



Clinical trial results:

A Phase 2, Multicenter Study of the EZH2 Inhibitor Tazemetostat in Adult Subjects with Relapsed or Refractory Malignant Mesothelioma with BAP1 loss of function.

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2016-001139-10 |
| Trial protocol | FR GB |
| Global end of trial date | 25 June 2018 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 26 February 2021 |
| First version publication date | 26 February 2021 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | EZH-203 |
|-----------------------|---------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Epizyme, Inc. |
| Sponsor organisation address | 400 Technology Square, Cambridge, United States, 02139 |
| Public contact | Shefali Agarwal, Epizyme, Inc., 001 855500-1011, clinicaltrials@epizyme.com |
| Scientific contact | Shefali Agarwal, Epizyme, Inc., 001 855500-1011, clinicaltrials@epizyme.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 | 08 June 2020 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 25 June 2018 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

Part 1 (Pharmacokinetics):

To assess the pharmacokinetic (PK) and safety profile of single (Cycle 1 day 1) and repeated doses (Cycle 1 day 2 onwards) of 800 mg tazemetostat administered as 400 mg tablets in subjects with relapsed or refractory malignant mesothelioma regardless of BRCA1 associated protein 1 (BAP1) status.

Part 2 (Efficacy):

To assess disease control rate (DCR) at 12 weeks (consisting of complete response [CR], partial response [PR], or stable disease [SD]) according to modified Response Evaluation Criteria in Solid Tumors [RECIST] for thoracic disease or RECIST 1.1 elsewhere in subjects with relapsed or refractory BAP1-deficient malignant mesothelioma treated with tazemetostat.

Protection of trial subjects:

The procedures set out in the study protocol pertaining to the conduct, evaluation, and documentation of this study were designed to ensure that the Sponsor and Investigators are by Good Clinical Practice (GCP) as described in the International Conference on Harmonisation (ICH) Tripartite Guideline E6 (R1). Compliance with these regulations also constituted compliance with the ethical principles described in the current revision of the Declaration of Helsinki. The study was also carried out in keeping with local legal and regulatory requirements.

Subject confidentiality was strictly held in trust by the Sponsor and/or their designee(s), participating Investigators, and site staff.

Background therapy: -

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 08 August 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United States: 23 |
| Country: Number of subjects enrolled | United Kingdom: 37 |
| Country: Number of subjects enrolled | France: 14 |
| Worldwide total number of subjects | 74 |
| EEA total number of subjects | 51 |

Notes:

Subjects enrolled per age group

| | |
|----------|---|
| In utero | 0 |
|----------|---|

| | |
|---|----|
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 31 |
| From 65 to 84 years | 42 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening Period extends from Day -21 to Day -1. Screening laboratory assessments may be used as Day 1 assessments if performed within 72 hours of the first dose of study treatment.

Period 1

| | |
|------------------------------|--|
| Period 1 title | Intent-to-Treat (ITT) (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|-----------|---|
| Arm title | Relapsed or refractory MM with or without BAP1-deficiency |
|-----------|---|

Arm description:

Eligible subjects were enrolled into 2 different parts:

- Part 1 – Subjects with relapsed or refractory malignant mesothelioma regardless of BAP1 status
- Part 2 – Subjects with relapsed or refractory BAP1-deficient malignant mesothelioma

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | Tazemetostat |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects enrolled in Part 1 were to receive a single 800 mg tazemetostat dose on Cycle 1 Day 1. Starting on Cycle 1 Day 2, tazemetostat was to be administered at a dose of 800 mg twice daily (BID). Subjects enrolled in Part 2 were to receive tazemetostat 800 mg BID starting on Cycle 1 Day 1. Subjects continued on study treatment until disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study. Subjects may have received tazemetostat for an approximate duration of 12 months.

