



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 $1.25 \text{ mg}/\text{m}^2$ 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 $105 \text{ mg}/\text{m}^2$ 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 $1.25 \text{ mg}/\text{m}^2$ 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 $210 \text{ mg}/\text{m}^2$ intravenously on Day 2 and Day 5 of each 21-day cycle in combination with Topotecan at a dose of $1.25 \text{ mg}/\text{m}^2$ 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 $1.25 \text{ mg}/\text{m}^2$ 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/m² 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 $1.25 \text{ mg}/\text{m}^2$ 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 $210 \text{ mg}/\text{m}^2$ intravenously on Day 2 and Day 5 of each 21-day cycle in combination with Topotecan at a dose of $1.25 \text{ mg}/\text{m}^2$ 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 standard deviation | 51 ± 4 | 63 ± 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/m² intravenously on Day 2 and Day 5 of each 21-day cycle in combination with Topotecan at a dose of 1.25 mg/m² 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: 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) ^{[1][2]} |
| 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:

[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 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 | | | |

Statistical analyses

No statistical analyses for this end point

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) ^{[3][4]} |
|-----------------|---|

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 (mm³) 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 DLT 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:

[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 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 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 Vital Signs

| | |
|-----------------|---|
| End point title | Safety Run-in Part: Number of Subjects with Clinically Significant Changes From Baseline in Vital Signs ^[7] ^[8] |
|-----------------|---|

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:

[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 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 ^{[9][10]} |
|-----------------|---|

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:

[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 |
|-----------------|--|

End point description:

The laboratory measurements included hematology and biochemistry. Number of participants with clinically significant abnormalities with Grade greater than or equals to (\geq) 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: 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) ^[13] |
|-----------------|---|

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:

[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 | 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: 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) ^[14] |
|-----------------|--|

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:

[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 | 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) ^[15] |
|-----------------|--|

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:

[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%) | 6.4 (4.2 to 7.6) | | | |

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) ^[16] |
|-----------------|--|

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:

[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 | 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) ^[17] |
|-----------------|---|

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:

[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: 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 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 ^[18] |
|-----------------|--|

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:

[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 | 73 | | | |
| Units: subjects | | | | |
| TEAEs | 73 | | | |
| Treatment Related TEAEs | 67 | | | |

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 ^[19] |
|-----------------|--|

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:

[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 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 ^[20] |
|-----------------|---|

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:

[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 | 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) ^[21] |
|-----------------|--|

End point description:

The laboratory measurements included hematology and biochemistry. Number of subjects with clinically significant abnormalities with Grade greater than or equals to (\geq) 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:

[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 | | | | |
| 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: 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: Overall Survival (OS)

| | |
|---|---|
| End point title | Safety Run-in Part: Overall Survival (OS) ^[29] |
| 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:

[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 | 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: 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) ^[30] |
|-----------------|--|

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:

[30] - 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 ^[31] | 0 ^[32] | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | () | () | | |

Notes:

[31] - Data was not assessed.

[32] - Data was not assessed.

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) ^[33] |
|-----------------|--|

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:

[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 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 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 ^[34] |
|-----------------|---|

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:

[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: 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: 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 ^[35] |
|-----------------|--|

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:

[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: 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 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 ^[36] |
|-----------------|--|

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:

[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 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 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 ^[37] |
|-----------------|---|

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:

[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/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 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 ^[38] |
|-----------------|---|

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:

[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 | | | | |
| 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 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 ^[39] |
|-----------------|--|

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:

[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/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: 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 |
|-----------------|---|

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:

[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 | | | | |
| 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 ^[41] |
|-----------------|--|

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:

[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) | 12.2 (± 9.9) | 11.2 (± 9.9) | | |

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: 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 ^[43] |
|-----------------|--|

End point description:

Ceoi was the observed concentration at the end of the infusion period. This was taken directly from the observed Berzosertib 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:

[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 | | | | |
| 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: Dose Normalized Maximum Observed Plasma Concentration (C_{max}/Dose) of Berzosertib

| | |
|-----------------|---|
| End point title | Safety Run-in Part: Dose Normalized Maximum Observed Plasma Concentration (C _{max} /Dose) of Berzosertib ^[44] |
|-----------------|---|

End point description:

Dose normalized was calculated as C_{max} obtained directly from the concentration versus time curve divided by dose. C_{max}/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:

[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/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 Immediately Before Next Dosing (Ctrough) of Berzosertib

| | |
|-----------------|---|
| End point title | Safety Run-in Part: Plasma Observed Concentration Immediately Before Next Dosing (Ctrough) of Berzosertib ^[45] |
|-----------------|---|

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:

[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: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | 4.84 (\pm 22.3) | 8.57 (\pm 23.6) | | |

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 ^[46] |
|-----------------|---|

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/AUC_{0-inf}, where AUC_{0-inf} was estimated by determining the total area under the curve of the concentration versus time curve extrapolated to infinity. AUC_{0-inf} was calculated as AUC_{0-t} + C_{last} pred/Lambda Z, where C_{last} 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:

[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: 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: 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. $Racc(C_{max}) = (C_{max} \text{ after multiple dose}) / (C_{max} \text{ after single dose})$. 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: 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 ^[48] |
|-----------------|---|

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:

[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 | | | | |
| 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 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: Apparent Volume of Distribution During Terminal Phase (V_z) of Berzosertib

| | |
|-----------------|--|
| End point title | Safety Run-in Part: Apparent Volume of Distribution During Terminal Phase (V _z) of Berzosertib ^[50] |
|-----------------|--|

End point description:

V_z: the distribution of a study drug between plasma and the rest of the body after oral dosing. For single dose $V_z = \text{Dose} / (\text{AUC}_{0-\text{inf}} \times \text{Lambda Z})$, where $\text{AUC}_{0-\text{inf}} = (\text{AUC}_{0-t} + \text{Clast pred} / \text{Lambda Z})$. 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:

[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: 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: Last Sampling Time (t_{last}) of Berzosertib

| | |
|-----------------|--|
| End point title | Safety Run-in Part: Last Sampling Time (t _{last}) of Berzosertib ^[51] |
|-----------------|--|

End point description:

last 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:

[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: 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: 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/m² intravenously on Day 2 and Day 5 of each 21-day cycle in combination with Topotecan at a dose of 1.25 mg/m² 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/m²) intravenously on Day 2 and Day 5 of each 21-day cycle in combination with Topotecan at a dose of 1.25 mg/m² 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 occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 73 (1.37%) 0 / 1 0 / 0 | 0 / 3 (0.00%) 0 / 0 0 / 0 | |
| Metabolism and nutrition disorders Hypoglycaemia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 73 (1.37%) 0 / 1 0 / 0 | 0 / 3 (0.00%) 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 occurrences (all) Cancer pain alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) Metastases to central nervous system alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) | 1 / 73 (1.37%) 1 1 / 73 (1.37%) 1 1 / 73 (1.37%) 1 | 0 / 3 (0.00%) 0 0 / 3 (0.00%) 0 0 / 3 (0.00%) 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 occurrences (all) | 4 / 73 (5.48%) 4 | 0 / 3 (0.00%) 0 | |
| Mucosal inflammation alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) | 4 / 73 (5.48%) 4 | 0 / 3 (0.00%) 0 | |
| Oedema peripheral alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) | 3 / 73 (4.11%) 3 | 0 / 3 (0.00%) 0 | |
| Pain alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) | 2 / 73 (2.74%) 2 | 0 / 3 (0.00%) 0 | |
| Pyrexia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) | 5 / 73 (6.85%) 9 | 0 / 3 (0.00%) 0 | |
| Secretion discharge alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) | 1 / 73 (1.37%) 1 | 0 / 3 (0.00%) 0 | |
| Swelling face alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) | 1 / 73 (1.37%) 1 | 0 / 3 (0.00%) 0 | |
| Hyperthermia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) | 1 / 73 (1.37%) 1 | 0 / 3 (0.00%) 0 | |
| Immune system disorders | | | |

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

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

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

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

| | | |
|---|----------------|----------------|
| 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 |

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

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

| | | | |
|---------------------------------|------------------|----------------|--|
| subjects affected / exposed | 1 / 73 (1.37%) | 0 / 3 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastrointestinal disorders | | | |
| Gastroesophageal 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 |

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

| | | | |
|---|----------------|----------------|--|
| 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 | | | |

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

| | | | |
|--|---------------------|--------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 73 (1.37%) 1 | 0 / 3 (0.00%) 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) | 2 / 73 (2.74%) 2 | 0 / 3 (0.00%) 0 | |
| Back pain alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) | 2 / 73 (2.74%) 2 | 0 / 3 (0.00%) 0 | |
| Muscle spasms alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) | 2 / 73 (2.74%) 2 | 0 / 3 (0.00%) 0 | |
| Muscular weakness alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) | 1 / 73 (1.37%) 1 | 0 / 3 (0.00%) 0 | |
| Pain in extremity alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) | 1 / 73 (1.37%) 1 | 0 / 3 (0.00%) 0 | |
| Infections and infestations | | | |
| Bronchiolitis alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) | 1 / 73 (1.37%) 1 | 0 / 3 (0.00%) 0 | |
| Bronchitis alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) | 1 / 73 (1.37%) 1 | 0 / 3 (0.00%) 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 occurrences (all) | 4 / 73 (5.48%) 4 | 1 / 3 (33.33%) 1 | |
| Metabolism and nutrition disorders Hyperkalaemia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) | 1 / 73 (1.37%) 1 | 0 / 3 (0.00%) 0 | |
| Decreased appetite alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) | 18 / 73 (24.66%) 22 | 0 / 3 (0.00%) 0 | |
| Electrolyte imbalance alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) | 1 / 73 (1.37%) 1 | 0 / 3 (0.00%) 0 | |
| Gout alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) | 1 / 73 (1.37%) 1 | 0 / 3 (0.00%) 0 | |
| Hyperglycaemia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) | 4 / 73 (5.48%) 4 | 0 / 3 (0.00%) 0 | |
| Hypoalbuminaemia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) | 7 / 73 (9.59%) 8 | 0 / 3 (0.00%) 0 | |
| Hypochloraemia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) | 1 / 73 (1.37%) 1 | 0 / 3 (0.00%) 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 | <ul style="list-style-type: none">• 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 | <ul style="list-style-type: none">• 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 | <ul style="list-style-type: none">• 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 | <ul style="list-style-type: none">• 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