Clinical trial results:
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

Summary

EudraCT number	2017-000383-15
Trial protocol	Outside EU/EEA
Global end of trial date	01 February 2023

Results information

Result version number	v1 (current)
This version publication date	30 July 2023
First version publication date	30 July 2023

Trial information

Trial identification

Sponsor protocol code	BAY806946/19176

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03458728
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, +49 30 300139003, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, +49 30 300139003, clinical-trials-contact@bayer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001757-PIP02-15
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 February 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 February 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Phase 1: 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.
Phase 2: 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

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 April 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 31
Worldwide total number of subjects	31
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	14

Adolescents (12-17 years)	14
Adults (18-64 years)	3
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 14 centers in United States between 30 APR 2018 (First subject first visit) and 05 JUL 2022 (Last subject last visit).

Pre-assignment

Screening details:

41 subjects were screened into the study (signed informed consent form (ICF)). 10 subjects were screening failed.

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Copanlisib 28mg/m*2, Total

Arm description:

Copanlisib was administered Intravenous (IV) on Days 1, 8 and 15 of each 28-day treatment cycle. Treatment was continued until radiological progressive disease, unacceptable toxicity, withdrawal of consent, death or other event specified by the protocol. Copanlisib 28mg/m*2, Total included AMD0 (5 subjects who were under the original DLT criteria) and AMD1+ (19 subjects who were under the amended DLT criteria).

Arm type	Experimental
Investigational medicinal product name	Copanlisib
Investigational medicinal product code	BAY80-6946
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered on Day 1, Day 8 and Day 15 of every 28-day cycle.

Arm title	Copanlisib 35mg/m*2

Arm description:

Copanlisib was administered Intravenous (IV) on Days 1, 8 and 15 of each 28-day treatment cycle. Treatment was continued until radiological progressive disease, unacceptable toxicity, withdrawal of consent, death or other event specified by the protocol.

Arm type	Experimental
Investigational medicinal product name	Copanlisib
Investigational medicinal product code	BAY80-6946
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered on Day 1, Day 8 and Day 15 of every 28-day cycle.

Number of subjects in period 1	Copanlisib 28mg/m*2, Total	Copanlisib 35mg/m*2
Started	24	7
Started treatment	24	7
Terminated treatment	24	7
Completed	0	0
Not completed	24	7
Physician decision	1	-
Consent withdrawn by subject	-	1
Adverse event, non-fatal	1	-
Progressive disease - clinical assessment	1	-
Progressive disease - radiological progression	21	6

Baseline characteristics

Reporting groups	
Reporting group title	Copanlisib 28mg/m*2, Total
Reporting group description:	
Copanlisib was administered Intravenous (IV) on Days 1, 8 and 15 of each 28-day treatment cycle. Treatment was continued until radiological progressive disease, unacceptable toxicity, withdrawal of consent, death or other event specified by the protocol. Copanlisib 28mg/m*2, Total included AMD0 (5 subjects who were under the original DLT criteria) and AMD1+ (19 subjects who were under the amended DLT criteria).	
Reporting group title	Copanlisib 35mg/m*2
Reporting group description:	
Copanlisib was administered Intravenous (IV) on Days 1, 8 and 15 of each 28-day treatment cycle. Treatment was continued until radiological progressive disease, unacceptable toxicity, withdrawal of consent, death or other event specified by the protocol.	

Reporting group values	Copanlisib 28mg/m*2, Total	Copanlisib 35mg/m*2	Total
Number of subjects	24	7	31
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	11	3	14
Adolescents (12-17 years)	10	4	14
Adults (18-64 years)	3	0	3
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	12.5	12.3	
standard deviation	± 4.6	± 3.8	-
Gender Categorical Units: Subjects			
Female	10	3	13
Male	14	4	18
Race Units: Subjects			
ASIAN	1	2	3
BLACK OR AFRICAN AMERICAN	3	1	4
NOT REPORTED	3	1	4
WHITE	17	3	20
Ethnicity Units: Subjects			
HISPANIC OR LATINO	5	1	6
NOT HISPANIC OR LATINO	18	6	24
NOT REPORTED	1	0	1

End points

End points reporting groups

Reporting group title	Copanlisib 28mg/m*2, Total

Reporting group description:

Copanlisib was administered Intravenous (IV) on Days 1, 8 and 15 of each 28-day treatment cycle. Treatment was continued until radiological progressive disease, unacceptable toxicity, withdrawal of consent, death or other event specified by the protocol. Copanlisib 28mg/m*2, Total included AMD0 (5 subjects who were under the original DLT criteria) and AMD1+ (19 subjects who were under the amended DLT criteria).

Reporting group title	Copanlisib 35mg/m*2

Reporting group description:

Copanlisib was administered Intravenous (IV) on Days 1, 8 and 15 of each 28-day treatment cycle. Treatment was continued until radiological progressive disease, unacceptable toxicity, withdrawal of consent, death or other event specified by the protocol.

Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects with at least one intake of study drug.

Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis

Subject analysis set description:

The SAF population was defined as all subjects with at least one intake of study drug.

Subject analysis set title	PK analysis set
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects with at least one intake of study drug and with at least one valid measurement for copanlisib after first dosing were included in the copanlisib PK analysis.

Subject analysis set title	Copanlisib_Phase 1
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Copanlisib was administered on Day 1, Day 8, and Day 15 of every 28-day cycle. Subjects received copanlisib IV infusion with intermittent (3 weeks on / 1 week off) dosing schedule at the assigned dose level.

Subject analysis set title	Copanlisib_Phase 2
Subject analysis set type	Sub-group analysis

Subject analysis set description:

As the study was terminated before the initiation of phase 2, data was not collected in phase 2.

Primary: Phase 1: Number of subjects with Dose limiting toxicity (DLT)

End point title	Phase 1: Number of subjects with Dose limiting toxicity (DLT)[1]

End point description:

DLT was 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 was the first cycle of therapy.
DLT analysis was performed on SAF.

End point type	Primary

End point timeframe:

Cycle 1

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All endpoints were analyzed using descriptive statistical methods.

End point values	Copanlisib 28mg/m*2, Total	Copanlisib 35mg/m*2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	7		
Units: Subjects	3	2		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1: 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.

End point title	Phase 1: 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.[2]

End point description:

Maximum tolerated dose (MTD) for copanlisib was defined as the highest dose level where 6 patients have been treated and ≤ 1 participant experienced a DLT. This endpoint was performed on SAF.

End point type	Primary

End point timeframe:

Cycle 1 (28 days)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All endpoints were analyzed using descriptive statistical methods.

End point values	Copanlisib_Phase 1			
Subject group type	Subject analysis set			
Number of subjects analysed	31			
Units: mg/m*2/d				
number (not applicable)	28			

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1: Number of subjects with Treatment-emergent adverse events (TEAEs)

End point title	Phase 1: Number of subjects with Treatment-emergent adverse events (TEAEs)[3]

End point description:

TEAE was 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).
This endpoint was performed on SAF.

End point type	Primary

End point timeframe:

After the first study intervention up to 30 days after the last dose of the study drug intake (end of safety

follow up), with a maximum of 145 days.

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All endpoints were analyzed using descriptive statistical methods.

End point values	Copanlisib 28mg/m*2, Total	Copanlisib 35mg/m*2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	7		
Units: Subjects	24	7		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1: Number of subjects with Serious Adverse Events (SAEs)

End point title	Phase 1: Number of subjects with Serious Adverse Events (SAEs)[4]

End point description:

This endpoint was performed on SAF.

End point type	Primary

End point timeframe:

Up to 150 days.

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All endpoints were analyzed using descriptive statistical methods.

End point values	Copanlisib 28mg/m*2, Total	Copanlisib 35mg/m*2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	7		
Units: Subjects	10	0		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1: Number of participants with Treatment-related Adverse Events (AEs).

End point title	Phase 1: Number of participants with Treatment-related Adverse Events (AEs).[5]

End point description:

This endpoint was performed on SAF.

End point type	Primary

End point timeframe:

Up to 145 days.

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All endpoints were analyzed using descriptive statistical methods.

End point values	Copanlisib 28mg/m*2, Total	Copanlisib 35mg/m*2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	7		
Units: Subjects	5	0		

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2: Progression-free survival (PFS)

End point title	Phase 2: Progression-free survival (PFS)[6]

End point description:

End point type	Primary

End point timeframe:

Data was not collected for this endpoint due to study was terminated before the initiation of phase 2.

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Data was not collected for this endpoint due to study was terminated before the initiation of phase 2.

End point values	Copanlisib_Phase 2			
Subject group type	Subject analysis set			
Number of subjects analysed	0[7]			
Units: Subjects				

Notes:

[7] - Data was not collected due to termination of phase 2.

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2: Disease control rate (DCR)

End point title	Phase 2: Disease control rate (DCR)[8]

End point description:

The DCR was defined as the number of subjects with disease control divided by the number of subjects in FAS or per protocol set (PPS) in the indication.

End point type	Primary

End point timeframe:

Data was not collected for this endpoint due to study was terminated before the initiation of phase 2.

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Data was not collected for this endpoint due to study was terminated before the initiation of phase 2.

End point values	Copanlisib_Phase 2			
Subject group type	Subject analysis set			
Number of subjects analysed	0[9]			
Units: Subjects				

Notes:

[9] - Data was not collected due to termination of phase 2.

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2: Objective response rate (ORR)

End point title	Phase 2: Objective response rate (ORR)[10]

End point description:

ORR was defined separately in each indication, as the number of responders divided by the number of subjects in FAS in the indication.

End point type	Primary

End point timeframe:

Data was not collected for this endpoint due to study was terminated before the initiation of phase 2.

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Data was not collected for this endpoint due to study was terminated before the initiation of phase 2.

End point values	Copanlisib_Phase 2			
Subject group type	Subject analysis set			
Number of subjects analysed	0[11]			
Units: Subjects				

Notes:

[11] - Data was not collected due to termination of phase 2.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Copanlisib maximum drug concentration (Cmax)

End point title	Phase 1: Copanlisib maximum drug concentration (Cmax)

End point description:

Cmax: maximum concentration after the 3rd dose in a sequence of 3 nominal doses of 28 mg/m2 [each dose infused over 1 hour at 168-hour interval]
Cmax analysis was performed on PK analysis set.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 and Day 15

End point values	Copanlisib_Phase 1			
Subject group type	Subject analysis set			
Number of subjects analysed	30			
Units: µg/L				
geometric mean (geometric coefficient of variation)	359 (± 22.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Area under the curve (AUC(0-168))

End point title	Phase 1: Area under the curve (AUC(0-168))

End point description:

AUC(0-168): Area under the concentration-time curve [AUC] from 0 to 168 hours after the 3rd dose in a sequence of 3 nominal doses of 28 mg/m2 [each dose infused over 1 hour at 168-hour interval].
AUC(0-168) analysis was performed on PK analysis set.

End point type	Secondary

End point timeframe:

On cycle 1, day 1 (C1D1) and cycle 1, day 15 (C1D15)

End point values	Copanlisib_Phase 1			
Subject group type	Subject analysis set			
Number of subjects analysed	30			
Units: µg·h/L				
geometric mean (geometric coefficient of variation)	2900 (± 35.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Objective response rate (ORR)

End point title	Phase 1: Objective response rate (ORR)

End point description:

ORR by dose cohort is defined as the number of responders divided by the number of subjects in FAS in the indication.
The analysis of ORR was performed on FAS.

End point type	Secondary

End point timeframe:
Up to 150 days

End point values	Copanlisib 28mg/m*2, Total	Copanlisib 35mg/m*2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	7		
Units: Subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Duration of response (DOR)

End point title	Phase 2: Duration of response (DOR)

End point description:

End point type	Secondary

End point timeframe:
Data was not collected for this endpoint due to study was terminated before the initiation of phase 2.

End point values	Copanlisib_Phase 2			
Subject group type	Subject analysis set			
Number of subjects analysed	0[12]			
Units: Subjects				

Notes:
[12] - Data was not collected due to termination of phase 2.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: PFS in each indication except for osteosarcoma

End point title	Phase 2: PFS in each indication except for osteosarcoma

End point description:

End point type	Secondary

End point timeframe:
Data was not collected for this endpoint due to study was terminated before the initiation of phase 2.

End point values	Copanlisib_Phase 2			
Subject group type	Subject analysis set			
Number of subjects analysed	0[13]			
Units: Subjects				

Notes:

[13] - Data was not collected due to termination of phase 2.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Overall survival (OS)

End point title	Phase 2: Overall survival (OS)

End point description:

End point type	Secondary

End point timeframe:

Data was not collected for this endpoint due to study was terminated before the initiation of phase 2.

End point values	Copanlisib_Phase 2			
Subject group type	Subject analysis set			
Number of subjects analysed	0[14]			
Units: Subjects				

Notes:

[14] - Data was not collected due to termination of phase 2.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Number of participants with Treatment-emergent AEs

End point title	Phase 2: Number of participants with Treatment-emergent AEs

End point description:

End point type	Secondary

End point timeframe:

Data was not collected for this endpoint due to study was terminated before the initiation of phase 2.

End point values	Copanlisib_Phase 2			
Subject group type	Subject analysis set			
Number of subjects analysed	0[15]			
Units: Subjects				

Notes:

[15] - Data was not collected due to termination of phase 2.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Number of subjects with treatment emergent SAEs

End point title	Phase 2: Number of subjects with treatment emergent SAEs

End point description:

End point type	Secondary

End point timeframe:

Data was not collected for this endpoint due to study was terminated before the initiation of phase 2.

End point values	Copanlisib_Phase 2			
Subject group type	Subject analysis set			
Number of subjects analysed	0[16]			
Units: Subjects				

Notes:

[16] - Data was not collected due to termination of phase 2.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Number of subjects with treatment-emergent clinically significant change in laboratory parameters, ECGs and vital signs

End point title	Phase 2: Number of subjects with treatment-emergent clinically significant change in laboratory parameters, ECGs and vital signs

End point description:

End point type	Secondary

End point timeframe:

Data was not collected for this endpoint due to study was terminated before the initiation of phase 2.

End point values	Copanlisib_Phase 2			
Subject group type	Subject analysis set			
Number of subjects analysed	0[17]			
Units: Subjects				

Notes:

[17] - Data was not collected due to termination of phase 2.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

After the first study intervention up to 30 days after the last dose of the study drug intake (end of safety follow up), with a maximum of 145 days. Death (all-cause) were collected with a maximum of 150 days.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Copanlisib 35mg/m*2

Reporting group description:

Copanlisib was administered Intravenous (IV) on Days 1, 8 and 15 of each 28-day treatment cycle. Treatment was continued until radiological progressive disease,unacceptable toxicity, withdrawal of consent, death or other event specified by the protocol.

Reporting group title	Copanlisib 28mg/m*2, Total

Reporting group description:

Copanlisib was administered Intravenous (IV) on Days 1, 8 and 15 of each 28-day treatment cycle. Treatment was continued until radiological progressive disease, unacceptable toxicity, withdrawal of consent, death or other event specified by the protocol. Copanlisib 28mg/m*2, Total included AMD0 (5 subjects who were under the original DLT criteria) and AMD1+ (19 subjects who were under the amended DLT criteria)

Serious adverse events	Copanlisib 35mg/m*2	Copanlisib 28mg/m*2, Total	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 7 (0.00%)	10 / 24 (41.67%)	
number of deaths (all causes)	5	20	
number of deaths resulting from adverse events	0	0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			

subjects affected / exposed	0 / 7 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Spinal cord compression			
subjects affected / exposed	0 / 7 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			

subjects affected / exposed	0 / 7 (0.00%)	5 / 24 (20.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 7 (0.00%)	2 / 24 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 7 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 7 (0.00%)	3 / 24 (12.50%)	
occurrences causally related to treatment / all	0 / 0	8 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Copanlisib 35mg/m*2	Copanlisib 28mg/m*2, Total	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	23 / 24 (95.83%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	2 / 7 (28.57%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 7 (28.57%)	10 / 24 (41.67%)	
occurrences (all)	2	42	
Hypotension			
subjects affected / exposed	1 / 7 (14.29%)	7 / 24 (29.17%)	
occurrences (all)	2	7	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 7 (42.86%)	10 / 24 (41.67%)	
occurrences (all)	7	14	
Gait disturbance			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	0 / 7 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	4 / 7 (57.14%)	8 / 24 (33.33%)	
occurrences (all)	7	19	
Non-cardiac chest pain			
subjects affected / exposed	1 / 7 (14.29%)	4 / 24 (16.67%)	
occurrences (all)	1	5	
Vessel puncture site pain			

subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Throat irritation			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Tachypnoea			
subjects affected / exposed	2 / 7 (28.57%)	3 / 24 (12.50%)	
occurrences (all)	2	4	
Pleural effusion			
subjects affected / exposed	0 / 7 (0.00%)	3 / 24 (12.50%)	
occurrences (all)	0	3	
Nasal congestion			
subjects affected / exposed	0 / 7 (0.00%)	3 / 24 (12.50%)	
occurrences (all)	0	3	
Hypoxia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Epistaxis			
subjects affected / exposed	0 / 7 (0.00%)	3 / 24 (12.50%)	
occurrences (all)	0	3	
Dyspnoea			
subjects affected / exposed	1 / 7 (14.29%)	5 / 24 (20.83%)	
occurrences (all)	2	7	
Cough			
subjects affected / exposed	1 / 7 (14.29%)	6 / 24 (25.00%)	
occurrences (all)	1	7	
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Irritability			
subjects affected / exposed	0 / 7 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	3	
Insomnia			

subjects affected / exposed	1 / 7 (14.29%)	3 / 24 (12.50%)	
occurrences (all)	1	3	
Hallucination			
subjects affected / exposed	0 / 7 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Depression			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Anxiety			
subjects affected / exposed	2 / 7 (28.57%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
Agitation			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Investigations			
Amylase increased			
subjects affected / exposed	0 / 7 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 7 (0.00%)	6 / 24 (25.00%)	
occurrences (all)	0	6	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 7 (14.29%)	6 / 24 (25.00%)	
occurrences (all)	2	8	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 7 (28.57%)	6 / 24 (25.00%)	
occurrences (all)	2	11	
Blood cholesterol increased			
subjects affected / exposed	1 / 7 (14.29%)	5 / 24 (20.83%)	
occurrences (all)	1	5	
Blood creatinine increased			
subjects affected / exposed	2 / 7 (28.57%)	4 / 24 (16.67%)	
occurrences (all)	4	4	
Blood lactate dehydrogenase increased			

subjects affected / exposed	0 / 7 (0.00%)	5 / 24 (20.83%)	
occurrences (all)	0	6	
C-reactive protein increased			
subjects affected / exposed	0 / 7 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Carbon dioxide decreased			
subjects affected / exposed	0 / 7 (0.00%)	3 / 24 (12.50%)	
occurrences (all)	0	8	
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
High density lipoprotein decreased			
subjects affected / exposed	0 / 7 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
International normalised ratio increased			
subjects affected / exposed	0 / 7 (0.00%)	3 / 24 (12.50%)	
occurrences (all)	0	3	
Lipase increased			
subjects affected / exposed	0 / 7 (0.00%)	5 / 24 (20.83%)	
occurrences (all)	0	7	
Lymphocyte count decreased			
subjects affected / exposed	3 / 7 (42.86%)	13 / 24 (54.17%)	
occurrences (all)	7	35	
Neutrophil count decreased			
subjects affected / exposed	2 / 7 (28.57%)	6 / 24 (25.00%)	
occurrences (all)	9	14	
Neutrophil count increased			
subjects affected / exposed	0 / 7 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	3	
Protein total decreased			
subjects affected / exposed	0 / 7 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Weight decreased			
subjects affected / exposed	2 / 7 (28.57%)	3 / 24 (12.50%)	
occurrences (all)	3	6	

White blood cell count decreased			
subjects affected / exposed	5 / 7 (71.43%)	12 / 24 (50.00%)	
occurrences (all)	7	21	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 7 (14.29%)	4 / 24 (16.67%)	
occurrences (all)	1	4	
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Thermal burn			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	1 / 7 (14.29%)	2 / 24 (8.33%)	
occurrences (all)	2	2	
Pericardial effusion			
subjects affected / exposed	0 / 7 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Sinus tachycardia			
subjects affected / exposed	3 / 7 (42.86%)	6 / 24 (25.00%)	
occurrences (all)	4	7	
Nervous system disorders			
Tremor			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	1 / 7 (14.29%)	9 / 24 (37.50%)	
occurrences (all)	3	11	
Dizziness			
subjects affected / exposed	0 / 7 (0.00%)	3 / 24 (12.50%)	
occurrences (all)	0	3	
Somnolence			
subjects affected / exposed	0 / 7 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	

Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	3 / 7 (42.86%)	7 / 24 (29.17%)	
occurrences (all)	4	21	
Anaemia			
subjects affected / exposed	3 / 7 (42.86%)	13 / 24 (54.17%)	
occurrences (all)	8	38	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Dry eye			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	4 / 7 (57.14%)	15 / 24 (62.50%)	
occurrences (all)	7	22	
Oral pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	4 / 7 (57.14%)	7 / 24 (29.17%)	
occurrences (all)	12	11	
Hypoaesthesia oral			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	2 / 7 (28.57%)	8 / 24 (33.33%)	
occurrences (all)	3	8	
Constipation			
subjects affected / exposed	4 / 7 (57.14%)	4 / 24 (16.67%)	
occurrences (all)	4	6	

Abdominal pain			
subjects affected / exposed	2 / 7 (28.57%)	5 / 24 (20.83%)	
occurrences (all)	2	9	
Abdominal distension			
subjects affected / exposed	0 / 7 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Stomatitis			
subjects affected / exposed	0 / 7 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	3	
Skin and subcutaneous tissue disorders			
Skin hyperpigmentation			
subjects affected / exposed	1 / 7 (14.29%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Pruritus			
subjects affected / exposed	1 / 7 (14.29%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Pain of skin			
subjects affected / exposed	0 / 7 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 7 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	1 / 7 (14.29%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Pain in extremity			
subjects affected / exposed	2 / 7 (28.57%)	8 / 24 (33.33%)	
occurrences (all)	2	12	
Neck pain			
subjects affected / exposed	1 / 7 (14.29%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Myalgia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	

Back pain			
subjects affected / exposed	1 / 7 (14.29%)	7 / 24 (29.17%)	
occurrences (all)	1	12	
Arthralgia			
subjects affected / exposed	0 / 7 (0.00%)	6 / 24 (25.00%)	
occurrences (all)	0	7	
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Hyperglycaemia			
subjects affected / exposed	4 / 7 (57.14%)	17 / 24 (70.83%)	
occurrences (all)	8	44	
Hyperkalaemia			
subjects affected / exposed	0 / 7 (0.00%)	4 / 24 (16.67%)	
occurrences (all)	0	5	
Hypermagnesaemia			
subjects affected / exposed	1 / 7 (14.29%)	6 / 24 (25.00%)	
occurrences (all)	1	7	
Hyperphosphataemia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Hypertriglyceridaemia			
subjects affected / exposed	1 / 7 (14.29%)	3 / 24 (12.50%)	
occurrences (all)	2	3	
Hyperuricaemia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Decreased appetite			
subjects affected / exposed	1 / 7 (14.29%)	6 / 24 (25.00%)	
occurrences (all)	4	8	
Hypouricaemia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	3	
Hypophosphataemia			

subjects affected / exposed	1 / 7 (14.29%)	7 / 24 (29.17%)	
occurrences (all)	1	11	
Hyponatraemia			
subjects affected / exposed	2 / 7 (28.57%)	11 / 24 (45.83%)	
occurrences (all)	3	16	
Hypokalaemia			
subjects affected / exposed	0 / 7 (0.00%)	4 / 24 (16.67%)	
occurrences (all)	0	8	
Hypoglycaemia			
subjects affected / exposed	0 / 7 (0.00%)	3 / 24 (12.50%)	
occurrences (all)	0	10	
Hypocalcaemia			
subjects affected / exposed	0 / 7 (0.00%)	8 / 24 (33.33%)	
occurrences (all)	0	12	
Hypoalbuminaemia			
subjects affected / exposed	2 / 7 (28.57%)	10 / 24 (41.67%)	
occurrences (all)	2	16	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 April 2019	The primary driver of this protocol amendment was 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 revised 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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported