Clinical trial results:
A Phase II, Open-label, Single-arm Study of Berzosertib (M6620) in Combination With Topotecan in Participants With Relapsed Platinum-resistant Small-Cell Lung Cancer (DDRiver SCLC 250)

Summary

EudraCT number	2020-004231-25
Trial protocol	FR IT ES
Global end of trial date	21 July 2023

Results information

Result version number	v1 (current)
This version publication date	03 August 2024
First version publication date	03 August 2024

Trial information

Trial identification

Sponsor protocol code	MS201923_0050

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04768296
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Healthcare KGaA, Darmstadt, Germany
Sponsor organisation address	Frankfurter Strasse 250, Darmstadt, Germany, 64293
Public contact	Communication Centre, Merck Healthcare KGaA, Darmstadt, Germany, +49 6151725200, service@merckgroup.com
Scientific contact	Communication Centre, Merck Healthcare KGaA, Darmstadt, Germany, +49 6151725200, service@merckgroup.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 July 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 July 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this trial was to assess efficacy, safety, tolerability and pharmacokinetics (PK) of Berzosertib in combination with Topotecan in subjects with relapsed, platinum-resistant small-cell lung cancer (SCLC). This trial was conducted in two parts: safety run-in part and main part. The safety run-in part was conducted in Japan.

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 March 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Spain: 23
Country: Number of subjects enrolled	United States: 10
Country: Number of subjects enrolled	China: 17
Country: Number of subjects enrolled	Japan: 6
Worldwide total number of subjects	76
EEA total number of subjects	43

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	45
From 65 to 84 years	31
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

First Subject Forst Visit: 29-Mar-2021; Last Subject Last Visit: 21-Jul-2023

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Safety run-in Part (DL 1): Berzosertib + Topotecan

Arm description:

Subjects received Berzosertib at a dose of 105 milligrams per square meter (mg/m^2) intravenously on Day 2 and Day 5 of each 21-day cycle in combination with Topotecan at a dose of 1.25 mg/m^2 intravenously on Days 1 through 5 of each 21-day cycle in safety run-in part until disease progression or other criteria for study intervention discontinuation are met.

Arm type	Experimental
Investigational medicinal product name	Berzosertib
Investigational medicinal product code	M6620
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Berzosertib was administered at a dose of 105 mg/m^2 intravenously on Day 2 and Day 5 of each 21-day cycle until disease progression or other criteria for study intervention discontinuation are met.

Investigational medicinal product name	Topotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Topotecan was administered at a dose of 1.25 mg/m^2 intravenously on Days 1 through 5 of each 21-day cycle until disease progression or other criteria for study intervention discontinuation are met.

Arm title	Safety run-in Part (DL2)+Main Part: Berzosertib + Topotecan

Arm description:

Subjects received Berzosertib at a dose of 210 mg/m^2 intravenously on Day 2 and Day 5 of each 21-day cycle in combination with Topotecan at a dose of 1.25 mg/m^2 intravenously on Days 1 through 5 of each 21-day cycle in safety run-in part until disease progression or other criteria for study intervention discontinuation are met.

Arm type	Experimental
Investigational medicinal product name	Topotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Topotecan was administered at a dose of 1.25 mg/m^2 intravenously on Days 1 through 5 of each 21-

day cycle until disease progression or other criteria for study intervention discontinuation are met.

Investigational medicinal product name	Berzosertib
Investigational medicinal product code	M6620
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Berzosertib was administered at a dose of 210 mg/m^2 intravenously on Day 2 and Day 5 of each 21-day cycle until disease progression or other criteria for study intervention discontinuation are met.

Number of subjects in period 1	Safety run-in Part (DL 1): Berzosertib + Topotecan	Safety run-in Part (DL2)+Main Part: Berzosertib + Topotecan
Started	3	73
Completed	2	66
Not completed	1	7
STOP LONG-TERM FOLLOW-UP AS PER SPONSOR'S DECISION	1	7

Baseline characteristics

Reporting groups

Reporting group title	Safety run-in Part (DL 1): Berzosertib + Topotecan

Reporting group description:

Subjects received Berzosertib at a dose of 105 milligrams per square meter (mg/m^2) intravenously on Day 2 and Day 5 of each 21-day cycle in combination with Topotecan at a dose of 1.25 mg/m^2 intravenously on Days 1 through 5 of each 21-day cycle in safety run-in part until disease progression or other criteria for study intervention discontinuation are met.

Reporting group title	Safety run-in Part (DL2)+Main Part: Berzosertib + Topotecan

Reporting group description:

Subjects received Berzosertib at a dose of 210 mg/m^2 intravenously on Day 2 and Day 5 of each 21-day cycle in combination with Topotecan at a dose of 1.25 mg/m^2 intravenously on Days 1 through 5 of each 21-day cycle in safety run-in part until disease progression or other criteria for study intervention discontinuation are met.

Reporting group values	Safety run-in Part (DL 1): Berzosertib + Topotecan	Safety run-in Part (DL2)+Main Part: Berzosertib + Topotecan	Total
Number of subjects	3	73	76
Age categorical Units: Subjects			
Age Continuous Units: Years			
arithmetic mean	51	63	
standard deviation	± 4	± 7.8	-
Sex: Female, Male Units: subjects			
Female	1	16	17
Male	2	57	59
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	3	19	22
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	1	1
White	0	42	42
More than one race	0	1	1
Unknown or Not Reported	0	10	10
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	1	1
Not Hispanic or Latino	3	63	66
Unknown or Not Reported	0	9	9

Subject analysis sets

Subject analysis set title	Safety run-in Part (DL 2): Berzosertib + Topotecan
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects received Berzosertib at a dose of 210 mg/m^2 intravenously on Day 2 and Day 5 of each 21-day cycle in combination with Topotecan at a dose of 1.25 mg/m^2 intravenously on Days 1 through 5 of each 21-day cycle in safety run-in part until disease progression or other criteria for study intervention discontinuation are met.

Reporting group values	Safety run-in Part (DL 2): Berzosertib + Topotecan		
Number of subjects	3		
Age categorical Units: Subjects			
Age Continuous Units: Years arithmetic mean standard deviation	 0 ±		
Sex: Female, Male Units: subjects			
Female Male			
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native Asian Native Hawaiian or Other Pacific Islander Black or African American White More than one race Unknown or Not Reported			
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino Not Hispanic or Latino Unknown or Not Reported			

End points

End points reporting groups

Reporting group title	Safety run-in Part (DL 1): Berzosertib + Topotecan

Reporting group description:

Subjects received Berzosertib at a dose of 105 milligrams per square meter (mg/m^2) intravenously on Day 2 and Day 5 of each 21-day cycle in combination with Topotecan at a dose of 1.25 mg/m^2 intravenously on Days 1 through 5 of each 21-day cycle in safety run-in part until disease progression or other criteria for study intervention discontinuation are met.

Reporting group title	Safety run-in Part (DL2)+Main Part: Berzosertib + Topotecan

Reporting group description:

Subjects received Berzosertib at a dose of 210 mg/m^2 intravenously on Day 2 and Day 5 of each 21-day cycle in combination with Topotecan at a dose of 1.25 mg/m^2 intravenously on Days 1 through 5 of each 21-day cycle in safety run-in part until disease progression or other criteria for study intervention discontinuation are met.

Subject analysis set title	Safety run-in Part (DL 2): Berzosertib + Topotecan
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects received Berzosertib at a dose of 210 mg/m^2 intravenously on Day 2 and Day 5 of each 21-day cycle in combination with Topotecan at a dose of 1.25 mg/m^2 intravenously on Days 1 through 5 of each 21-day cycle in safety run-in part until disease progression or other criteria for study intervention discontinuation are met.

Primary: Safety Run-in Part: Number of Subjects With Dose Limiting Toxicities (DLTs)

End point title	Safety Run-in Part: Number of Subjects With Dose Limiting Toxicities (DLTs)[1][2]

End point description:

DLT is defined as drug-related: Neutropenia Grade 4 for greater than (>) 7 days' duration; Febrile neutropenia (that is absolute neutrophil count less than (<) 1000 per millimeter cube (mm^3) with single temperature of > 38.3 degree Celsius or a sustained temperature of greater than or equal to (>=) 38 degree Celsius for more than 1 hour; Infection (documented clinically or microbiologically) with Grades 3 or 4 neutropenia; Thrombocytopenia >= Grade 3; Grade >= 3 non-hematological AEs. DLT analysis set: all subjects who were administered any dose of any study intervention in Safety Run-in Part in Japan and meet at least one of the following criteria: Received at least 80% of planned cumulative dose of study intervention during the DLT and completed the DLT period. The final decision on evaluability is made by the SMC; Experienced at least 1 DL T during the DLT period, regardless of the administered cumulative dose of study intervention and completion of the DLT period.

End point type	Primary

End point timeframe:

Up to Cycle 1 Day 21 (each cycle is of 21 days)

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: Only descriptive data was planned to be reported for this endpoint.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for safety run-in part only.

End point values	Safety run-in Part (DL 1): Berzosertib + Topotecan	Safety run-in Part (DL 2): Berzosertib + Topotecan		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3	3		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Main Part: Objective Response Rate According to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 as assessed by Independent Review Committee (IRC)

End point title	Main Part: Objective Response Rate According to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 as assessed by Independent Review Committee (IRC)[3][4]

End point description:

Objective response rate was defined as percentage of subjects with either a confirmed complete response (CR) or partial response (PR) from first administration of study treatment to first observation of progressive disease (PD). CR: Disappearance of all target and non-target lesions. PR: At least a 30 percent (%) decrease in the sum of diameters of target lesions, taking as reference the baseline sum of their diameters, and no unequivocal progression of non-target lesions. PD: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on the study, or unequivocal progression of non-target lesions, or appearance of any new lesion. Full Analysis Set (FAS) included all subjects who were administered at least 1 dose of berzosertib.

End point type	Primary

End point timeframe:

Time from first administration of study treatment up to 27.7 months

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: Only descriptive data was planned to be reported for this endpoint.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for main part only.

End point values	Safety run-in Part (DL2)+Main Part: Berzosertib +			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: percentage of subjects				
number (confidence interval 95%)	5.5 (1.5 to 13.4)			

Statistical analyses

No statistical analyses for this end point

Primary: Safety Run-in Part: Number of Subjects with Treatment-Emergent Adverse Events (TEAEs) and Treatment-Related TEAEs

End point title	Safety Run-in Part: Number of Subjects with Treatment-

	Emergent Adverse Events (TEAEs) and Treatment-Related TEAEs[5][6]

End point description:

An adverse event (AE) is defined as any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study intervention, whether considered related to the study intervention or not. A serious AE was an AE that resulted in any of the following outcomes: death; life threatening; persistent/significant disability/incapacity; initial or prolonged inpatient hospitalization; congenital anomaly/birth defect or was otherwise considered medically important. TEAEs were defined as events with onset date or worsening during the on-treatment period. TEAEs included both serious and non-serious TEAEs. Treatment-related TEAEs is defined as reasonably related to the study intervention. Safety (SAF) Analysis Set included all subjects who were administered at least 1 dose of berzosertib.

End point type	Primary

End point timeframe:

Time from first administration of study treatment up to 27.7 months

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: Only descriptive data was planned to be reported for this endpoint.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for safety run-in part only.

End point values	Safety run-in Part (DL 1): Berzosertib + Topotecan	Safety run-in Part (DL 2): Berzosertib + Topotecan		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3	3		
Units: subjects				
TEAEs	3	3		
Treatment Related TEAEs	3	3		

Statistical analyses

No statistical analyses for this end point

Primary: Safety Run-in Part: Number of Subjects with Clinically Significant Changes From Baseline in 12-Lead Electrocardiogram (ECG) Findings

End point title	Safety Run-in Part: Number of Subjects with Clinically Significant Changes From Baseline in 12-Lead Electrocardiogram (ECG) Findings[7][8]

End point description:

ECG parameters included PR interval, RR interval, QT interval, QRS duration, QTc intervals (derived using Fridericia's correction method) and heart rate. A 12-lead ECG was recorded with the subject in a supine position after a rest of at least 5 minutes using an ECG machine. Clinical significance was decided by investigator. Number of subjects with clinically significant changes from baseline in 12-Lead ECGs were reported. Safety (SAF) Analysis Set included all subjects who were administered at least 1 dose of berzosertib.

End point type	Primary

End point timeframe:

Time from first administration of study treatment up to 27.7 months

Notes:

[7] - 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: Only descriptive data was planned to be reported for this endpoint.

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for safety run-in part only.

End point values	Safety run-in Part (DL 1): Berzosertib + Topotecan	Safety run-in Part (DL 2): Berzosertib + Topotecan		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3	3		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Safety Run-in Part: Number of Subjects with Clinically Significant Changes From Baseline in Vital Signs

End point title	Safety Run-in Part: Number of Subjects with Clinically Significant Changes From Baseline in Vital Signs[9][10]

End point description:

Vital signs included body temperature, heart rate, systolic and diastolic blood pressure and respiration rate. Number of subjects with clinically significant changes from baseline in vital signs were reported. Clinical significance was decided by Investigator. Safety (SAF) Analysis Set included all subjects who were administered at least 1 dose of berzosertib.

End point type	Primary

End point timeframe:

Time from first administration of study treatment up to 27.7 months

Notes:

[9] - 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: Only descriptive data was planned to be reported for this endpoint.

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for safety run-in part only.

End point values	Safety run-in Part (DL 1): Berzosertib + Topotecan	Safety run-in Part (DL 2): Berzosertib + Topotecan		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3	3		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Safety Run-in Part: Number of Subjects With Clinically Significant Abnormalities in Laboratory Values Reported as Treatment Emergent Adverse

Events (TEAEs)

End point title	Safety Run-in Part: Number of Subjects With Clinically Significant Abnormalities in Laboratory Values Reported as Treatment Emergent Adverse Events (TEAEs)[11][12]

End point description:

The laboratory measurements included hematology and biochemistry. Number of participants with clinically significant abnormalities with Grade greater than or equals to (>=) 3 in laboratory values reported as TEAEs as per NCI-CTCAE, v5.0 graded from Grade 1 to 5. Grade 1: Mild; Grade 2: Moderate; Grade 3: Severe; Grade 4: Life-threatening; Grade 5: Death. Clinically Significance was decided by investigator. Safety (SAF) Analysis Set included all subjects who were administered at least 1 dose of berzosertib.

End point type	Primary

End point timeframe:

Time from first administration of study treatment up to 27.7 months

Notes:

[11] - 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: Only descriptive data was planned to be reported for this endpoint.

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for safety run-in part only.

End point values	Safety run-in Part (DL 1): Berzosertib + Topotecan	Safety run-in Part (DL 2): Berzosertib + Topotecan		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3	3		
Units: subjects				
Hematology	0	3		
Biochemistry	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Main Part: Duration of Response (DoR) according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 as Assessed by Independent Review Committee (IRC)

End point title	Main Part: Duration of Response (DoR) according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 as Assessed by Independent Review Committee (IRC)[13]

End point description:

DOR: the time from first documentation of objective response (Complete Response [CR] or Partial Response [PR]) to the date of first documentation of progression disease (PD) or death due to any cause, whichever occurred first. CR: Disappearance of all target and non-target lesions. PR: At least a 30 percent (%) decrease in the sum of diameters of target lesions, taking as reference the baseline sum of their diameters, and no unequivocal progression of non-target lesions. PD: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on the study, or unequivocal progression of non-target lesions, or appearance of any new lesion. FAS was used. Due to small number of subjects with a response, data was not summarized; however, individual subject data is reported for this endpoint. Here, "Number of Subjects Analyzed" = subjects who were evaluable for this endpoint and "n" = specific subjects evaluated in the arm.

End point type	Secondary

End point timeframe:

From first documented objective response to PD or death due to any cause, assessed up to 27.7 months

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for main part only.

End point values	Safety run-in Part (DL2)+Main Part: Berzosertib +			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: months				
number (not applicable)				
Subject 1: n = 1	8.5			
Subject 2: n = 1	2.8			
Subject 3: n = 1	2.6			
Subject 4: n = 1	2.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Main Part: Overall Survival (OS)

End point title	Main Part: Overall Survival (OS)[14]

End point description:

Overall survival is defined as the time from first administration of study treatment to the date of death. Full Analysis Set (FAS) included all subjects who were administered at least 1 dose of berzosertib.

End point type	Secondary

End point timeframe:

Time from first administration of study treatment to the date of death, assessed up to 27.7 months

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for main part only.

End point values	Safety run-in Part (DL2)+Main Part: Berzosertib +			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: months				
median (confidence interval 95%)	6.4 (4.2 to 7.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Main Part: Progression-free Survival (PFS) According to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 as Assessed by Independent Review Committee (IRC)

End point title	Main Part: Progression-free Survival (PFS) According to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 as Assessed by Independent Review Committee (IRC)[15]

End point description:

PFS was defined as the time is defined as the time from first administration of study treatment to the date of the first documentation of PD or death due to any cause, whichever occurs first. PD: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on the study, or unequivocal progression of non-target lesions, or appearance of any new lesion. Full Analysis Set (FAS) included all subjects who were administered at least 1 dose of berzosertib.

End point type	Secondary

End point timeframe:

Time from first administration of study treatment to the date of the first documentation of PD or death due to any cause, assessed up to 27.7 months

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for main part only.

End point values	Safety run-in Part (DL2)+Main Part: Berzosertib +			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: months				
median (confidence interval 95%)	2.2 (1.5 to 2.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Main Part: Number of Subjects with Treatment-Emergent Adverse Events (TEAEs) and Treatment-Related TEAEs

End point title	Main Part: Number of Subjects with Treatment-Emergent Adverse Events (TEAEs) and Treatment-Related TEAEs[16]

End point description:

An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical study participant, temporally associated with the use of study intervention, whether considered related to the study intervention or not. A serious AE was an AE that resulted in any of the following outcomes: death; life threatening; persistent/significant disability/incapacity; initial or prolonged inpatient hospitalization; congenital anomaly/birth defect or was otherwise considered medically important. TEAEs were defined as events with onset date or worsening during the on-treatment period. TEAEs included both serious and non-serious TEAEs. Treatment-related TEAEs is defined as reasonably related to the study intervention. Safety (SAF) Analysis Set included all subjects who were administered at least 1 dose of berzosertib.

End point type	Secondary

End point timeframe:

Time from first administration of study treatment up to 27.7 months

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for main part only.

End point values	Safety run-in Part (DL2)+Main Part: Berzosertib +			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: subjects				
TEAEs	73			
Treatment Related TEAEs	67			

Statistical analyses

No statistical analyses for this end point

Secondary: Main Part: Change From Baseline in Physical Functioning Measured by European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)

End point title	Main Part: Change From Baseline in Physical Functioning Measured by European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)[17]

End point description:

The EORTC QLQ-C30 is a subject completed 30 item questionnaire that is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, six single items and a global health status/QoL scale. For the physical functioning scale, subjects self-rated levels of difficulty in doing strenuous activities, taking a walk, how much they needed to stay in bed or a chair, or needed help with eating, dressing, bathing, using the toilet. The physical functioning scale had 4 possible scores (1=not at all, 2=a little, 3=quite a bit, 4=very much). Scores were averaged and transformed to 0 to 100. Higher scores indicate better functioning. A positive change from baseline indicates improvement in physical functioning. Full Analysis Set (FAS) included all subjects who were administered at least 1 dose of berzosertib. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (Cycle 1 Day 1), end of treatment (up to 62 weeks). Each cycle is of 21 days

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for main part only.

End point values	Safety run-in Part (DL2)+Main Part: Berzosertib +			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: score on a scale				

arithmetic mean (standard deviation)	-4.0 (± 20.67)			

Statistical analyses

No statistical analyses for this end point

Secondary: Main Part: Number of Subjects Who Improved, Worsened or Remained Stable in European Organization for the Research and Treatment of Cancer Quality of Life and Lung Cancer Specific Questionnaire (EORTC QLQ-LC13)

End point title	Main Part: Number of Subjects Who Improved, Worsened or Remained Stable in European Organization for the Research and Treatment of Cancer Quality of Life and Lung Cancer Specific Questionnaire (EORTC QLQ-LC13)[18]

End point description:

EORTC QLQ-LC13 is the lung cancer module of EORTC QLQ-C30 and includes questions specific to the disease associated symptoms (dyspnea, cough, hemoptysis, and site specific pain), treatment-related symptoms (sore mouth, dysphagia, neuropathy and alopecia), and analgesic use of lung cancer patients. The scale was transformed to a range of 0 to 100 using standard EORTC algorithm. Higher score indicates worse symptoms, and improvement was defined as a decrease of at least 10 points, worsening was defined as an increase of at least 10 points. All scales which had not improved nor worsened were considered stable. Full Analysis Set (FAS) included all subjects who were administered at least 1 dose of berzosertib. Here, "number of subjects analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (Cycle 1 Day 1), end of treatment (up to 62 weeks). Each cycle is of 21 days

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for main part only.

End point values	Safety run-in Part (DL2)+Main Part: Berzosertib +			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: subjects				
Improvement in Cough	6			
Stable in Cough	20			
Worsened in Cough	7			
Improvement in Chest Pain	7			
Stable in Chest Pain	22			
Worsened in Chest Pain	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Main Part: Number of Subjects with Clinically Significant Changes From Baseline in 12-Lead Electrocardiogram (ECG) Findings

End point title	Main Part: Number of Subjects with Clinically Significant Changes From Baseline in 12-Lead Electrocardiogram (ECG) Findings[19]

End point description:

ECG parameters included PR interval, RR interval, QT interval, QRS duration, QTc intervals (derived using Fridericia's correction method) and heart rate. A 12-lead ECG was recorded with the subject in a supine position after a rest of at least 5 minutes using an ECG machine. Clinical significance was decided by investigator. Number of subjects with clinically significant changes from baseline in 12-Lead ECGs were reported. Safety (SAF) Analysis Set included all subjects who were administered at least 1 dose of berzosertib.

End point type	Secondary

End point timeframe:

Time from first administration of study treatment up to 27.7 months

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for main part only.

End point values	Safety run-in Part (DL2)+Main Part: Berzosertib +			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Main Part: Number of Subjects With Clinically Significant Abnormalities in Laboratory Values Reported as Treatment Emergent Adverse Events (TEAEs)

End point title	Main Part: Number of Subjects With Clinically Significant Abnormalities in Laboratory Values Reported as Treatment Emergent Adverse Events (TEAEs)[20]

End point description:

The laboratory measurements included hematology and biochemistry. Number of subjects with clinically significant abnormalities with Grade greater than or equals to (>=) 3 in laboratory values reported as TEAEs as per NCI-CTCAE, v5.0 graded from Grade 1 to 5. Grade 1: Mild; Grade 2: Moderate; Grade 3: Severe; Grade 4: Life-threatening; Grade 5: Death. Clinically Significance was decided by investigator. Safety (SAF) Analysis Set included all subjects who were administered at least 1 dose of berzosertib.

End point type	Secondary

End point timeframe:

Time from first administration of study treatment up to 27.7 months

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for main part only.

End point values	Safety run-in Part (DL2)+Main Part: Berzosertib +			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: subjects				
Anemia	18			
Lymphocyte count decreased	17			
Neutrophil count decreased	28			
Platelet count decreased	26			
White blood cell decreased	19			
Alanine aminotransferase increased	2			
Alkaline phosphatase increased	1			
Aspartate transaminase increased	1			
Blood Bilirubin increased	3			
Hypokalemia	8			
Hyponatremia	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Main Part: Number of Subjects with Clinically Significant Changes From Baseline in Vital Signs

End point title	Main Part: Number of Subjects with Clinically Significant Changes From Baseline in Vital Signs[21]

End point description:

Vital signs included body temperature, heart rate, systolic and diastolic blood pressure and respiration rate. Number of subjects with clinically significant changes from baseline in vital signs were reported. Clinical significance was decided by Investigator. Safety (SAF) Analysis Set included all subjects who were administered at least 1 dose of berzosertib.

End point type	Secondary

End point timeframe:

Time from first administration of study treatment up to 27.7 months

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for main part only.

End point values	Safety run-in Part (DL2)+Main Part: Berzosertib +			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-in Part: Objective Response Rate According to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 as Assessed by Investigator

End point title	Safety Run-in Part: Objective Response Rate According to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 as Assessed by Investigator[22]

End point description:

Objective response rate was defined as percentage of subjects with either a confirmed complete response (CR) or partial response (PR) from first administration of study treatment to first observation of progressive disease (PD). CR: Disappearance of all target and non-target lesions. PR: At least a 30 percent (%) decrease in the sum of diameters of target lesions, taking as reference the baseline sum of their diameters, and no unequivocal progression of non-target lesions. PD: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on the study, or unequivocal progression of non-target lesions, or appearance of any new lesion. Full Analysis Set (FAS) included all subjects who were administered at least 1 dose of berzosertib.

End point type	Secondary

End point timeframe:

Time from first administration of study treatment up to 27.7 months

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for safety run-in part only.

End point values	Safety run-in Part (DL 1): Berzosertib + Topotecan	Safety run-in Part (DL 2): Berzosertib + Topotecan		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3	3		
Units: percentage of subjects				
number (confidence interval 95%)	33.3 (0.8 to 90.6)	0.0 (0.0 to 70.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-in Part: Duration of Response (DoR) according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 as Assessed by Investigator

End point title	Safety Run-in Part: Duration of Response (DoR) according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 as Assessed by Investigator[23]

End point description:

DOR was defined for subjects with objective response, as the time from first documentation of objective response (Complete Response [CR] or Partial Response [PR]) to the date of first documentation of progression disease (PD) or death due to any cause, whichever occurred first. CR: Disappearance of all target and non-target lesions. PR: At least a 30 percent (%) decrease in the sum of diameters of target lesions, taking as reference the baseline sum of their diameters, and no unequivocal progression of non-target lesions. PD: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on the study, or unequivocal progression of non-target lesions, or appearance of any new lesion. Full Analysis Set (FAS) included all subjects who were administered at least 1 dose of

berzosertib. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Time from first administration of study treatment up to 27.7 months

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for safety run-in part only.

End point values	Safety run-in Part (DL 1): Berzosertib + Topotecan	Safety run-in Part (DL 2): Berzosertib + Topotecan		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	1	0[24]		
Units: months				
number (not applicable)	7.2			

Notes:

[24] - None of the subjects have objective response.

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-in Part: Progression-free Survival (PFS) According to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 as Assessed by Investigator

End point title	Safety Run-in Part: Progression-free Survival (PFS) According to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 as Assessed by Investigator[25]

End point description:

PFS was defined as the time is defined as the time from first administration of study treatment to the date of the first documentation of PD or death due to any cause, whichever occurs first. PD: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on the study, or unequivocal progression of non-target lesions, or appearance of any new lesion. Full Analysis Set (FAS) included all subjects who were administered at least 1 dose of berzosertib.

End point type	Secondary

End point timeframe:

Time from first administration of study treatment to the date of the first documentation of PD or death due to any cause, assessed up to 27.7 months

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for safety run-in part only.

End point values	Safety run-in Part (DL 1): Berzosertib + Topotecan	Safety run-in Part (DL 2): Berzosertib + Topotecan		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3	3		
Units: months				
median (full range (min-max))	14.3 (4.0 to 14.3)	3.3 (1.2 to 8.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-in Part: Change From Baseline in Physical Functioning Measured by European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)

End point title	Safety Run-in Part: Change From Baseline in Physical Functioning Measured by European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)[26]

End point description:

The EORTC QLQ-C30 is a subject completed 30 item questionnaire that is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, six single items and a global health status/QoL scale. For the physical functioning scale, subjects self-rated levels of difficulty in doing strenuous activities, taking a walk, how much they needed to stay in bed or a chair, or needed help with eating, dressing, bathing, using the toilet. The physical functioning scale had 4 possible scores (1=not at all, 2=a little, 3=quite a bit, 4=very much). Scores were averaged and transformed to 0 to 100. Higher scores indicate better functioning. A positive change from baseline indicates improvement in physical functioning. As per changes in planned analysis, the endpoint related to quality of life for safety run-in part was not assessed.

End point type	Secondary

End point timeframe:

Baseline (Cycle 1 Day 1), end of treatment (up to 64 weeks). Each cycle is of 21 days

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for safety run-in part only.

End point values	Safety run-in Part (DL 1): Berzosertib + Topotecan	Safety run-in Part (DL 2): Berzosertib + Topotecan		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	0[27]	0[28]		
Units: score on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[27] - Data was not assessed.

[28] - Data was not assessed.

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-in Part: Change From Baseline in Cough, Dyspnea and Chest Pain Measured by European Organization for the Research and Treatment of Cancer Quality of Life and Lung Cancer Specific Questionnaire (EORTC QLQ-LC13)

End point title	Safety Run-in Part: Change From Baseline in Cough, Dyspnea and Chest Pain Measured by European Organization for the

	Research and Treatment of Cancer Quality of Life and Lung Cancer Specific Questionnaire (EORTC QLQ-LC13)[29]

End point description:

EORTC QLQ-LC13 consisted of 13 questions relating to disease symptoms specific to lung cancer and treatment side effects typical of treatment with chemotherapy and radiotherapy. The EORTC QLQ-LC13 module generated one multiple-item score assessing dyspnea and a series of single item scores assessing coughing, hemoptysis, sore mouth, dysphagia, peripheral neuropathy, alopecia, pain in chest, pain in arms or shoulder and pain in other parts. Score range: 0 (no burden of symptom domain or single symptom item) to 100 (highest burden of symptoms for symptom domains and single items). As per changes in planned analysis, the endpoint related to quality of life for safety run-in part was not assessed.

End point type	Secondary

End point timeframe:

Baseline (Cycle 1 Day 1), end of treatment (up to 64 weeks). Each cycle is of 21 days

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for safety run-in part only.

End point values	Safety run-in Part (DL 1): Berzosertib + Topotecan	Safety run-in Part (DL 2): Berzosertib + Topotecan		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	0[30]	0[31]		
Units: score on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[30] - Data was not assessed.

[31] - Data was not assessed.

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-in Part: Overall Survival (OS)

End point title	Safety Run-in Part: Overall Survival (OS)[32]

End point description:

Overall survival is defined as the time from first administration of study treatment to the date of death. Full Analysis Set (FAS) included all subjects who were administered at least 1 dose of berzosertib and "999" signifies that due to small number of events, median and upper limit of 95% Confidence Interval from Kaplan-Meier survival curves could not be derived.

End point type	Secondary

End point timeframe:

Time from first administration of study treatment to the date of death, assessed up to 27.7 months

Notes:

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for safety run-in part only.

End point values	Safety run-in Part (DL 1): Berzosertib + Topotecan	Safety run-in Part (DL 2): Berzosertib + Topotecan		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3	3		
Units: months				
median (confidence interval 95%)	999 (8.0 to 999)	15.3 (10.0 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-in Part: Area Under the Plasma Concentration-Time Curve from Time Zero Extrapolated to Infinity (AUC0-inf) of Berzosertib

End point title	Safety Run-in Part: Area Under the Plasma Concentration-Time Curve from Time Zero Extrapolated to Infinity (AUC0-inf) of Berzosertib[33]

End point description:

AUC0-inf was calculated by combining AUC0-t and AUCextra. AUCextra represents an extrapolated value obtained by Clast pred/Lambda z, where Clast pred was the calculated plasma concentration at the last sampling time point at which the measured plasma concentration is at or above the Lower Limit of quantification (LLOQ) and Lambda z was the apparent terminal rate constant determined by log-linear regression analysis of the measured plasma concentrations of the terminal log-linear phase. Pharmacokinetic Analysis Set (PKS) included all subjects who were administered at least 1 complete infusion of berzosertib in the Safety Run-in Part in Japan and for whom at least 1 quantifiable post-dose plasma concentration of berzosertib was obtained.

End point type	Secondary

End point timeframe:

Pre-dose, 1, 2, 3 and 7 hours post-dose on Cycle 1 Day 2 (each cycle is of 21 days)

Notes:

[33] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for safety run-in part only.

End point values	Safety run-in Part (DL 1): Berzosertib + Topotecan	Safety run-in Part (DL 2): Berzosertib + Topotecan		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3	3		
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)	2460 (± 1.4)	4310 (± 8.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-in Part: Dose Normalized Area Under the Plasma

Concentration-Time Curve from Time Zero to the Last Sampling Time (AUC0-tlast/Dose) of Berzosertib

End point title	Safety Run-in Part: Dose Normalized Area Under the Plasma Concentration-Time Curve from Time Zero to the Last Sampling Time (AUC0-tlast/Dose) of Berzosertib[34]

End point description:

AUC0-t/Dose was defined as AUC from time of dosing to the time of the last measurable concentration divided by dose. AUC0-t/dose was measured in hour*nanogram per milliliter per milligram (h*ng/mL/mg). Pharmacokinetic Analysis Set (PKS) included all subjects who were administered at least 1 complete infusion of berzosertib in the Safety Run-in Part in Japan and for whom at least 1 quantifiable post-dose plasma concentration of berzosertib was obtained.

End point type	Secondary

End point timeframe:

Pre-dose, 1, 2, 3 and 7 hours post-dose on Cycle 1 Day 2 (each cycle is of 21 days)

Notes:

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for safety run-in part only.

End point values	Safety run-in Part (DL 1): Berzosertib + Topotecan	Safety run-in Part (DL 2): Berzosertib + Topotecan		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3	3		
Units: h*ng/mL/mg				
geometric mean (geometric coefficient of variation)	12.2 (± 9.9)	11.1 (± 9.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-in Part: Area Under the Plasma Concentration-Time Curve from Time Zero to the Last Sampling Time (AUC0-tlast) of Berzosertib

End point title	Safety Run-in Part: Area Under the Plasma Concentration-Time Curve from Time Zero to the Last Sampling Time (AUC0-tlast) of Berzosertib[35]

End point description:

Area under the plasma concentration versus time curve from time zero to the last sampling time t at which the concentration was at or above the lower limit of quantification (LLOQ). AUC0-t was calculated according to the mixed log-linear trapezoidal rule. Pharmacokinetic Analysis Set (PKS) included all subjects who were administered at least 1 complete infusion of berzosertib in the Safety Run-in Part in Japan and for whom at least 1 quantifiable post-dose plasma concentration of berzosertib was obtained.

End point type	Secondary

End point timeframe:

Pre-dose, 1, 2, 3 and 7 hours post-dose on Cycle 1 Day 2 (each cycle is of 21 days)

Notes:

[35] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for safety run-in part only.

End point values	Safety run-in Part (DL 1): Berzosertib + Topotecan	Safety run-in Part (DL 2): Berzosertib + Topotecan		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3	3		
Units: hour*nanogram per milliliter (h*ng/mL)				
geometric mean (geometric coefficient of variation)	2330 (± 0.8)	4090 (± 7.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Main Part: Change From Baseline in Health State as Measured by Visual Analogue Scale (VAS) Component of European Quality of Life 5-dimensions 5 Level Scale (EQ-5D-5L)

End point title	Main Part: Change From Baseline in Health State as Measured by Visual Analogue Scale (VAS) Component of European Quality of Life 5-dimensions 5 Level Scale (EQ-5D-5L)[36]

End point description:

EQ-5D-5L is comprised of the following 5 participant-reported dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The responses are used to derive overall score using a visual analog scale (VAS) that ranged from 0 to 100, where 0 is the worst health you can imagine and 100 is the best health you can imagine. Full Analysis Set (FAS) included all subjects who were administered at least 1 dose of berzosertib. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (Cycle 1 Day 1), end of treatment (up to 62 weeks). Each cycle is of 21 days

Notes:

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for main part only.

End point values	Safety run-in Part (DL2)+Main Part: Berzosertib +			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: score on a scale				
arithmetic mean (standard deviation)	-6.3 (± 19.67)			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-in Part: Area Under the Plasma Concentration-Time Curve from Time Zero to 48 Hours (AUC0-48h) of Berzosertib

End point title	Safety Run-in Part: Area Under the Plasma Concentration-Time Curve from Time Zero to 48 Hours (AUC0-48h) of Berzosertib[37]

End point description:

Area under the concentration-time curve from pre-dose (time 0) to 48 hours post-dose calculated using the linear-log trapezoidal rule. Pharmacokinetic Analysis Set (PKS) included all subjects who were administered at least 1 complete infusion of berzosertib in the Safety Run-in Part in Japan and for whom at least 1 quantifiable post-dose plasma concentration of berzosertib was obtained.

End point type	Secondary

End point timeframe:

Pre-dose, 1, 2, 3 and 7 hours post-dose on Cycle 1 Day 2 (each cycle is of 21 days)

Notes:

[37] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for safety run-in part only.

End point values	Safety run-in Part (DL 1): Berzosertib + Topotecan	Safety run-in Part (DL 2): Berzosertib + Topotecan		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3	3		
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)	2160 (± 2.0)	3790 (± 5.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-in Part: Dose Normalized Area Under the Plasma Concentration-Time Curve from Time Zero Extrapolated to Infinity (AUC0-inf/Dose) of Berzosertib

End point title	Safety Run-in Part: Dose Normalized Area Under the Plasma Concentration-Time Curve from Time Zero Extrapolated to Infinity (AUC0-inf/Dose) of Berzosertib[38]

End point description:

AUC0-inf/Dose was defined as AUC extrapolated to infinity divided by dose. Pharmacokinetic Analysis Set (PKS) included all subjects who were administered at least 1 complete infusion of berzosertib in the Safety Run-in Part in Japan and for whom at least 1 quantifiable post-dose plasma concentration of berzosertib was obtained.

End point type	Secondary

End point timeframe:

Pre-dose, 1, 2, 3 and 7 hours post-dose on Cycle 1 Day 2 (each cycle is of 21 days)

Notes:

[38] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for safety run-in part only.

End point values	Safety run-in Part (DL 1): Berzosertib + Topotecan	Safety run-in Part (DL 2): Berzosertib + Topotecan		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3	3		
Units: h*ng/mL/mg				
geometric mean (geometric coefficient of variation)	12.8 (± 11.0)	11.7 (± 11.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-in Part: Area Under the Plasma Concentration-Time Curve from Time Zero to 72 Hours (AUC0-72h) of Berzosertib

End point title	Safety Run-in Part: Area Under the Plasma Concentration-Time Curve from Time Zero to 72 Hours (AUC0-72h) of Berzosertib[39]

End point description:

Area under the concentration-time curve from pre-dose (time 0) to 72 hours post-dose calculated using the linear-log trapezoidal rule

End point type	Secondary

End point timeframe:

Pre-dose, 1, 2, 3 and 7 hours post-dose on Cycle 1 Day 2 (each cycle is of 21 days)

Notes:

[39] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for safety run-in part only.

End point values	Safety run-in Part (DL 1): Berzosertib + Topotecan	Safety run-in Part (DL 2): Berzosertib + Topotecan		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3	3		
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)	2340 (± 0.8)	4110 (± 7.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-in Part: Dose Normalized Area Under the Plasma Concentration-Time Curve from Time Zero to 72 Hours (AUC0-72h/Dose) of Berzosertib

End point title	Safety Run-in Part: Dose Normalized Area Under the Plasma Concentration-Time Curve from Time Zero to 72 Hours (AUC0-72h/Dose) of Berzosertib[40]

End point description:

AUC0-72 hour/Dose was defined as AUC from time of dosing to 72 hours divided by dose.

End point type	Secondary

End point timeframe:

Pre-dose, 1, 2, 3 and 7 hours post-dose on Cycle 1 Day 2 (each cycle is of 21 days)

Notes:

[40] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for safety run-in part only.

End point values	Safety run-in Part (DL 1): Berzosertib + Topotecan	Safety run-in Part (DL 2): Berzosertib + Topotecan		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3	3		
Units: h*ng/mL/mg				
geometric mean (geometric coefficient of variation)	12.2 (± 9.9)	11.2 (± 9.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-in Part: Dose Normalized Area Under the Plasma Concentration-Time Curve from Time Zero to 48 Hours (AUC0-48h/Dose) of Berzosertib

End point title	Safety Run-in Part: Dose Normalized Area Under the Plasma Concentration-Time Curve from Time Zero to 48 Hours (AUC0-48h/Dose) of Berzosertib[41]

End point description:

AUC0-48 hour/Dose was defined as AUC from time of dosing to 48 hours divided by dose.
Pharmacokinetic Analysis Set (PKS) included all subjects who were administered at least 1 complete infusion of berzosertib in the Safety Run-in Part in Japan and for whom at least 1 quantifiable post-dose plasma concentration of berzosertib was obtained.

End point type	Secondary

End point timeframe:

Pre-dose, 1, 2, 3 and 7 hours post-dose on Cycle 1 Day 2 (each cycle is of 21 days)

Notes:

[41] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for safety run-in part only.

End point values	Safety run-in Part (DL 1): Berzosertib + Topotecan	Safety run-in Part (DL 2): Berzosertib + Topotecan		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3	3		
Units: h*ng/mL/mg				
geometric mean (geometric coefficient of variation)	11.3 (± 9.7)	10.3 (± 8.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-in Part: Maximum Observed Plasma Concentration (Cmax) of Berzosertib

End point title	Safety Run-in Part: Maximum Observed Plasma Concentration (Cmax) of Berzosertib[42]

End point description:

Cmax was obtained directly from the plasma concentration versus time curve.

End point type	Secondary

End point timeframe:

Pre-dose, 1, 2, 3 and 7 hours post-dose on Cycle 1 Day 2 (each cycle is of 21 days)

Notes:

[42] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for safety run-in part only.

End point values	Safety run-in Part (DL 1): Berzosertib + Topotecan	Safety run-in Part (DL 2): Berzosertib + Topotecan		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3	3		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	259 (± 23.5)	446 (± 17.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-in Part: Dose Normalized Maximum Observed Plasma Concentration (Cmax/Dose) of Berzosertib

End point title	Safety Run-in Part: Dose Normalized Maximum Observed Plasma Concentration (Cmax/Dose) of Berzosertib[43]

End point description:

Dose normalized was calculated as Cmax obtained directly from the concentration versus time curve divided by dose. Cmax/dose was measured in nanogram per milliliter per milligram (ng/mL/mg).

End point type	Secondary

End point timeframe:

Pre-dose, 1, 2, 3 and 7 hours post-dose on Cycle 1 Day 2 (each cycle is of 21 days)

Notes:

[43] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for safety run-in part only.