| Number of subjects in period 1 | Relapsed or refractory MM with or without BAP1-deficiency |
|------------------------------------|---|
| Started | 74 |
| Completed | 0 |
| Not completed | 74 |
| Consent withdrawn by subject | 1 |
| Disease progression | 65 |
| Death | 5 |
| Subject enrolled in rollover study | 3 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------------------|
| Reporting group title | Intent-to-Treat (ITT) |
|-----------------------|-----------------------|

Reporting group description: -

| Reporting group values | Intent-to-Treat (ITT) | Total | |
|--|-----------------------|-------|--|
| Number of subjects | 74 | 74 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 31 | 31 | |
| From 65-84 years | 42 | 42 | |
| 85 years and over | 1 | 1 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 25 | 25 | |
| Male | 49 | 49 | |

Subject analysis sets

| | |
|----------------------------|--------|
| Subject analysis set title | Part 1 |
|----------------------------|--------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

Part 1: Subjects with relapsed or refractory malignant mesothelioma regardless of BAP1 status.

| | |
|----------------------------|--------|
| Subject analysis set title | Part 2 |
|----------------------------|--------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

Subjects with relapsed or refractory BAP1-deficient malignant mesothelioma.

| | |
|----------------------------|--|
| Subject analysis set title | NEEDED for single arm trial statistical comparison |
|----------------------------|--|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

Subject analysis set included only to permit selection as a comparison arm for statistical analysis

| Reporting group values | Part 1 | Part 2 | NEEDED for single arm trial statistical comparison |
|--|--------|--------|--|
| Number of subjects | 13 | 61 | 1 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |

| | | | |
|--|----|----|--|
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 7 | 24 | |
| From 65-84 years | 5 | 37 | |
| 85 years and over | 1 | 0 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 3 | 22 | |
| Male | 10 | 39 | |

End points

End points reporting groups

| | |
|--|---|
| Reporting group title | Relapsed or refractory MM with or without BAP1-deficiency |
| Reporting group description: | |
| Eligible subjects were enrolled into 2 different parts: | |
| <ul style="list-style-type: none">• Part 1 – Subjects with relapsed or refractory malignant mesothelioma regardless of BAP1 status• Part 2 – Subjects with relapsed or refractory BAP1-deficient malignant mesothelioma | |
| Subject analysis set title | Part 1 |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Part 1: Subjects with relapsed or refractory malignant mesothelioma regardless of BAP1 status. | |
| Subject analysis set title | Part 2 |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Subjects with relapsed or refractory BAP1-deficient malignant mesothelioma. | |
| Subject analysis set title | NEEDED for single arm trial statistical comparison |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Subject analysis set included only to permit selection as a comparison arm for statistical analysis | |

Primary: Part 2: Disease control rate [DCR (CR+PR+SD)] at Week 12

| | |
|---|--|
| End point title | Part 2: Disease control rate [DCR (CR+PR+SD)] at Week 12 |
| End point description: | |
| The DCR at Week 12 is defined as the percentage of subjects with a response of complete response (CR), partial response (PR) or stable disease (SD) at the Week 12 assessment, as per modified RECIST (Nowak, 2005) for thoracic disease or RECIST 1.1 elsewhere. | |
| End point type | Primary |
| End point timeframe: | |
| At week 12 | |

| End point values | Part 2 | NEEDED for single arm trial statistical comparison | | |
|-----------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 61 | 1 | | |
| Units: Subjects | 61 | 1 | | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Disease control rate |
| Comparison groups | Part 2 v NEEDED for single arm trial statistical comparison |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 62 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[1] |
| Parameter estimate | Disease Control Rate (DCR) |
| Point estimate | 51.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 40 |
| upper limit | 62.7 |

Notes:

[1] - DCR (CR+PR+SD) at Week 12

Subject analysis set "NEEDED for single arm trial statistical comparison" was included only to permit selection as a comparison arm for statistical analysis, as indicated in question 82 of the EudraCT & EU CTR Frequently asked questions.

The given number for 'Number of subjects included in analysis' is automatically calculated and states 62. This is incorrect and the number included in the analysis = 61 subjects.

Primary: Part 1b): Adverse Events and clinical laboratory tests

| | |
|--|---|
| End point title | Part 1b): Adverse Events and clinical laboratory tests ^[2] |
| End point description: | |
| This endpoint was evaluated only descriptively. Thus, no statistical hypothesis were tested. | |
| End point type | Primary |
| End point timeframe: | |
| Overall trial | |

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis were tested

| End point values | Part 1 | | | |
|-----------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 13 | | | |
| Units: 1.1 | | | | |
| number (not applicable) | 13 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Part 1a): PK parameters

| | |
|--|--|
| End point title | Part 1a): PK parameters ^[3] |
| End point description: | |
| Maximum plasma concentration(C _{max}), time of C _{max} (T _{max}), area under the plasma concentration-time curve (AUC) from time 0 to the time of the last quantifiable concentration (AUC _{0-t}), AUC from time 0 extrapolated to infinity (AUC _{0-∞}) (single dose only), and the apparent terminal elimination half-life (t _{1/2}) of tazemetostat after administration as 400 mg tablets. | |
| No statistical analysis for this endpoint. | |
| End point type | Primary |
| End point timeframe: | |
| Day 1, 8 and 15 | |

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: All PK parameters were to be calculated using actual times. Population estimates of CL/F, Vd/F, and Ka for tazemetostat were to be calculated with a non-linear mixed-effects model using NONMEM 7 software. The effect of subject characteristics such as age, weight, body surface area, and gender on the PK parameters may have been investigated. The PK data from this study may be combined with data from other studies to determine the final population PK model.

| | | | | |
|-----------------------------|----------------------|--|--|--|
| End point values | Part 1 | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 13 | | | |
| Units: 1.1 | | | | |
| number (not applicable) | 13 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected on or after the date of first dose of study drug through 30 days after the last dose.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 18.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------|
| Reporting group title | Part 1 |
|-----------------------|--------|

Reporting group description:

Subjects with relapsed or refractory malignant mesothelioma regardless of BAP1 status

| | |
|-----------------------|--------|
| Reporting group title | Part 2 |
|-----------------------|--------|

Reporting group description: -

| Serious adverse events | Part 1 | Part 2 | |
|---|-----------------|------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | 23 / 61 (37.70%) | |
| number of deaths (all causes) | 1 | 7 | |
| number of deaths resulting from adverse events | 0 | 1 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancer pain | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant ascites | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant melanoma | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma of skin | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Electrocardiogram ST segment elevation | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Electrocardiogram T wave inversion | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oxygen saturation decreased | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Air embolism | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Embolism | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 61 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Pericardial effusion | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 2 / 61 (3.28%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|----------------|----------------|--|
| Pericarditis constrictive | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 2 / 61 (3.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial flutter | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Syncope | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascites | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Incarcerated umbilical hernia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal perforation | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumoperitoneum | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 2 / 61 (3.28%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 3 / 61 (4.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Pneumonia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 2 / 61 (3.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Liver abscess | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Systemic infection | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 2 / 61 (3.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Part 1 | Part 2 | |
|---|-------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 13 / 13 (100.00%) | 59 / 61 (96.72%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancer pain | | | |
| subjects affected / exposed | 3 / 13 (23.08%) | 18 / 61 (29.51%) | |
| occurrences (all) | 3 | 33 | |
| Malignant ascites | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 4 | |
| Skin papilloma | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 2 / 61 (3.28%) | |
| occurrences (all) | 0 | 4 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Embolism | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 4 / 13 (30.77%) | 22 / 61 (36.07%) | |
| occurrences (all) | 4 | 28 | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 8 / 61 (13.11%) | |
| occurrences (all) | 1 | 10 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 6 / 61 (9.84%) | |
| occurrences (all) | 1 | 8 | |

| | | | |
|--|----------------|----------------|--|
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 3 / 61 (4.92%) | |
| occurrences (all) | 0 | 5 | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 2 / 61 (3.28%) | |
| occurrences (all) | 1 | 3 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 2 / 61 (3.28%) | |
| occurrences (all) | 0 | 2 | |
| Catheter site pain | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Chills | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 61 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Inflammation | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Reproductive system and breast disorders | | | |
| Erectile dysfunction | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 2 / 61 (3.28%) | |
| occurrences (all) | 0 | 2 | |
| Dysmenorrhoea | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Vaginal discharge | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Vaginal prolapse | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Vulvovaginal dryness | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 7 / 13 (53.85%) | 14 / 61 (22.95%) | |
| occurrences (all) | 13 | 19 | |
| Cough | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | 17 / 61 (27.87%) | |
| occurrences (all) | 2 | 17 | |
| Dysphonia | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | 3 / 61 (4.92%) | |
| occurrences (all) | 2 | 3 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 3 / 61 (4.92%) | |
| occurrences (all) | 0 | 3 | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 2 / 61 (3.28%) | |
| occurrences (all) | 2 | 2 | |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 2 / 61 (3.28%) | |
| occurrences (all) | 0 | 2 | |
| Productive cough | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 2 / 61 (3.28%) | |
| occurrences (all) | 0 | 2 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 2 / 61 (3.28%) | |
| occurrences (all) | 0 | 2 | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 2 / 61 (3.28%) | |
| occurrences (all) | 0 | 2 | |
| Dyspnoea exertional | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 61 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Rales | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Throat irritation | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 61 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Wheezing | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 1 / 61 (1.64%) | |
| occurrences (all) | 1 | 1 | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Depression | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Investigations | | | |
| Weight decreased | | | |

| | | |
|---|-----------------|------------------|
| subjects affected / exposed | 0 / 13 (0.00%) | 12 / 61 (19.67%) |
| occurrences (all) | 0 | 15 |
| Blood creatine increased | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 2 / 61 (3.28%) |
| occurrences (all) | 0 | 3 |
| Lymphocyte count decreased | | |
| subjects affected / exposed | 2 / 13 (15.38%) | 0 / 61 (0.00%) |
| occurrences (all) | 3 | 0 |
| Activated partial thromboplastin time prolonged | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) |
| occurrences (all) | 0 | 1 |
| Alanine aminotransferase increased | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) |
| occurrences (all) | 0 | 1 |
| Aspartate aminotransferase increased | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) |
| occurrences (all) | 0 | 1 |
| Blood fibrinogen increased | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) |
| occurrences (all) | 0 | 1 |
| Blood magnesium decreased | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) |
| occurrences (all) | 0 | 1 |
| Blood thyroid stimulating hormone increased | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) |
| occurrences (all) | 0 | 1 |
| Blood urea increased | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) |
| occurrences (all) | 0 | 1 |
| Breath sounds abnormal | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) |
| occurrences (all) | 0 | 1 |
| C-reactive protein increased | | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Electrocardiogram T wave abnormal | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| International normalised ratio increased | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Neutrophil count increased | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Weight increased | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Injury, poisoning and procedural complications | | | |
| Joint injury | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 2 / 61 (3.28%) | |
| occurrences (all) | 0 | 2 | |
| Procedural pain | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 1 / 61 (1.64%) | |
| occurrences (all) | 2 | 1 | |
| Contusion | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Fall | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Muscle strain | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Cardiac disorders | | | |

| | | | |
|-----------------------------|----------------|-----------------|--|
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 2 / 61 (3.28%) | |
| occurrences (all) | 0 | 2 | |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 2 / 61 (3.28%) | |
| occurrences (all) | 0 | 2 | |
| Cardiac tamponade | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Pericarditis constrictive | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 2 | |
| Sinus bradycardia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Nervous system disorders | | | |
| Dysgeusia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 8 / 61 (13.11%) | |
| occurrences (all) | 0 | 11 | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 4 / 61 (6.56%) | |
| occurrences (all) | 0 | 5 | |
| Headache | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 3 / 61 (4.92%) | |
| occurrences (all) | 0 | 4 | |
| Lethargy | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 2 / 61 (3.28%) | |
| occurrences (all) | 0 | 2 | |
| Ataxia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Balance disorder | | | |

| | | | |
|--------------------------------------|----------------|------------------|--|
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Cognitive disorder | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Neuralgia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 61 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Presyncope | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Tardive dyskinesia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 2 | |
| Tremor | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 13 / 61 (21.31%) | |
| occurrences (all) | 0 | 17 | |
| Leukocytosis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Ear and labyrinth disorders | | | |
| Hypoacusis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Eye disorders | | | |

| | | | |
|----------------------------------|-----------------|------------------|--|
| Dry eye | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 2 | |
| Visual acuity reduced | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 6 / 13 (46.15%) | 15 / 61 (24.59%) | |
| occurrences (all) | 6 | 22 | |
| Vomiting | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | 15 / 61 (24.59%) | |
| occurrences (all) | 4 | 18 | |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | 11 / 61 (18.03%) | |
| occurrences (all) | 2 | 14 | |
| Abdominal distension | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | 5 / 61 (8.20%) | |
| occurrences (all) | 2 | 8 | |
| Constipation | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 7 / 61 (11.48%) | |
| occurrences (all) | 0 | 7 | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 4 / 61 (6.56%) | |
| occurrences (all) | 1 | 5 | |
| Dry mouth | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 3 / 61 (4.92%) | |
| occurrences (all) | 0 | 3 | |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 2 / 61 (3.28%) | |
| occurrences (all) | 1 | 2 | |
| Flatulence | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 3 / 61 (4.92%) | |
| occurrences (all) | 0 | 3 | |
| Gastrooesophageal reflux disease | | | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 1 / 13 (7.69%) | 1 / 61 (1.64%) | |
| occurrences (all) | 1 | 1 | |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 2 / 61 (3.28%) | |
| occurrences (all) | 0 | 2 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Ascites | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 61 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Diverticulum | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 61 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Eructation | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 61 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Large intestine polyp | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Mouth ulceration | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Dry skin | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 3 / 61 (4.92%) | |
| occurrences (all) | 1 | 3 | |
| Dermal cyst | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 2 / 61 (3.28%) | |
| occurrences (all) | 1 | 2 | |

| | | |
|-----------------------------|----------------|----------------|
| Night sweats | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 2 / 61 (3.28%) |
| occurrences (all) | 1 | 2 |
| Rash | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 2 / 61 (3.28%) |
| occurrences (all) | 1 | 3 |
| Dermatitis acneiform | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 1 / 61 (1.64%) |
| occurrences (all) | 1 | 1 |
| Erythema | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 2 / 61 (3.28%) |
| occurrences (all) | 0 | 2 |
| Alopecia | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) |
| occurrences (all) | 0 | 1 |
| Decubitus ulcer | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) |
| occurrences (all) | 0 | 2 |
| Eczema | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) |
| occurrences (all) | 0 | 1 |
| Hyperhidrosis | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) |
| occurrences (all) | 0 | 1 |
| Intertrigo | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) |
| occurrences (all) | 0 | 1 |
| Petechiae | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) |
| occurrences (all) | 0 | 1 |
| Rash maculo-papular | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) |
| occurrences (all) | 0 | 4 |
| Scar pain | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) |
| occurrences (all) | 0 | 1 |

| | | | |
|--|----------------------|---------------------|--|
| Skin induration subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 1 / 61 (1.64%) 1 | |
| Skin lesion subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 1 / 61 (1.64%) 1 | |
| Skin mass subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 1 / 61 (1.64%) 1 | |
| Urticaria subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 1 / 61 (1.64%) 1 | |
| Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 1 / 61 (1.64%) 1 | |
| Dysuria subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 1 / 61 (1.64%) 1 | |
| Urinary retention subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 1 / 61 (1.64%) 1 | |
| Urine odour abnormal subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 1 / 61 (1.64%) 1 | |
| Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 1 / 61 (1.64%) 1 | |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 3 / 13 (23.08%) 3 | 4 / 61 (6.56%) 5 | |
| Arthralgia subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 2 | 1 / 61 (1.64%) 1 | |

| | | | |
|-----------------------------------|----------------|-----------------|--|
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 6 / 61 (9.84%) | |
| occurrences (all) | 0 | 8 | |
| Arthropathy | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 2 | |
| Myalgia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| spinal column stenosis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Infections and infestations | | | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 8 / 61 (13.11%) | |
| occurrences (all) | 0 | 11 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 5 / 61 (8.20%) | |
| occurrences (all) | 1 | 5 | |
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 3 / 61 (4.92%) | |
| occurrences (all) | 1 | 3 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 4 / 61 (6.56%) | |
| occurrences (all) | 0 | 4 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 2 / 61 (3.28%) | |
| occurrences (all) | 0 | 2 | |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 2 / 61 (3.28%) | |
| occurrences (all) | 0 | 3 | |
| Rash pustular | | | |

| | | |
|-----------------------------|----------------|----------------|
| subjects affected / exposed | 0 / 13 (0.00%) | 2 / 61 (3.28%) |
| occurrences (all) | 0 | 2 |
| Rhinitis | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 2 / 61 (3.28%) |
| occurrences (all) | 0 | 2 |
| Vaginal infection | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 2 / 61 (3.28%) |
| occurrences (all) | 0 | 2 |
| Bronchitis | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) |
| occurrences (all) | 0 | 1 |
| Cellulitis | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) |
| occurrences (all) | 0 | 1 |
| Cystitis | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) |
| occurrences (all) | 0 | 1 |
| Dermatophytosis | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) |
| occurrences (all) | 0 | 1 |
| Device related infection | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) |
| occurrences (all) | 0 | 1 |
| Gastroenteritis | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) |
| occurrences (all) | 0 | 1 |
| Groin abscess | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) |
| occurrences (all) | 0 | 1 |
| Infected skin ulcer | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) |
| occurrences (all) | 0 | 1 |
| lung infection | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) |
| occurrences (all) | 0 | 1 |
| Oropharyngeal candidiasis | | |

| | | | |
|------------------------------------|-----------------|------------------|--|
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Paronychia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Skin infection | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Tooth abscess | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Tooth infection | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Viral rhinitis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Vulvovaginal mycotic infection | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | 22 / 61 (36.07%) | |
| occurrences (all) | 3 | 27 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 3 / 61 (4.92%) | |
| occurrences (all) | 1 | 3 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 3 / 61 (4.92%) | |
| occurrences (all) | 0 | 8 | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 2 / 61 (3.28%) | |
| occurrences (all) | 0 | 3 | |

| | | | |
|-----------------------------|----------------|----------------|--|
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 1 / 61 (1.64%) | |
| occurrences (all) | 1 | 1 | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 3 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 61 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 25 April 2016 | <ul style="list-style-type: none">• Updated exclusion criteria to exclude Subjects who are pregnant or breastfeeding• Updated dose modification and clarified actions taken in case of a secondary neoplasm• Updated frequency of pregnancy testing• Removed urinalysis for laboratory testing |
| 13 April 2017 | <ul style="list-style-type: none">• To include feedback obtained from Principal Investigators during site initiation visits• To incorporate changes in study procedures documented as Note to File• To resolve inconsistencies within sections of the protocol• To amend the optional tumor biopsy to an optional paired tumor biopsy• To clarify BAP1 loss inclusion criteria preference for IHC in the mesothelioma tumor sample |
| 27 November 2017 | <ul style="list-style-type: none">• Updated text on phototoxicity to also include specific measures to avoid UV exposure.• Updated text to clarify subjects' duration of treatment• Updated text on the definition of "post-menopausal" per the definition of The American Association of Clinical Endocrinologists that is most commonly accepted.• Updated text on pregnancy testing to align the text in section 8.3.3.3 with footnote in Table 1: Study assessments |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported