements per time point (e.g. laboratory values, vital signs, etc.), the following rules will be used (unless otherwise specified):

- Before the start of the study drug administration (i.e., for screening and baseline value), the latest measurement at scheduled visits will be used. Unscheduled visits will be used, if there are no measurements at scheduled visits. If the latter is the case, the last unscheduled visit will be used.
- In case of repeated measurements at any post baseline time point, the first measurement at scheduled visits will be used. Unscheduled visits will be used, if there are no measurements at scheduled visits. If the latter is the case, the first unscheduled visit will be used.

4.5.4 Overall extent of exposure

As a general rule, and in accordance with the Oncology Therapeutic Area Standard, leading '0 mg' (prior to the first positive amount of drug) and trailing '0 mg' records (not followed by any positive amount of drug), will not be included in the calculation of any drug duration or amount.

Overall extent of exposure (OEE) for study treatment, respectively, is defined as the time from first respective study drug intake (day_{first}) until last study drug intake (day_{last}), including 7 additional days in order to consider the weekly dosing regimen, and is calculated as:

$OEE = day_{last} - day_{first} + 7$

If the respective treatment ends with dose interruptions, the day of the last actual dose will be considered to be day_{last}.

4.6 Validity Review

The results of the validity review meeting (VRM)/ blinded review meeting (BRM) will be documented in the Validity Review Report (VRR) and may comprise decisions and details relevant for statistical evaluation. Any changes to the statistical analysis prompted by the results of the validity review meeting will be documented in an amendment and, if applicable, in a supplement to this SAP.

5. Analysis Sets

5.1 Assignment of analysis sets

Final decisions regarding the assignment of patients to analysis sets will be made during the review of study data and documented in the final list of important deviations, validity findings and assignment to analysis set(s) (see section 4.5.4).

Full analysis set (FAS)

The FAS population is defined as 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.

Safety analysis set (SAF)

The SAF population is defined as 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.

PK analysis set

The popPK is defined as 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.

6. Statistical Methodology

Statistical analyses in this section will be carried out for Phase I (dose escalation) and Phase II (extension) parts, respectively. The analysis methods for Phase II part will be amended based on an amended protocol after the completion of the Phase I part, to provide updated information on RP2D and other related topics.

6.1 Population characteristics

Population characteristics will be summarized in the FAS, unless otherwise specified.

6.1.1 Disposition

Disposition at the end of screening will be summarized for all enrolled patients.

Disposition at the end of treatment and for the follow-up periods will be summarized by cohort and overall for Phase I part; and by indication and overall for Phase II part.

6.1.2 Protocol deviations

Frequency tables of protocol deviations by category and deviation coded term will be summarized by cohort and overall for Phase I part, by indication and overall for Phase II part.

6.1.3 Demographics and other baseline characteristics

Demographics variables and baseline characteristics will be summarized by cohort and overall for Phase I part; and by indication and overall for Phase II part. Summary statistics will be presented for continuous variables. Frequency tables will be presented for categorical variables.

Demographic variables include age, gender, race, ethnicity. Age will be analyzed as continuous variable and in addition, categorized with the following categories: 6 month - < 1 year, 1 year - < 2 years, 2 years - < 6 years, 6 years - < 12 years; 12 years - < 18 years, ≥ 18 years.

The following additional baseline characteristics will be analyzed:

- Date of diagnosis and stage of disease
- Tumor site and size, site(s) and date(s) of metastases, type of surgery conducted
- Most recent histology of tumor
- Most recent staging and grading of tumor
- Assessment of baseline toxicity
- Karnofsky / Lansky performance status

6.1.4 Medical history

Medical history findings are defined as the conditions that started before signing of informed consent and considered relevant for the patients' study eligibility. The medical history findings will be coded by Medical Dictionary for Regulatory Activities (MedDRA, version 21.1 or later, if more updated version is available by the time of analysis). Medical history will be presented for each MedDRA Primary System Organ Class (SOC) and Preferred Term by cohort and overall for Phase I part, and by indication and overall for Phase II part.

6.1.5 Prior and concomitant medication

Prior and concomitant medications will be coded by Anatomical Therapeutic Chemical (ATC) classification system according to the World Health Organization Drug Dictionary (WHO-DD, version 2019MAR or later). Summaries will be provided by ATC class and subclass separately for Phase I (by cohort and overall) and Phase II (by indication and overall). Note that the same medication can appear multiple times in the table as it can have several ATC codes.

A medication that has been stopped after first administration of study treatment is considered as concomitant and otherwise as prior. Medications with missing start and stop date but flagged as being ongoing at end of study will be considered to have started prior to start of study medication and end after stop of study medication.

6.1.5.1 Prior anti-cancer therapy

In addition to general prior medications, prior anti-cancer therapy will be further analyzed by cohort and overall for Phase I part, as well as by indication and overall for Phase II part for the following:

- The minimum, median, and maximum number of prior systemic anti-cancer therapy lines
- Number of patients with 1, 2, 3 and $\geq$ 4 lines of therapy
- History of prior stem cell transplant
- Time since last systemic anti-cancer therapy
- Time between the start day of last course of systemic anti-cancer therapy and the day of confirmation of the most recent progression (categorized as $\leq$ 6 months, > 6 to 12 months and >12 months)
- Prior anti-cancer therapies (displayed by ATC classes, Bayer drug groupings (BDGs) and preferred drug names, respectively)
- Anti-cancer therapies during follow-up (displayed by ATC classes, BDGs and preferred drug names, respectively)

6.1.6 Treatment duration and exposure

Descriptive statistical summaries for the following variables will be provided by cohort for Phase I part and by indication for Phase II part:

- Overall extent of exposure (OEE, as defined in section 4.5.4)
- Number of cycles

- Number of infusions during treatment phase
- For patients with dose delay or interruption, the number of dose delays or interruptions per patient and their reasons will be summarized.

In addition, the following analyses will be provided by cycle for Phase I part (by cohort) and Phase II part (by indication), respectively:

- Total amount actually administered
- Mean dose intensity (mg/m^2)
- Percent of planned dose received (i.e., Actual dose [mg] / Planned dose [mg] × 100%). Copanlisib will be administered IV on Days 1, 8 and 15 of each 28-day treatment cycle. Completed cycles therefore have a planned dose of 3 × X mg, where X is the planned dose for a patient, depending on the dose level assigned to him/her. For incomplete cycles, the planned dose depends on the number of days (d) in that cycle:
  - X mg if $0 < d < 8$
  - $2 \times X$ mg if $8 \leq d < 15$
  - $3 \times X$ mg if $d \geq 15$

6.2 Efficacy

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.

6.2.1 Phase I part

Efficacy analyses of Phase I part will be performed in the FAS by cohort and by indication, respectively.

ORR is defined separately in each indication, as the number of responders divided by the number of patients of the FAS in the indication. A patient is a responder if the patient has a tumor response on-study of complete response (CR) or partial response (PR), based on radiological assessments utilizing Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 for solid tumor or modified Lugano Classification 2014 for lymphoma, or SIOPEN or Curie score for neuroblastoma patients with MIBG-avid disease. Patients for whom overall best response is not CR or PR, as well as patients without any post-baseline tumor assessment will be considered non-responders. ORR and 95% Clopper-Pearson exact confidence intervals will be computed for each cohort and each indication.

6.2.2 Phase II part

6.2.2.1 Primary Efficacy Analyses

- ORR, defined the same as above, is the primary efficacy endpoint in neuroblastoma, Ewing sarcoma and rhabdomyosarcoma, while DCR is the primary efficacy endpoints in osteosarcoma. DCR is defined as the number of patients with disease control divided by the number of patients with osteosarcoma in the FAS. 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.

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 (3).

- PFS, considered as the co-primary endpoint for osteosarcoma patients, is defined as the time from first intake of study drug to disease progression according to RECIST1.1 for solid tumor patients or death (if death occurs before progression is documented). Censoring rules listed in Table 6–1 will be applied (PFS = End Date – Date of first intake of study drug).

  PFS will be summarized for patients reaching Stage 2 by KM estimates (4). KM plot will be presented with number of subjects at risk and number of events at the bottom. Median survival time, as well as 25% and 75% percentiles, with 95% confidence intervals will be estimated by product-limit method (5).

Table 6–1 Censoring rules

Situation	End Date	Censored	Reason for Censoring
No baseline or post-baseline disease assessment	Treatment start date (i.e., censored at day 1)	Yes	No baseline or post-baseline disease assessment
PD or death (no more than one missing tumor assessment)	Date of the first PD or death	No	N/A
PD or death after two or more consecutive tumor assessments	Date of the last assessment before missing assessments	Yes	Missed more than one disease assessment
Subject discontinued from study for reasons other than PD or death	Date of the last assessment without PD	Yes	Subject discontinued from study due to a reason other than PD or death
Subject still on study at the time of data cutoff without PD	Date of the last assessment without PD	Yes	Subjects is still alive without PD
New systemic anti-cancer therapy started prior to PD	Date of the last assessment before starting the new anti-cancer therapy	Yes	New anti-cancer therapy started

6.2.2.2 Secondary Efficacy Analyses

DOR, PFS (except for osteosarcoma) and OS will be considered as secondary endpoints for each indication. They will be analyzed separately for each indication reaching Stage 2, in the same way as described above for PFS as the co-primary endpoint of osteosarcoma patients.

- Analyses of DOR will be carried out for responders only (i.e. patients with CR or PR). DOR is defined as the time from the date of first observed tumor response until first subsequent PD or death (if death occurs before progression is documented) due to any cause, with censoring rules in Table 6–1 (for DOR, the first situation does not apply; and all situations are referred to as those occurring after the first tumor response. DOR = end date – date of first response).
- PFS in each indication except for osteosarcoma is defined as the time from first intake of study drug to disease progression according to RECIST1.1 for solid tumor patients

(except for osteosarcoma) and SIOPEN or Curie score for neuroblastoma patients with MIBG-avid disease, or death (if death occurs before progression is documented). Censoring rules listed in Table 6–1 will be applied.

- OS is defined as the time from first intake of study drug until death from any cause, with censoring rules listed below in Table 6–2.

Table 6–2 OS censoring rules

Situation	End Date	Censored	Reason for Censoring
Death on or prior to database cutoff date	Date of Death	No	N/A
Death occurred or subject known to be alive after database cutoff date	Database cut-off date	Yes	Alive as of data cut-off date
Last known alive date is on or prior to data cutoff date	Last known alive date	Yes	The reasons are based on the study CRF: e.g., subjects lost to follow up, withdrew consent etc.

6.2.3 Subgroup Analyses

Subgroup analyses will be performed for Phase I and Phase II parts, respectively.

Subgroup levels to be analyzed are:

- Age group (< 1 year vs. 1 year - 6 years vs. > 6 years)
- Gender (male vs. female)
- Race (white vs. others)
- Prior lines of therapy (1 vs. >1)
- Prior stem cell transplant (Yes vs. No)

6.3 Safety

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. Safety analyses will be performed by cohort for Phase I part and by indication for Phase II part in the SAF. Such safety analyses will also be performed by age group (< 1 year vs. 1 year - 6 years vs. > 6 years).

6.3.1 Adverse Events (AEs)

Adverse events will be coded by MedDRA (version 21.1 or later). Severity of AEs and hematological/biochemical toxicities based on laboratory measurements will be graded using National Cancer Institute (NCI) Common Terminology Criteria Adverse Event (CTCAE, version 4.03) dictionary. AEs will be classified by the investigator as related or not related to study drug.

All TEAEs

TEAE is defined as any event arising or worsening after start of study drug administration until 30 days after the last dose of the study drug intake (end of safety follow-up). In the case

where it is not possible to define an AE as treatment-emergent or not, the AE will be classified by the worst case; i.e. treatment-emergent.

An overall summary of TEAEs will be provided. TEAEs, drug-related (copanlisib), procedure-related, and/or serious TEAEs will be summarized by MedDRA (SOC and preferred term) and worst grade based on CTCAE. The analyses will be repeated by age group (< 1 year vs. 1 year - 6 years vs. > 6 years).

TEAEs Leading to Permanent Discontinuation of Study Treatment, Copanlisib Interruption and/or Dose Reduction

The number and percentage of patients who discontinued study treatment due to TEAE or required a dose reduction or interruption caused by a TEAE will be summarized separately for each cohort of Phase I part, and for each indication of Phase II part. The incidences of these TEAEs will be presented also separately by drug relationship. Patients who discontinued study treatment, required a dose reduction or interruption caused by a TEAE will be listed separately for each cohort of Phase I part or each indication of Phase II part: patient ID, histology, sponsor AE identifier, investigator AE term, MedDRA SOC and preferred term, NCI-CTCAE term and toxicity grade, start and stop dates of study drug administration, start and stop date of AE, drug related (yes/no), protocol required procedure related (yes/no), outcome.

6.3.2 Deaths and Serious Adverse Events

Patients listings will be provided by cohort for Phase I part and by indication for Phase II part, respectively:

- Patients who died before treatment (only present if any): patient ID, age, sex, race, date of inform consent, sponsor AE identifier, date of death, cause of death.
- Patients who died during treatment up to 30 days after last dose of study drug intake: patient ID, age, sex, race, sponsor AE identifier, start and stop date of study drug, relative days to start / stop of study drug, weeks on treatment, date of death, cause of death, MedDRA SOC and preferred term, reported AE term, toxicity grade, drug related (yes/no) and protocol required procedure related (yes/no).
- Patients with treatment-emergent serious adverse events (SAE)s: patient ID, age, sex, race, sponsor AE identifier, start and stop date of study drug, relative days to start / stop of study drug, weeks on treatment, date of death, cause of death, MedDRA SOC and preferred term, reported AE term, toxicity grade, drug related (yes/no), protocol required procedure related (yes/no), outcome, and action taken.

6.3.3 MTD and RP2D Determination

Dose-limiting toxicities

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. DLTs include both non-hematological AEs and hematological AEs. The classified DLT criteria are listed in the protocol Section 7.4.1.3.

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.

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. (See dose adjustment in Rolling-6 design in Table 3–1)

Individual listing of DLTs will be presented by cohort.

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 area under the curve (AUC)s (i.e., model predicted AUC(0-168) after the third infusion of the assigned dose size for each patient) in the cohort with the highest dose level being within ± 25% of the adult exposure after dosing recommended for copanlisib development. Equivalence will be addressed in a separate modeling and simulation (M&S) report.

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. 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).

6.3.4 Pregnancies

The results of pregnancy tests will be listed by cohort of Phase I part and by indication of Phase II part, respectively. Any pregnancy will be documented.

6.3.5 Clinical Laboratory Parameters

Results of the clinical laboratory evaluations (coagulation, hematology, chemistry and urinalysis) will be summarized by visit and overall with worst grade. Worst grades for hematological and biochemical toxicities will be calculated according to CTCAE, version 4.03 based on laboratory measurements. For tables displaying treatment-emergent laboratory abnormalities, patients with specimen collection between start of treatment and 30 days after the last dose of the study drug intake will be included.

Summary statistics will also be presented for the change from baseline for each quantitative clinical laboratory variable, including quantitative urinalysis variables, at each post-baseline

visit. For these variables, the number and percentage of patients with transitions from worst grade at baseline to worst grade at post-baseline visits relative to the respective laboratory's reference ranges will be presented by study periods, treatment or safety follow-up. For the change in worst grade of hematological toxicities under treatment the latest observation will be taken. In case there is more than one observation for the same latest time, the worst grade will be taken. In addition to the above summary, specific glucose evaluation will be described in the next section.

6.3.6 Glucose Evaluation

Glucose will be displayed by worst CTCAE grade in SAF for pre-dose and post-dose measurements on Cycle 1 Day 1 and on subsequent infusion days according to the instructions given in Table 6–3.

Table 6–3 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.

Changes from respective pre-dose (defined as the first pre-dose glucose measurement in each visit) in glucose will be summarized using descriptive statistics at each visit and analysis time point by pre-dose fasting status.

Change in hemoglobin A1c (HbA1c) values by visit and overall (during study treatment) will be summarized by descriptive statistics.

6.3.7 Further Safety Parameters

Results of physical examination, vital signs (including weight, height, BSA, heart rate, respiration rate, body temperature, and blood pressure), electrocardiogram (ECG) and Lansky-Karnofsky performance status score will be summarized with descriptive statistics and/or frequency tables. Vital signs and ECG data will be summarized by visit and timepoint, including change from baseline where appropriate.

The overall interpretation of the 12-lead (or 15-lead) ECG and the ECG diagnosis, as well as the overall interpretation of the echocardiogram and the corresponding diagnosis will be summarized by visit. Frequency and shift tables for number of patients by interpretation of ECG as abnormal will be performed at all-time points, as well as frequencies and shift tables for clinical relevance of ECG. The number of patients with abnormal cardiac function will be displayed for echocardiogram and multiple gated acquisition (MUGA) by visit.

The number of patients requiring post dosing antihypertensive treatment (including an overview of the maximum blood pressure according to CTCAE grading, medication used and outcome after antihypertensive treatment), and patients with non-infectious pneumonitis

requiring corticosteroids will be displayed descriptively. The number of patients with abnormal blood pressure (according to CTCAE grading) will be displayed by visit and post-dose hypertension grade.

6.4 Pharmacokinetics/pharmacodynamics

Plasma samples for measurement of copanlisib (BAY 1163877) concentrations will be collected from all patients for copanlisib during Cycle 1 (or, optionally, during Cycle 2 if it was not done on Cycle 1) on Days 1 and 15 according to Table 6–4.

Table 6–4 Blood sample collection for copanlisib PK assessment

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

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

Concentration data of copanlisib from this study will be analyzed separately by cohort for Phase I part and by indication for Phase II part in PK analysis set to estimate the individual maximum drug concentration (C_{max}) and AUC(0-168) on Cycle 1 Day 1 and Day 15. Besides, these analyses will also be done by age subgroup (< 1 year, 1 year - 6 years and > 6 years). Any further statistical analysis will be described in a separate M&S report.

6.5 Biomarker/ pharmacodynamics (PD) evaluation

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 and pharmacodynamics sampling will be collected from all patients (except ≤ 1 year old) at screening, Cycle 1 Day 15 and end of treatment. Biomarker data collected in the clinical database will be listed.

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

PD:

- The change in phosphorylated AKT (pAKT) relative to total AKT in surrogate tissue (platelet rich plasma)
- The maximum change from baseline of insulin and C-peptide during copanlisib treatment

Biomarker:

- 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.

Further exploratory statistical analyses may be performed and relationships between biomarker data and clinical outcome will be evaluated in a separate report. The biomarker results may be reported separately from the main clinical study report (CSR).

7. Document history and changes in the planned statistical analysis

None.

8. References

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