End point values	Safety run-in Part (DL 1): Berzosertib + Topotecan	Safety run-in Part (DL 2): Berzosertib + Topotecan		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3	3		
Units: ng/mL/mg				
geometric mean (geometric coefficient of variation)	1.35 (± 27.5)	1.21 (± 24.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-in Part: Plasma Observed Concentration at the End of the Infusion (Ceoi) of Berzosertib

End point title	Safety Run-in Part: Plasma Observed Concentration at the End of the Infusion (Ceoi) of Berzosertib[44]

End point description:

Ceoi was the observed concentration at the end of the infusion period. This was taken directly from the observed Berzosetib concentration-time data. Pharmacokinetic Analysis Set (PKS) included all subjects who were administered at least 1 complete infusion of berzosertib in the Safety Run-in Part in Japan and for whom at least 1 quantifiable post-dose plasma concentration of berzosertib was obtained.

End point type	Secondary

End point timeframe:

Pre-dose, 1, 2, 3 and 7 hours post-dose on Cycle 1 Day 2 and Cycle 1 Day 5 (each cycle is of 21 days)

Notes:

[44] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for safety run-in part only.

End point values	Safety run-in Part (DL 1): Berzosertib + Topotecan	Safety run-in Part (DL 2): Berzosertib + Topotecan		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3	3		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 2	259 (± 23.5)	446 (± 17.7)		
Cycle 1 Day 5	341 (± 23.1)	500 (± 42.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-in Part: Apparent Total Body Clearance (CL) of Berzosertib

End point title	Safety Run-in Part: Apparent Total Body Clearance (CL) of Berzosertib[45]

End point description:

CL was a measure of the rate at which a drug was metabolized or eliminated by normal biological processes. CL was calculated as Dose/AUC0-inf, where AUC0-inf was estimated by determining the total area under the curve of the concentration versus time curve extrapolated to infinity. AUC0-inf was calculated as AUC0-t + Clast pred/Lambda Z, where Clast pred was the calculated plasma concentration at the last sampling time point at which the measured plasma concentration was at or above the lower limit of quantification (LLQ) and Lambda Z was the apparent terminal rate constant determined from the terminal slope of the log-transformed plasma concentration curve. Pharmacokinetic Analysis Set (PKS) included all subjects who were administered at least 1 complete infusion of berzosertib in the Safety Run-in Part in Japan and for whom at least 1 quantifiable post-dose plasma concentration of berzosertib was obtained.

End point type	Secondary

End point timeframe:

Pre-dose, 1, 2, 3 and 7 hours post-dose on Cycle 1 Day 2 (each cycle is of 21 days)

Notes:

[45] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for safety run-in part only.

End point values	Safety run-in Part (DL 1): Berzosertib + Topotecan	Safety run-in Part (DL 2): Berzosertib + Topotecan		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3	3		
Units: liter per hour				
geometric mean (geometric coefficient of variation)	77.8 (± 11.0)	85.4 (± 11.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-in Part: Plasma Observed Concentration Immediately Before Next Dosing (Ctrough) of Berzosertib

End point title	Safety Run-in Part: Plasma Observed Concentration Immediately Before Next Dosing (Ctrough) of Berzosertib[46]

End point description:

Ctrough was the plasma concentration observed immediately before next dosing. Pharmacokinetic Analysis Set (PKS) included all subjects who were administered at least 1 complete infusion of berzosertib in the Safety Run-in Part in Japan and for whom at least 1 quantifiable post-dose plasma concentration of berzosertib was obtained.

End point type	Secondary

End point timeframe:

Pre-dose, 1, 2, 3 and 7 hours post-dose on Cycle 1 Day 5 (each cycle is of 21 days)

Notes:

[46] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The data was planned to be reported for safety run-in part only.

End point values	Safety run-in Part (DL 1): Berzosertib + Topotecan	Safety run-in Part (DL 2): Berzosertib + Topotecan		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3	3		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	4.84 (± 22.3)	8.57 (± 23.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-in Part: Accumulation Ratio for Maximum Observed Plasma Concentration [Racc(Cmax)] of Berzosertib

End point title	Safety Run-in Part: Accumulation Ratio for Maximum Observed Plasma Concentration [Racc(Cmax)] of Berzosertib[47]

End point description:

The accumulation ratio is to assess the increase in maximum concentration with multiple dosing. Racc(Cmax) = (Cmax after multiple dose)/ (Cmax after single dose). Pharmacokinetic Analysis Set (PKS) included all subjects who were administered at least 1 complete infusion of berzosertib in the Safety Run-in Part in Japan and for whom at least 1 quantifiable post-dose plasma concentration of berzosertib was obtained.

End point type	Secondary

End point timeframe:

Pre-dose, 1, 2, 3 and 7 hours post-dose on Cycle 1 Day 2 (each cycle is of 21 days)

Notes:

[47] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for safety run-in part only.

End point values	Safety run-in Part (DL 1): Berzosertib + Topotecan	Safety run-in Part (DL 2): Berzosertib + Topotecan		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3	3		
Units: ratio				
geometric mean (geometric coefficient of variation)	1.32 (± 16.3)	1.12 (± 24.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-in Part: Last Sampling Time (tlast) of Berzosertib

End point title	Safety Run-in Part: Last Sampling Time (tlast) of Berzosertib[48]

End point description:

tlast is defined as the last sampling time at which the concentration is at or above the lower limit of quantification. Pharmacokinetic Analysis Set (PKS) included all subjects who were administered at least 1 complete infusion of berzosertib in the Safety Run-in Part in Japan and for whom at least 1 quantifiable post-dose plasma concentration of berzosertib was obtained.

End point type	Secondary

End point timeframe:

Pre-dose, 1, 2, 3 and 7 hours post-dose on Cycle 1 Day 2 (each cycle is of 21 days)

Notes:

[48] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for safety run-in part only.

End point values	Safety run-in Part (DL 1): Berzosertib + Topotecan	Safety run-in Part (DL 2): Berzosertib + Topotecan		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3	3		
Units: hours				
geometric mean (geometric coefficient of variation)	70.4 (± 0.3)	70.6 (± 0.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-in Part: Apparent Terminal Half-life (t1/2) of Berzosertib

End point title	Safety Run-in Part: Apparent Terminal Half-life (t1/2) of Berzosertib[49]

End point description:

T1/2 was defined as the time required for the concentration or amount of drug in the body to be reduced by one-half. T1/2 was calculated by natural log 2 divided by Lambda z. Lambda z was determined from the terminal slope of the log-transformed plasma concentration curve using linear regression method. Pharmacokinetic Analysis Set (PKS) included all subjects who were administered at least 1 complete infusion of berzosertib in the Safety Run-in Part in Japan and for whom at least 1 quantifiable post-dose plasma concentration of berzosertib was obtained.

End point type	Secondary

End point timeframe:

Pre-dose, 1, 2, 3 and 7 hours post-dose on Cycle 1 Day 2 (each cycle is of 21 days)

Notes:

[49] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for safety run-in part only.

End point values	Safety run-in Part (DL 1): Berzosertib + Topotecan	Safety run-in Part (DL 2): Berzosertib + Topotecan		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3	3		
Units: hours				
geometric mean (geometric coefficient of variation)	17.6 (± 10.1)	17.0 (± 13.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-in Part: Time to Reach the Maximum Observed Plasma Concentration (tmax) of Berzosertib

End point title	Safety Run-in Part: Time to Reach the Maximum Observed Plasma Concentration (tmax) of Berzosertib[50]

End point description:

Tmax was obtained directly from the plasma concentration versus time curve. Pharmacokinetic Analysis Set (PKS) included all subjects who were administered at least 1 complete infusion of berzosertib in the Safety Run-in Part in Japan and for whom at least 1 quantifiable post-dose plasma concentration of berzosertib was obtained.

End point type	Secondary

End point timeframe:

Pre-dose, 1, 2, 3 and 7 hours post-dose on Cycle 1 Day 2 (each cycle is of 21 days)

Notes:

[50] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for safety run-in part only.

End point values	Safety run-in Part (DL 1): Berzosertib + Topotecan	Safety run-in Part (DL 2): Berzosertib + Topotecan		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3	3		
Units: hours				
median (full range (min-max))	1.17 (1.13 to 1.2)	1.20 (1.17 to 1.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-in Part: Apparent Volume of Distribution During Terminal Phase (Vz) of Berzosertib

End point title	Safety Run-in Part: Apparent Volume of Distribution During Terminal Phase (Vz) of Berzosertib[51]

End point description:

Vz: the distribution of a study drug between plasma and the rest of the body after oral dosing. For single dose Vz = Dose/(AUC0-inf*Lambda Z), where AUC0-inf = (AUC0-t + Clast pred/Lambda Z). Clastpred was the calculated plasma concentration at the last sampling time point at which the measured plasma concentration was at or above the LLOQ and Lambda Z = the apparent terminal rate constant determined from the terminal slope of the log-transformed plasma concentration curve. Pharmacokinetic Analysis Set (PKS) included all subjects who were administered at least 1 complete infusion of berzosertib in the Safety Run-in Part in Japan and for whom at least 1 quantifiable post-dose plasma concentration of berzosertib was obtained.

End point type	Secondary

End point timeframe:

Pre-dose, 1, 2, 3 and 7 hours post-dose on Cycle 1 Day 2 (each cycle is of 21 days)

Notes:

[51] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for safety run-in part only.

End point values	Safety run-in Part (DL 1): Berzosertib + Topotecan	Safety run-in Part (DL 2): Berzosertib + Topotecan		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3	3		
Units: liters				
geometric mean (geometric coefficient of variation)	1980 (± 4.2)	2100 (± 5.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Run-in Part: Change From Baseline in Health State as Measured by Visual Analogue Scale (VAS) Component of European Quality of Life 5-dimensions 5 Level Scale (EQ-5D-5L)

End point title	Safety Run-in Part: Change From Baseline in Health State as Measured by Visual Analogue Scale (VAS) Component of European Quality of Life 5-dimensions 5 Level Scale (EQ-5D-5L)[52]

End point description:

EQ-5D-5L is comprised of the following 5 participant-reported dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The responses are used to derive overall score using a visual analog scale (VAS) that ranged from 0 to 100, where 0 is the worst health you can imagine and 100 is the best health you can imagine. As per changes in planned analysis, the endpoint related to quality of life for safety run-in part was not assessed.

End point type	Secondary

End point timeframe:

Baseline (Cycle 1 Day 1), end of treatment (up to 64 weeks). Each cycle is of 21 days

Notes:

[52] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The data was planned to be reported for safety run-in part only.

End point values	Safety run-in Part (DL 1): Berzosertib + Topotecan	Safety run-in Part (DL 2): Berzosertib + Topotecan		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	0[53]	0[54]		
Units: score on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[53] - Data was not assessed.

[54] - Data was not assessed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Time from first administration of study treatment up to 27.7 months	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups	
Reporting group title	Safety run-in Part (DL2) + Main Part: Berzosertib + Topotecan

Reporting group description:

Subjects received Berzosertib at a dose of 210 mg/m^2 intravenously on Day 2 and Day 5 of each 21-day cycle in combination with Topotecan at a dose of 1.25 mg/m^2 intravenously on Days 1 through 5 of each 21-day cycle in safety run-in part until disease progression or other criteria for study intervention discontinuation are met.

Reporting group title	Safety run-in Part (DL 1): Berzosertib + Topotecan

Reporting group description:

Subjects received Berzosertib at a dose of 105 milligrams per square meter (mg/m^2) intravenously on Day 2 and Day 5 of each 21-day cycle in combination with Topotecan at a dose of 1.25 mg/m^2 intravenously on Days 1 through 5 of each 21-day cycle in safety run-in part until disease progression or other criteria for study intervention discontinuation are met.

Serious adverse events	Safety run-in Part (DL2) + Main Part: Berzosertib + Topotecan	Safety run-in Part (DL 1): Berzosertib + Topotecan	
Total subjects affected by serious adverse events			
subjects affected / exposed	31 / 73 (42.47%)	0 / 3 (0.00%)	
number of deaths (all causes)	63	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to central nervous system			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General physical health deterioration			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Asthenia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	6 / 73 (8.22%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 7	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute respiratory distress syndrome			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemoptysis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Neutrophil count decreased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 73 (2.74%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	2 / 73 (2.74%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Spinal compression fracture			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Seizure			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	3 / 73 (4.11%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelosuppression			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	4 / 73 (5.48%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	4 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	4 / 73 (5.48%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vestibular disorder			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 73 (2.74%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Liver injury			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	2 / 73 (2.74%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	4 / 73 (5.48%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
COVID-19 pneumonia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	3 / 73 (4.11%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung abscess			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal sepsis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Serratia sepsis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 73 (2.74%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumonia pneumococcal			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	

Pneumonia bacterial			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypoglycaemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Safety run-in Part (DL2) + Main Part: Berzosertib + Topotecan	Safety run-in Part (DL 1): Berzosertib + Topotecan	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	70 / 73 (95.89%)	3 / 3 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Cancer pain			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Metastases to central nervous system			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Orthostatic hypotension			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Hypertension			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	4 / 73 (5.48%)	0 / 3 (0.00%)	
occurrences (all)	4	0	
Hypotension			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 73 (2.74%)	0 / 3 (0.00%)	
occurrences (all)	3	0	
Deep vein thrombosis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Pallor			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 73 (2.74%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Phlebitis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	6	0	
General disorders and administration site conditions			
Gait disturbance			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Asthenia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	18 / 73 (24.66%)	0 / 3 (0.00%)	
occurrences (all)	31	0	
Chest discomfort			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	2 / 73 (2.74%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Chest pain			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Chills			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 73 (2.74%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Face oedema			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Fatigue			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	10 / 73 (13.70%)	1 / 3 (33.33%)	
occurrences (all)	12	1	
Generalised oedema			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Influenza like illness			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Injection site pruritus			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Localised oedema			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 73 (2.74%)	0 / 3 (0.00%)	
occurrences (all)	2	0	

Malaise			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	4 / 73 (5.48%)	0 / 3 (0.00%)	
occurrences (all)	4	0	
Mucosal inflammation			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	4 / 73 (5.48%)	0 / 3 (0.00%)	
occurrences (all)	4	0	
Oedema peripheral			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	3 / 73 (4.11%)	0 / 3 (0.00%)	
occurrences (all)	3	0	
Pain			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 73 (2.74%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Pyrexia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	5 / 73 (6.85%)	0 / 3 (0.00%)	
occurrences (all)	9	0	
Secretion discharge			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Swelling face			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Hyperthermia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			

Hypersensitivity			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Pleuritic pain			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Pleural effusion			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 73 (2.74%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Pneumothorax			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Aphonia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Cough			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	7 / 73 (9.59%)	0 / 3 (0.00%)	
occurrences (all)	8	0	
Dysphonia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 73 (2.74%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Dyspnoea			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	11 / 73 (15.07%)	0 / 3 (0.00%)	
occurrences (all)	14	0	
Dyspnoea exertional			
alternative dictionary used:			

MedDRA 26.0			
subjects affected / exposed	3 / 73 (4.11%)	0 / 3 (0.00%)	
occurrences (all)	3	0	
Dyspnoea paroxysmal nocturnal			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Epistaxis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	6 / 73 (8.22%)	0 / 3 (0.00%)	
occurrences (all)	6	0	
Haemoptysis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	4 / 73 (5.48%)	0 / 3 (0.00%)	
occurrences (all)	4	0	
Hypoxia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Nasal congestion			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Productive cough			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 73 (2.74%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Pulmonary embolism			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Sputum discoloured			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Wheezing			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Anxiety			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 73 (2.74%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Confusional state			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Depression			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Insomnia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	5 / 73 (6.85%)	0 / 3 (0.00%)	
occurrences (all)	5	0	
Product issues			
Device malfunction			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Investigations			
Activated partial thromboplastin time prolonged			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 73 (2.74%)	0 / 3 (0.00%)	
occurrences (all)	4	0	
Alanine aminotransferase increased			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	7 / 73 (9.59%)	0 / 3 (0.00%)		
occurrences (all)	7	0		
C-reactive protein increased				
alternative dictionary used: MedDRA 26.0				
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)		
occurrences (all)	1	0		
Aspartate aminotransferase decreased				
alternative dictionary used: MedDRA 26.0				
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)		
occurrences (all)	1	0		
Aspartate aminotransferase increased				
alternative dictionary used: MedDRA 26.0				
subjects affected / exposed	7 / 73 (9.59%)	0 / 3 (0.00%)		
occurrences (all)	7	0		
Blood albumin decreased				
alternative dictionary used: MedDRA 26.0				
subjects affected / exposed	2 / 73 (2.74%)	0 / 3 (0.00%)		
occurrences (all)	2	0		
Blood alkaline phosphatase increased				
alternative dictionary used: MedDRA 26.0				
subjects affected / exposed	6 / 73 (8.22%)	0 / 3 (0.00%)		
occurrences (all)	8	0		
Blood bilirubin increased				
alternative dictionary used: MedDRA 26.0				
subjects affected / exposed	2 / 73 (2.74%)	0 / 3 (0.00%)		
occurrences (all)	2	0		
Blood cholesterol increased				
alternative dictionary used: MedDRA 26.0				
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)		
occurrences (all)	1	0		
Blood creatinine increased				
alternative dictionary used: MedDRA 26.0				

subjects affected / exposed	3 / 73 (4.11%)	0 / 3 (0.00%)	
occurrences (all)	4	0	
Blood glucose increased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Blood lactate dehydrogenase increased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 73 (2.74%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Blood lactic acid increased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Blood magnesium decreased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 73 (2.74%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Blood phosphorus decreased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Blood sodium decreased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Blood urea increased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Amylase increased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 73 (2.74%)	0 / 3 (0.00%)	
occurrences (all)	4	0	

CD4/CD8 ratio decreased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Electrocardiogram QT prolonged			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Gamma-glutamyltransferase increased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	4 / 73 (5.48%)	0 / 3 (0.00%)	
occurrences (all)	5	0	
Haemoglobin decreased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 73 (2.74%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Lipase increased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	6 / 73 (8.22%)	1 / 3 (33.33%)	
occurrences (all)	8	1	
Lymphocyte count decreased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	9 / 73 (12.33%)	0 / 3 (0.00%)	
occurrences (all)	21	0	
Neutrophil count decreased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	12 / 73 (16.44%)	0 / 3 (0.00%)	
occurrences (all)	18	0	
Platelet count decreased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	22 / 73 (30.14%)	0 / 3 (0.00%)	
occurrences (all)	45	0	
Platelet count increased			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Urine output decreased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Weight decreased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	6 / 73 (8.22%)	0 / 3 (0.00%)	
occurrences (all)	8	0	
White blood cell count decreased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	13 / 73 (17.81%)	0 / 3 (0.00%)	
occurrences (all)	22	0	
Creatinine renal clearance decreased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Compression fracture			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Fall			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Infusion related reaction			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 73 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Radiation oesophagitis			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Radiation pneumonitis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Spinal fracture			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Atrial fibrillation			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 73 (2.74%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Arrhythmia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Cardiac failure			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Sinus tachycardia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Tachycardia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	3 / 73 (4.11%)	0 / 3 (0.00%)	
occurrences (all)	5	0	
Nervous system disorders			
Disturbance in attention			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Dizziness			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	5 / 73 (6.85%)	0 / 3 (0.00%)	
occurrences (all)	6	0	
Dysgeusia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	3 / 73 (4.11%)	1 / 3 (33.33%)	
occurrences (all)	3	1	
Headache			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	7 / 73 (9.59%)	0 / 3 (0.00%)	
occurrences (all)	8	0	
Hemianopia homonymous			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Hemiparesis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Memory impairment			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Neuropathy peripheral			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 73 (2.74%)	1 / 3 (33.33%)	
occurrences (all)	2	1	
Paraesthesia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 73 (2.74%)	0 / 3 (0.00%)	
occurrences (all)	2	0	

Presyncope			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Seizure			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Transient aphasia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Tremor			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	48 / 73 (65.75%)	3 / 3 (100.00%)	
occurrences (all)	89	6	
Coagulopathy			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Febrile neutropenia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Leukopenia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 73 (2.74%)	1 / 3 (33.33%)	
occurrences (all)	2	1	
Myelosuppression			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Thrombocytopenia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	26 / 73 (35.62%)	3 / 3 (100.00%)	
occurrences (all)	45	3	
Thrombocytosis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Neutropenia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	23 / 73 (31.51%)	1 / 3 (33.33%)	
occurrences (all)	37	1	
Ear and labyrinth disorders			
Vestibular disorder			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Diplopia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Eye discharge			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Macular oedema			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Conjunctival pallor			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Gastrooesophageal reflux disease			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	3 / 73 (4.11%)	0 / 3 (0.00%)	
occurrences (all)	5	0	
Abdominal discomfort			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Abdominal distension			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Abdominal pain			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	3 / 73 (4.11%)	0 / 3 (0.00%)	
occurrences (all)	3	0	
Abdominal pain upper			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 73 (2.74%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Constipation			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	13 / 73 (17.81%)	1 / 3 (33.33%)	
occurrences (all)	16	1	
Diarrhoea			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	11 / 73 (15.07%)	0 / 3 (0.00%)	
occurrences (all)	12	0	
Dry mouth			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Dyspepsia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Dysphagia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Flatulence			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Gingival pain			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Haemorrhoids thrombosed			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Lip dry			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Lower gastrointestinal haemorrhage			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Nausea			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	20 / 73 (27.40%)	1 / 3 (33.33%)	
occurrences (all)	29	2	

Oral disorder			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Tooth loss			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Toothache			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 73 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	2	
Vomiting			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	10 / 73 (13.70%)	0 / 3 (0.00%)	
occurrences (all)	11	0	
Haemorrhoids			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Cholestasis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Hepatic pain			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Hyperbilirubinaemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Liver injury			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	3 / 73 (4.11%)	0 / 3 (0.00%)	
occurrences (all)	3	0	
Skin and subcutaneous tissue disorders			
Alopecia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	3 / 73 (4.11%)	2 / 3 (66.67%)	
occurrences (all)	3	2	
Decubitus ulcer			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Nail disorder			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Night sweats			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 73 (2.74%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Petechiae			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Photosensitivity reaction			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Pruritus			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 73 (2.74%)	0 / 3 (0.00%)	
occurrences (all)	3	0	
Rash			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Rash pruritic			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Skin lesion			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Acute kidney injury			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Choluria			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Nephrolithiasis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Renal impairment			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Hypothyroidism			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Immune-mediated hypothyroidism			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 73 (2.74%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Back pain			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 73 (2.74%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Muscle spasms			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 73 (2.74%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Muscular weakness			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Bronchiolitis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Bronchitis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Candida infection			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Diverticulitis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	5	0	
Herpes zoster reactivation			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Pneumonia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	8 / 73 (10.96%)	0 / 3 (0.00%)	
occurrences (all)	9	0	
Respiratory tract infection			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Sinusitis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 73 (2.74%)	0 / 3 (0.00%)	
occurrences (all)	3	0	
Wound infection			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	

COVID-19			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	4 / 73 (5.48%)	1 / 3 (33.33%)	
occurrences (all)	4	1	
Metabolism and nutrition disorders			
Hyperkalaemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Decreased appetite			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	18 / 73 (24.66%)	0 / 3 (0.00%)	
occurrences (all)	22	0	
Electrolyte imbalance			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Gout			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Hyperglycaemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	4 / 73 (5.48%)	0 / 3 (0.00%)	
occurrences (all)	4	0	
Hypoalbuminaemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	7 / 73 (9.59%)	0 / 3 (0.00%)	
occurrences (all)	8	0	
Hypochloraemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Hypokalaemia			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	8 / 73 (10.96%)	0 / 3 (0.00%)	
occurrences (all)	9	0	
Hypomagnesaemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	4 / 73 (5.48%)	0 / 3 (0.00%)	
occurrences (all)	5	0	
Hyponatraemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	5 / 73 (6.85%)	0 / 3 (0.00%)	
occurrences (all)	11	0	
Hypophosphataemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	3 / 73 (4.11%)	0 / 3 (0.00%)	
occurrences (all)	4	0	
Malnutrition			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 73 (1.37%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Hypocalcaemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	6 / 73 (8.22%)	0 / 3 (0.00%)	
occurrences (all)	8	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 November 2020	• To eliminate the potential risk for increased toxicity in participants with such history. • To provide additional instructions for guidance prior to dosing, treatment interruption and resumption. • To provide more specific guidance about premedication and granulocyte colony-stimulating-factor (G-CSF) administration
23 December 2020	• The Safety Run-in Part in Japan • Assessments of patient-reported outcomes (PROs) • An additional exclusion criterion for QTc, modification on the exclusion criterion regarding New York Heart Association Classification and the wash-out period for previous anticancer antibody or antibody drug conjugates • Additional minor Sponsor modifications
21 June 2021	• All country-specific changes into a single global amendment • Clarification of weak DDI potential of berzosertib via CYP3A4 inhibition and recommendations on precautions for coadministration of certain CYP3A4 substrates • Merck standards updates.
08 February 2022	• To increase the scientific value of the study, enabling the assessment of the effect size between the combination of berzosertib and topotecan and single agent topotecan • Berzosertib in combination with topotecan is potentially effective in relapsed SCLC, not only in platinum resistant SCLC • Randomized design part added to increase the scientific value of the study, enabling the assessment of the effect size between the combination of berzosertib and topotecan and single agent topotecan • Berzosertib in combination with topotecan is potentially effective in relapsed SCLC, not only in platinum resistant SCLC

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported