



Clinical trial results:

A Phase I/II, Open-Label, Safety, Pharmacokinetic, and Preliminary Efficacy Study of Oral Rucaparib in Patients with gBRCA Mutation Ovarian Cancer or Other Solid Tumor

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2011-004250-26 |
| Trial protocol | GB ES DE |
| Global end of trial date | 30 May 2019 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 14 June 2020 |
| First version publication date | 14 June 2020 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | CO-338-010 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01482715 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Clovis Oncology UK Ltd |
| Sponsor organisation address | Granta Centre, Granta Park, Great Abington, Cambridge, United Kingdom, CB21 6GP |
| Public contact | Dr Lindsey Rolfe, Clovis Oncology UK Ltd, +44 01223645500, lrolfe@clovisoncology.com |
| Scientific contact | Dr Lindsey Rolfe, Clovis Oncology UK Ltd, +44 01223645500, lrolfe@clovisoncology.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 | 29 August 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 27 March 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 May 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

1. To evaluate the safety profile of escalating doses of continuous daily oral rucaparib in patients with advanced solid tumors, and to determine the maximum tolerated dose and recommended Phase II Dose (Part 1 only)
2. To characterize the pharmacokinetic profile of oral rucaparib when administered as a continuous daily dose (Part 1 and Part 3 only)
3. To evaluate overall response rate in patients with platinum-sensitive, relapsed, high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer associated with a BRCA mutation[henceforth abbreviated to platinum- sensitive OC population]

Protection of trial subjects:

The following safety assessments were performed: Monitoring of adverse events (AEs), physical examination, clinical laboratory evaluations (hematology, serum chemistry, and urinalysis), vital signs, and 12-lead ECG.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 21 November 2011 |
| 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 | Spain: 2 |
| Country: Number of subjects enrolled | United Kingdom: 55 |
| Country: Number of subjects enrolled | United States: 58 |
| Country: Number of subjects enrolled | Israel: 15 |
| Country: Number of subjects enrolled | Canada: 6 |
| Worldwide total number of subjects | 136 |
| EEA total number of subjects | 57 |

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) | 103 |
| From 65 to 84 years | 33 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 15 investigative sites in the United States (6 sites), United Kingdom (5 sites), Spain (1 site), Israel (2 sites), and Canada (1 site).

Pre-assignment

Screening details:

Patients enrolled into Part 1, Part 2A, Part 2B, or Part 3 of the study, not into multiple parts.

Period 1

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

Arms

| | |
|------------------------------|------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Part 1 (Phase 1) |

Arm description:

Rucaparib 40 to 500 mg QD and 240 to 840 mg BID, for continuous 21-day cycles.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Rucaparib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Rucaparib 40 to 500 mg QD and 240 to 840 mg BID, for continuous 21-day cycles.

| | |
|------------------|-------------------|
| Arm title | Part 2A (Phase 2) |
|------------------|-------------------|

Arm description:

Rucaparib 600 mg BID for 21-day cycles.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Rucaparib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Rucaparib 600 mg BID for 21-day cycles.

| | |
|------------------|-------------------|
| Arm title | Part 2B (Phase 2) |
|------------------|-------------------|

Arm description:

Rucaparib 600 mg BID for 21-day cycles.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Rucaparib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Rucaparib 600 mg BID for 21-day cycles.

| | |
|---|------------------|
| Arm title | Part 3 (Phase 2) |
| Arm description: Rucaparib 600 mg BID for 21-day cycles. Patients also received a single administration of 600 mg rucaparib on both Day -7 and Day 1 for assessing the effect of food on PK. | |
| Arm type | Experimental |
| Investigational medicinal product name | Rucaparib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Rucaparib 600 mg BID for continuous 21-day cycles.

| Number of subjects in period 1 | Part 1 (Phase 1) | Part 2A (Phase 2) | Part 2B (Phase 2) |
|---------------------------------------|------------------|-------------------|-------------------|
| Started | 56 | 42 | 12 |
| Completed | 56 | 42 | 12 |

| Number of subjects in period 1 | Part 3 (Phase 2) |
|---------------------------------------|------------------|
| Started | 26 |
| Completed | 26 |

Baseline characteristics

Reporting groups

| | |
|---|-------------------|
| Reporting group title | Part 1 (Phase 1) |
| Reporting group description: Rucaparib 40 to 500 mg QD and 240 to 840 mg BID, for continuous 21-day cycles. | |
| Reporting group title | Part 2A (Phase 2) |
| Reporting group description: Rucaparib 600 mg BID for 21-day cycles. | |
| Reporting group title | Part 2B (Phase 2) |
| Reporting group description: Rucaparib 600 mg BID for 21-day cycles. | |
| Reporting group title | Part 3 (Phase 2) |
| Reporting group description: Rucaparib 600 mg BID for 21-day cycles. Patients also received a single administration of 600 mg rucaparib on both Day -7 and Day 1 for assessing the effect of food on PK. | |

| Reporting group values | Part 1 (Phase 1) | Part 2A (Phase 2) | Part 2B (Phase 2) |
|---|------------------|-------------------|-------------------|
| Number of subjects | 56 | 42 | 12 |
| Age categorical Units: Subjects | | | |
| In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over | | | |
| Age continuous Units: years | | | |
| median | 51.0 | 56.5 | 57.5 |
| full range (min-max) | 21.0 to 71.0 | 42.0 to 84.0 | 46.0 to 72.0 |
| Gender categorical Units: Subjects | | | |
| Female | 51 | 42 | 12 |
| Male | 5 | 0 | 0 |
| Race (NIH/OMB) Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 3 | 3 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 4 | 3 | 0 |
| White | 49 | 35 | 11 |
| More than one race | 0 | 1 | 0 |
| Unknown or Not Reported | 0 | 0 | 1 |

| Reporting group values | Part 3 (Phase 2) | Total | |
|---|------------------|-------|--|
| Number of subjects | 26 | 136 | |
| Age categorical Units: Subjects | | | |
| In utero | | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | | 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) | | 0 | |
| From 65-84 years | | 0 | |
| 85 years and over | | 0 | |
| Age continuous Units: years | | | |
| median | 59.5 | | |
| full range (min-max) | 39.0 to 79.0 | - | |
| Gender categorical Units: Subjects | | | |
| Female | 21 | 126 | |
| Male | 5 | 10 | |
| Race (NIH/OMB) Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | |
| Asian | 1 | 7 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| Black or African American | 2 | 9 | |
| White | 22 | 117 | |
| More than one race | 1 | 2 | |
| Unknown or Not Reported | 0 | 1 | |

End points

End points reporting groups

| | |
|---|------------------------|
| Reporting group title | Part 1 (Phase 1) |
| Reporting group description: Rucaparib 40 to 500 mg QD and 240 to 840 mg BID, for continuous 21-day cycles. | |
| Reporting group title | Part 2A (Phase 2) |
| Reporting group description: Rucaparib 600 mg BID for 21-day cycles. | |
| Reporting group title | Part 2B (Phase 2) |
| Reporting group description: Rucaparib 600 mg BID for 21-day cycles. | |
| Reporting group title | Part 3 (Phase 2) |
| Reporting group description: Rucaparib 600 mg BID for 21-day cycles. Patients also received a single administration of 600 mg rucaparib on both Day -7 and Day 1 for assessing the effect of food on PK. | |
| Subject analysis set title | Rucaparib 40-500 mg QD |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Rucaparib 40 to 500 mg QD for continuous 21-day cycles. | |
| Subject analysis set title | Rucaparib 40 mg QD |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Rucaparib 40 mg QD for continuous 21-day cycles. | |
| Subject analysis set title | Rucaparib 80 mg QD |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Rucaparib 80 mg QD for continuous 21-day cycles. | |
| Subject analysis set title | Rucaparib 160 mg QD |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Rucaparib 160 mg QD for continuous 21-day cycles. | |
| Subject analysis set title | Rucaparib 300 mg QD |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Rucaparib 300 mg QD for continuous 21-day cycles. | |
| Subject analysis set title | Rucaparib 500 mg QD |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Rucaparib 500 mg QD for continuous 21-day cycles. | |
| Subject analysis set title | Rucaparib 240 mg BID |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Rucaparib 240 mg BID for continuous 21-day cycles. | |
| Subject analysis set title | Rucaparib 360 mg BID |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Rucaparib 360 mg BID for continuous 21-day cycles. | |
| Subject analysis set title | Rucaparib 480 mg BID |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Rucaparib 480 mg BID for continuous 21-day cycles.

| | |
|----------------------------|----------------------|
| Subject analysis set title | Rucaparib 600 mg BID |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Rucaparib 600 mg BID for continuous 21-day cycles.

| | |
|----------------------------|----------------------|
| Subject analysis set title | Rucaparib 840 mg BID |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Rucaparib 840 mg BID for continuous 21-day cycles.

Primary: Overall Response Rate Per RECIST Version 1.1 (Part 2)

| | |
|-----------------|---|
| End point title | Overall Response Rate Per RECIST Version 1.1 (Part 2) ^{[1][2]} |
|-----------------|---|

End point description:

The confirmed response rate by RECIST v1.1 is defined as the proportion of patients with a confirmed Complete Response (CR) or Partial Response (PR) on subsequent tumor assessment at least 28 days after first response documentation. Analysis Population Description: Efficacy-Evaluable Population - all Part 2 patients who met eligibility criteria, received at least 1 dose of rucaparib, had measurable tumor lesions at baseline, and had at least 1 post-baseline disease assessment. 2 patients in Part 2A discontinued treatment due to an AE and did not have a post-baseline disease assessment.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Time from first dose to date of progression, up to approximately 8 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: Per protocol no statistical test was performed between arms for the ORR end point.

[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: This end point reports ORR for Part 2 patients only.

| End point values | Part 2A (Phase 2) | Part 2B (Phase 2) | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 40 | 12 | | |
| Units: Percentage of patients | | | | |
| number (confidence interval 95%) | 62.5 (45.8 to 77.3) | 58.3 (27.7 to 84.8) | | |

Statistical analyses

No statistical analyses for this end point

Primary: Dose Limiting Toxicity (DLT) Incidence

| | |
|-----------------|---|
| End point title | Dose Limiting Toxicity (DLT) Incidence ^[3] |
|-----------------|---|

End point description:

The number of Part 1 (Phase 1) patients who experienced dose limiting toxicities after one cycle (21 days) of study drug. Analysis Population Description: DLT-evaluable population - all patients enrolled into Part 1 of the study who received at least 17 complete days of rucaparib and completed Cycle 1 of treatment, or who experienced a DLT in Cycle 1. Note: A MTD was not established based on observation of DLTs in Cycle 1 of treatment. The 600 mg BID dose was considered to be the maximum dose with an acceptable toxicity profile that could be continuously administered to patients and was selected as the

recommended Phase 2 dose (RP2D).

| | |
|---|---------|
| End point type | Primary |
| End point timeframe: | |
| Cycle 1 Day 1 to Cycle 1 Day 21 | |
| 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: Statistical analyses was not performed for DLT end point. | |

| End point values | Rucaparib 40-500 mg QD | Rucaparib 240 mg BID | Rucaparib 360 mg BID | Rucaparib 480 mg BID |
|-------------------------------|------------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 26 | 3 | 8 | 9 |
| Units: Number of participants | 0 | 0 | 1 | 0 |

| End point values | Rucaparib 600 mg BID | Rucaparib 840 mg BID | | |
|-------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 7 | 3 | | |
| Units: Number of participants | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Primary: PK Profile of Rucaparib - Cmax (Part 1)

| | |
|--|--|
| End point title | PK Profile of Rucaparib - Cmax (Part 1) ^[4] |
| End point description: | |
| Cmax = maximum concentration following administration of rucaparib. Analysis Population Description: PK-evaluable population - all patients enrolled into Part 1 of the study who received at least one dose of rucaparib and had adequate PK assessments drawn for determination of the PK profile. For some arms, the number analyzed at Day 1 and Day 15 differs from the overall number based on number of evaluable samples collected at each time point. | |
| End point type | Primary |
| End point timeframe: | |
| Cycle 1 Day 1 to Cycle 1 Day 15, or approximately 15 days | |
| Notes: | |
| [4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. | |
| Justification: Statistical analyses are not performed for PK end points. | |

| End point values | Rucaparib 40 mg QD | Rucaparib 80 mg QD | Rucaparib 160 mg QD | Rucaparib 300 mg QD |
|-------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 3 | 3 | 4 ^[5] | 3 |
| Units: ng/mL | | | | |
| median (full range (min-max)) | | | | |
| Day 1 Cmax | 120 (98.9 to 168) | 119 (65.7 to 158) | 255 (107 to 426) | 700 (368 to 818) |

| | | | | |
|-------------|-------------------|------------------|------------------|-------------------|
| Day 15 Cmax | 159 (80.7 to 174) | 180 (108 to 237) | 267 (217 to 380) | 439 (340 to 1300) |
|-------------|-------------------|------------------|------------------|-------------------|

Notes:

[5] - Day 1 = 4 patients analyzed, Day 15 = 3 patients analyzed

| End point values | Rucaparib 500 mg QD | Rucaparib 240 mg BID | Rucaparib 360 mg BID | Rucaparib 480 mg BID |
|-------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 3 | 3 | 8 ^[6] | 9 ^[7] |
| Units: ng/mL | | | | |
| median (full range (min-max)) | | | | |
| Day 1 Cmax | 699 (629 to 1520) | 132 (123 to 401) | 603 (244 to 1170) | 1090 (312 to 2440) |
| Day 15 Cmax | 1250 (1170 to 1750) | 783 (619 to 1510) | 1220 (728 to 2320) | 2480 (922 to 6870) |

Notes:

[6] - Day 1 = 8 patients analyzed, Day 15 = 6 patients analyzed

[7] - Day 1 = 9 patients analyzed, Day 15 = 8 patients analyzed

| End point values | Rucaparib 600 mg BID | Rucaparib 840 mg BID | | |
|-------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 7 | 3 ^[8] | | |
| Units: ng/mL | | | | |
| median (full range (min-max)) | | | | |
| Day 1 Cmax | 972 (271 to 1790) | 954 (705 to 2470) | | |
| Day 15 Cmax | 2330 (477 to 3670) | 3030 (3000 to 3060) | | |

Notes:

[8] - Day 1 = 3 patients analyzed, Day 15 = 2 patients analyzed

Statistical analyses

No statistical analyses for this end point

Primary: PK Profile of Rucaparib - Tmax (Part 1)

| | |
|-----------------|--|
| End point title | PK Profile of Rucaparib - Tmax (Part 1) ^[9] |
|-----------------|--|

End point description:

Tmax = time to maximum concentration following administration of rucaparib. Analysis Population Description: PK-evaluable population - all patients enrolled into Part 1 of the study who received at least one dose of rucaparib and had adequate PK assessments drawn for determination of the PK profile. For some arms, the number analyzed at Day 1 and Day 15 differs from the overall number based on number of evaluable samples collected at each time point.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Cycle 1 Day 1 to Cycle 1 Day 15, or approximately 15 days

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: Statistical analyses are not performed for PK end points.

| End point values | Rucaparib 40 mg QD | Rucaparib 80 mg QD | Rucaparib 160 mg QD | Rucaparib 300 mg QD |
|-------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 3 | 3 | 4 ^[10] | 3 |
| Units: Hours | | | | |
| median (full range (min-max)) | | | | |
| Day 1 Tmax | 2.5 (1 to 4) | 1.5 (1 to 2.5) | 4 (4 to 6.05) | 2.5 (1 to 4.08) |
| Day 15 Tmax | 4 (1 to 4.05) | 2.5 (2.5 to 2.57) | 3.75 (2.5 to 4) | 2.53 (2.5 to 8) |

Notes:

[10] - Day 1 = 4 patients analyzed, Day 15 = 3 patients analyzed

| End point values | Rucaparib 500 mg QD | Rucaparib 240 mg BID | Rucaparib 360 mg BID | Rucaparib 480 mg BID |
|-------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 3 | 3 | 8 ^[11] | 9 ^[12] |
| Units: Hours | | | | |
| median (full range (min-max)) | | | | |
| Day 1 Tmax | 4 (4 to 4) | 6 (4.05 to 6) | 3.23 (1.5 to 6) | 2.5 (1.5 to 4) |
| Day 15 Tmax | 4 (4 to 4.17) | 1.5 (1 to 4) | 3.3 (0 to 6.33) | 1.51 (0 to 6) |

Notes:

[11] - Day 1 = 8 patients analyzed, Day 15 = 6 patients analyzed

[12] - Day 1 = 9 patients analyzed, Day 15 = 8 patients analyzed

| End point values | Rucaparib 600 mg BID | Rucaparib 840 mg BID | | |
|-------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 7 | 3 ^[13] | | |
| Units: Hours | | | | |
| median (full range (min-max)) | | | | |
| Day 1 Tmax | 4 (2.42 to 10) | 4 (2.5 to 8) | | |
| Day 15 Tmax | 4 (2.53 to 10) | 4.04 (4 to 4.07) | | |

Notes:

[13] - Day 1 = 3 patients analyzed, Day 15 = 2 patients analyzed

Statistical analyses

No statistical analyses for this end point

Primary: PK Profile of Rucaparib - AUC Last (Part 1)

| | |
|-----------------|---|
| End point title | PK Profile of Rucaparib - AUC Last (Part 1) ^[14] |
|-----------------|---|

End point description:

AUC last = Area under the plasma concentration-time curve from time 0 to the last recorded observation. Analysis Population Description: PK-evaluable population - all patients enrolled into Part 1 of the study who received at least one dose of rucaparib and had adequate PK assessments drawn for determination of the PK profile. For some arms, the number analyzed at Day 1 and Day 15 differs from the overall number based on number of evaluable samples collected at each time point.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Cycle 1 Day 1 to Cycle 1 Day 15, or approximately 15 days

Notes:

[14] - 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: Statistical analyses are not performed for PK end points.

| End point values | Rucaparib 40 mg QD | Rucaparib 80 mg QD | Rucaparib 160 mg QD | Rucaparib 300 mg QD |
|-------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 3 ^[15] | 3 | 4 ^[16] | 3 |
| Units: hr*ng/mL | | | | |
| median (full range (min-max)) | | | | |
| Day 1 AUC last | 915 (850 to 981) | 916 (555 to 930) | 2730 (1520 to 5230) | 5820 (3540 to 7860) |
| Day 15 AUC last | 2270 (889 to 2280) | 1870 (1340 to 2000) | 3510 (3130 to 5670) | 6090 (4020 to 18700) |

Notes:

[15] - Day 1 = 2 patients analyzed, Day 15 = 3 patients analyzed

[16] - Day 1 = 4 patients analyzed, Day 15 = 3 patients analyzed

| End point values | Rucaparib 500 mg QD | Rucaparib 240 mg BID | Rucaparib 360 mg BID | Rucaparib 480 mg BID |
|-------------------------------|------------------------|----------------------|----------------------|-----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 3 | 3 | 8 ^[17] | 9 ^[18] |
| Units: hr*ng/mL | | | | |
| median (full range (min-max)) | | | | |
| Day 1 AUC last | 7670 (6640 to 18700) | 875 (835 to 2430) | 4160 (1060 to 6670) | 6190 (1270 to 17200) |
| Day 15 AUC last | 16500 (13900 to 29200) | 6340 (5100 to 12600) | 9110 (5950 to 17200) | 19400 (7480 to 55100) |

Notes:

[17] - Day 1 = 8 patients analyzed, Day 15 = 6 patients analyzed

[18] - Day 1 = 9 patients analyzed, Day 15 = 8 patients analyzed

| End point values | Rucaparib 600 mg BID | Rucaparib 840 mg BID | | |
|-------------------------------|-----------------------|------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 7 | 3 ^[19] | | |
| Units: hr*ng/mL | | | | |
| median (full range (min-max)) | | | | |
| Day 1 AUC last | 6700 (1650 to 10900) | 5930 (5140 to 16700) | | |
| Day 15 AUC last | 19700 (3090 to 32600) | 24900 (24100 to 25700) | | |

Notes:

[19] - Day 1 = 3 patients analyzed, Day 15 = 2 patients analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS) According to RECIST v1.1, as Assessed by the Investigator (Part 2)

| | |
|-----------------|--|
| End point title | Progression-free Survival (PFS) According to RECIST v1.1, as Assessed by the Investigator (Part 2) ^[20] |
|-----------------|--|

End point description:

PFS is calculated as 1+ the number of days from the first dose of study drug to disease progression by RECIST, as determined by the investigator or death due to any cause, whichever occurs first. Analysis Population Description: Safety population - Consists of all Part 2 patients who received at least one dose of rucaparib.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Cycle 1 Day 1 to End of Treatment, up to approximately 51 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: This end point reports PFS for Part 2 patients only.

| End point values | Part 2A (Phase 2) | Part 2B (Phase 2) | | |
|----------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 42 | 12 | | |
| Units: Days | | | | |
| median (confidence interval 95%) | 260 (203 to 373) | 280 (40 to 551) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response Per RECIST Version 1.1 (Part 2)

| | |
|-----------------|--|
| End point title | Duration of Response Per RECIST Version 1.1 (Part 2) ^[21] |
|-----------------|--|

End point description:

Duration of response (DOR) for any confirmed RECIST CR or PR measured from the date of the first occurrence of a response until the first occurrence of PD per RECIST. For patients who continued treatment post-progression, the first date of progression was used for the analysis. Any patients with an ongoing response were censored at the date of the last post-baseline scan. Analysis Population Description: Safety population - all Part 2 patients with confirmed response per investigator.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Cycle 1 Day 1 to End of Treatment, up to approximately 48 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: This end point reports DOR for Part 2 patients only.

| End point values | Part 2A (Phase 2) | Part 2B (Phase 2) | | |
|----------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 25 | 7 | | |
| Units: Days | | | | |
| median (confidence interval 95%) | 270 (170 to 393) | 318 (106 to 497) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (Part 2B)

| | |
|-----------------|--|
| End point title | Overall Survival (Part 2B) ^[22] |
|-----------------|--|

End point description:

Overall survival (OS) is defined as the number of days from the date of first dose of study drug to the date of death, due to any cause. Patients without a documented event of death will be censored on the date of their last visit. Analysis Population Description: Safety population - Consists of all Part 2B patients who received at least one dose of rucaparib. Note: The upper confidence of the median is not reached due to not enough death events. 9999 is entered as a placeholder.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Cycle 1 Day 1 to date of death, assessed up to 38 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: This end point reports OS for Part 2B patients only.

| End point values | Part 2B (Phase 2) | | | |
|----------------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 12 | | | |
| Units: Days | | | | |
| median (confidence interval 95%) | 764 (166 to 9999) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Food Effect on PK of Rucaparib - Tmax (Part 1 and Part 3)

| | |
|-----------------|---|
| End point title | Food Effect on PK of Rucaparib - Tmax (Part 1 and Part 3) |
|-----------------|---|

End point description:

Tmax = time to maximum concentration following administration of rucaparib. The effect of food on rucaparib PK parameters was assessed over a 24hour period in blood samples from a subset of patients. Patients were given a single dose of 40 mg or 300 mg rucaparib (Part 1), or 600 mg rucaparib (Part 3) with and without a high-fat meal on Day -7 or Cycle 1 Day 1. On each day, patients underwent blood sampling for PK at the specified time points. Analysis Population Description: A subset of patients treated with either 40 mg, 300 mg, or 600 mg rucaparib.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day -7 to Cycle 1 Day 1, or approximately 7 days

| End point values | Rucaparib 40 mg QD | Rucaparib 300 mg QD | Rucaparib 600 mg BID | |
|-------------------------------|----------------------|----------------------|----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 3 | 6 | 26 | |
| Units: Hours | | | | |
| median (full range (min-max)) | | | | |
| Tmax Fasted | 4 (2.5 to 4.05) | 4.09 (2.5 to 24.22) | 4.02 (0.53 to 24.83) | |
| Tmax Fed | 2.55 (1 to 4.08) | 5.95 (2.53 to 10) | 7.83 (1.5 to 24.45) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Food Effect on PK of Rucaparib - Cmax (Part 1 and Part 3)

| | |
|-----------------|---|
| End point title | Food Effect on PK of Rucaparib - Cmax (Part 1 and Part 3) |
|-----------------|---|

End point description:

Cmax = maximum concentration following administration of rucaparib. The effect of food on rucaparib PK parameters was assessed over a 24-hour period in blood samples from a subset of patients. Patients were given a single dose of 40 mg or 300 mg rucaparib (Part 1), or 600 mg rucaparib (Part 3) with and without a high-fat meal on Day -7 or Cycle 1 Day 1. On each day, patients underwent blood sampling for PK at the specified time points. Analysis Population Description: A subset of patients treated with either 40 mg, 300 mg, or 600 mg rucaparib.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day -7 to Cycle 1 Day 1, or approximately 7 days

| End point values | Rucaparib 40 mg QD | Rucaparib 300 mg QD | Rucaparib 600 mg BID | |
|-------------------------------|----------------------|----------------------|----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 3 | 6 | 26 | |
| Units: ng/mL | | | | |
| median (full range (min-max)) | | | | |
| Cmax Fasted | 57.6 (45.2 to 131) | 424 (182 to 638) | 585 (127 to 3100) | |
| Cmax Fed | 71.1 (21.3 to 102) | 393 (177 to 1210) | 746 (198 to 2640) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Food Effect on PK of Rucaparib - AUC Last (Part 1 and Part 3)

| | |
|-----------------|---|
| End point title | Food Effect on PK of Rucaparib - AUC Last (Part 1 and Part 3) |
|-----------------|---|

End point description:

AUC last = Area under the plasma concentration-time curve from time 0 to the last recorded observation. The effect of food on rucaparib PK parameters was assessed over a 24-hour period in blood samples from a subset of patients. Patients were given a single dose of 40 mg or 300 mg rucaparib (Part 1), or 600 mg rucaparib (Part 3) with and without a high-fat meal on Day -7 or Cycle 1 Day 1. On each day, patients underwent blood sampling for PK at the specified time points. Analysis Population Description: A subset of patients treated with either 40 mg, 300 mg, or 600 mg rucaparib. For the 40 mg and 300 mg arms, the number analyzed at Day 1 and Day 15 differs from the overall number based on number of evaluable samples collected at each time point.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day -7 to Cycle 1 Day 1, or approximately 7 days

| End point values | Rucaparib 40 mg QD | Rucaparib 300 mg QD | Rucaparib 600 mg BID | |
|-------------------------------|----------------------|----------------------|-----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 3 ^[23] | 6 ^[24] | 26 | |
| Units: hr*ng/mL | | | | |
| median (full range (min-max)) | | | | |
| AUC Last Fasted | 468 (347 to 1410) | 5410 (2390 to 8680) | 7050 (1110 to 33000) | |
| AUC Last Fed | 794 (415 to 1170) | 6000 (2670 to 12100) | 10900 (1990 to 40400) | |

Notes:

[23] - Fasted = 3 patients analyzed, Fed = 2 patients analyzed

[24] - Fasted = 6 patients analyzed, Fed = 5 patients analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: QTcF Value Change From Baseline (Part 1)

| | |
|-----------------|--|
| End point title | QTcF Value Change From Baseline (Part 1) |
|-----------------|--|

End point description:

QTcF value change from baseline by daily dose corrected using Fridericia's method (QTcF). To evaluate the effects of rucaparib on the QT (interval from Q wave to T wave)/QTc (interval corrected for heart rate) interval, all patients underwent serial ECG monitoring at Screening, on Cycle 1 Day -1, Cycle 1 Day 1, Cycle 1 Day 15, Cycle 1 Day 22, on Day 1 of all subsequent cycles, at the EOT Visit, and as clinically indicated. Worst post-baseline QTcF value was used to categorize each patient. Analysis Population Description: Safety population - Consists of all Part 1 patients who received at least one dose of rucaparib. One patient in the 40 mg dose group had no Baseline evaluation and was excluded from analyses of change from Baseline.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Screening to End of Treatment, up to approximately 15 months

| End point values | Rucaparib 40 mg QD | Rucaparib 80 mg QD | Rucaparib 160 mg QD | Rucaparib 300 mg QD |
|---|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 5 | 3 | 4 | 9 |
| Units: Participants | | | | |
| QTcF Change from Baseline <30 msec | 5 | 3 | 4 | 9 |
| QTcF Change from Baseline ≥30 to <60 msec | 0 | 0 | 0 | 0 |
| QTcF Change from Baseline ≥60 msec | 0 | 0 | 0 | 0 |

| End point values | Rucaparib 500 mg QD | Rucaparib 240 mg BID | Rucaparib 360 mg BID | Rucaparib 480 mg BID |
|---|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 4 | 3 | 8 | 9 |
| Units: Participants | | | | |
| QTcF Change from Baseline <30 msec | 3 | 3 | 8 | 9 |
| QTcF Change from Baseline ≥30 to <60 msec | 1 | 0 | 0 | 0 |
| QTcF Change from Baseline ≥60 msec | 0 | 0 | 0 | 0 |

| End point values | Rucaparib 600 mg BID | Rucaparib 840 mg BID | | |
|---|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 7 | 3 | | |
| Units: Participants | | | | |
| QTcF Change from Baseline <30 msec | 7 | 3 | | |
| QTcF Change from Baseline ≥30 to <60 msec | 0 | 0 | | |
| QTcF Change from Baseline ≥60 msec | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from the date of first dose of study drug and within 28 days after last dose of study drug.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 19.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Part 1 (Phase 1) |
|-----------------------|------------------|

Reporting group description:

Rucaparib 40 to 500 mg QD, followed by 240 to 840 mg BID, for continuous 21-day cycles.

| | |
|-----------------------|-------------------|
| Reporting group title | Part 2A (Phase 2) |
|-----------------------|-------------------|

Reporting group description:

Rucaparib 600 mg BID for 21-day cycles.

| | |
|-----------------------|-------------------|
| Reporting group title | Part 2B (Phase 2) |
|-----------------------|-------------------|

Reporting group description:

Rucaparib 600 mg BID for 21-day cycles.

| | |
|-----------------------|------------------|
| Reporting group title | Part 3 (Phase 2) |
|-----------------------|------------------|

Reporting group description:

Rucaparib 600 mg BID for 21-day cycles.

| Serious adverse events | Part 1 (Phase 1) | Part 2A (Phase 2) | Part 2B (Phase 2) |
|---|------------------|-------------------|-------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 21 / 56 (37.50%) | 19 / 42 (45.24%) | 3 / 12 (25.00%) |
| number of deaths (all causes) | 4 | 4 | 1 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| B-cell type acute leukaemia | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 42 (2.38%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 7 / 56 (12.50%) | 4 / 42 (9.52%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 4 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 4 | 0 / 3 | 0 / 1 |
| Myelodysplastic syndrome | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 42 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Radius fracture | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 1 / 42 (2.38%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract stoma complication | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 42 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 42 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 42 (2.38%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 42 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 42 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 56 (1.79%) | 3 / 42 (7.14%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 42 (2.38%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 42 (2.38%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 42 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 42 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 56 (5.36%) | 0 / 42 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Generalised oedema | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 42 (2.38%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 1 / 42 (2.38%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Ascites | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 1 / 42 (2.38%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 42 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 42 (2.38%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematemesis | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 42 (2.38%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 2 / 42 (4.76%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestinal obstruction | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 42 (2.38%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 0 / 42 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Obstruction gastric | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 42 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 42 (2.38%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 3 / 42 (7.14%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 42 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Vaginal fistula | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 42 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 42 (2.38%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 42 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 42 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 42 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 42 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 42 (2.38%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 1 / 42 (2.38%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cytomegalovirus infection | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 42 (2.38%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 42 (2.38%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epiglottitis | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 42 (2.38%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 42 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 42 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Pneumonia | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 2 / 42 (4.76%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 42 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 42 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 42 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|------------------|--|--|
| Serious adverse events | Part 3 (Phase 2) | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 9 / 26 (34.62%) | | |
| number of deaths (all causes) | 4 | | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| B-cell type acute leukaemia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 3 / 26 (11.54%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 3 | | |
| Myelodysplastic syndrome | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 2 / 26 (7.69%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Radius fracture | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract stoma complication | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Headache | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Seizure | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Generalised oedema | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|----------------|--|--|--|
| Ascites | | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Constipation | | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal haemorrhage | | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haematemesis | | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intestinal obstruction | | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Large intestinal obstruction | | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nausea | | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Obstruction gastric | | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pancreatitis | | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Vaginal fistula | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|--|----------------------------------|--|--|
| Respiratory failure subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 26 (3.85%) 0 / 1 0 / 1 | | |
| Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 26 (0.00%) 0 / 0 0 / 0 | | |
| Infections and infestations Cellulitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 26 (0.00%) 0 / 0 0 / 0 | | |
| Cytomegalovirus infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 26 (0.00%) 0 / 0 0 / 0 | | |
| Diverticulitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 26 (0.00%) 0 / 0 0 / 0 | | |
| Epiglottitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 26 (0.00%) 0 / 0 0 / 0 | | |
| Influenza subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 26 (0.00%) 0 / 0 0 / 0 | | |
| Lower respiratory tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 26 (0.00%) 0 / 0 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Pneumonia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Part 1 (Phase 1) | Part 2A (Phase 2) | Part 2B (Phase 2) |
|---|------------------|-------------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 55 / 56 (98.21%) | 41 / 42 (97.62%) | 12 / 12 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 10 / 56 (17.86%) | 5 / 42 (11.90%) | 1 / 12 (8.33%) |
| occurrences (all) | 11 | 6 | 1 |
| Myelodysplastic syndrome | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 42 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 2 / 42 (4.76%) | 2 / 12 (16.67%) |
| occurrences (all) | 2 | 7 | 2 |
| Hypertension | | | |

| | | | |
|---|------------------------|------------------------|----------------------|
| subjects affected / exposed occurrences (all) | 1 / 56 (1.79%) 1 | 4 / 42 (9.52%) 8 | 2 / 12 (16.67%) 3 |
| Lymphoedema subjects affected / exposed occurrences (all) | 2 / 56 (3.57%) 3 | 1 / 42 (2.38%) 7 | 2 / 12 (16.67%) 2 |
| General disorders and administration site conditions | | | |
| Asthenia subjects affected / exposed occurrences (all) | 2 / 56 (3.57%) 2 | 13 / 42 (30.95%) 49 | 1 / 12 (8.33%) 2 |
| Axillary pain subjects affected / exposed occurrences (all) | 0 / 56 (0.00%) 0 | 1 / 42 (2.38%) 1 | 1 / 12 (8.33%) 1 |
| Chest pain subjects affected / exposed occurrences (all) | 3 / 56 (5.36%) 3 | 1 / 42 (2.38%) 1 | 0 / 12 (0.00%) 0 |
| Chills subjects affected / exposed occurrences (all) | 1 / 56 (1.79%) 1 | 5 / 42 (11.90%) 5 | 1 / 12 (8.33%) 1 |
| Early satiety subjects affected / exposed occurrences (all) | 1 / 56 (1.79%) 1 | 3 / 42 (7.14%) 3 | 0 / 12 (0.00%) 0 |
| Fatigue subjects affected / exposed occurrences (all) | 28 / 56 (50.00%) 48 | 30 / 42 (71.43%) 85 | 6 / 12 (50.00%) 8 |
| Influenza like illness subjects affected / exposed occurrences (all) | 2 / 56 (3.57%) 2 | 5 / 42 (11.90%) 8 | 1 / 12 (8.33%) 2 |
| Injection site bruising subjects affected / exposed occurrences (all) | 0 / 56 (0.00%) 0 | 0 / 42 (0.00%) 0 | 1 / 12 (8.33%) 1 |
| Malaise subjects affected / exposed occurrences (all) | 2 / 56 (3.57%) 2 | 1 / 42 (2.38%) 2 | 1 / 12 (8.33%) 1 |
| Mucosal inflammation | | | |

| | | | |
|---|------------------|------------------|-----------------|
| subjects affected / exposed | 3 / 56 (5.36%) | 2 / 42 (4.76%) | 0 / 12 (0.00%) |
| occurrences (all) | 4 | 2 | 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 4 / 56 (7.14%) | 1 / 42 (2.38%) | 0 / 12 (0.00%) |
| occurrences (all) | 5 | 1 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 3 / 56 (5.36%) | 4 / 42 (9.52%) | 0 / 12 (0.00%) |
| occurrences (all) | 4 | 6 | 0 |
| Peripheral swelling | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 3 / 42 (7.14%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 4 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 9 / 56 (16.07%) | 5 / 42 (11.90%) | 3 / 12 (25.00%) |
| occurrences (all) | 11 | 13 | 4 |
| Immune system disorders | | | |
| Allergy to arthropod bite | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 42 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Reproductive system and breast disorders | | | |
| Pelvic pain | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 5 / 42 (11.90%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 6 | 0 |
| Vaginal discharge | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 42 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 2 |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 2 / 42 (4.76%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 3 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 12 / 56 (21.43%) | 10 / 42 (23.81%) | 2 / 12 (16.67%) |
| occurrences (all) | 13 | 18 | 2 |
| Dysphonia | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 0 / 42 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 2 | 0 | 1 |
| Dyspnoea | | | |

| | | | |
|-----------------------------|------------------|------------------|-----------------|
| subjects affected / exposed | 11 / 56 (19.64%) | 11 / 42 (26.19%) | 1 / 12 (8.33%) |
| occurrences (all) | 16 | 16 | 1 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 3 / 42 (7.14%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Hypoxia | | | |
| subjects affected / exposed | 3 / 56 (5.36%) | 1 / 42 (2.38%) | 0 / 12 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| Nasal congestion | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 3 / 42 (7.14%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 3 | 0 |
| Nasal discomfort | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 42 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 7 / 56 (12.50%) | 7 / 42 (16.67%) | 1 / 12 (8.33%) |
| occurrences (all) | 7 | 12 | 1 |
| Pleural effusion | | | |
| subjects affected / exposed | 5 / 56 (8.93%) | 2 / 42 (4.76%) | 0 / 12 (0.00%) |
| occurrences (all) | 5 | 2 | 0 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 42 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Psychiatric disorders | | | |
| Agitation | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 42 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Anxiety | | | |
| subjects affected / exposed | 3 / 56 (5.36%) | 6 / 42 (14.29%) | 0 / 12 (0.00%) |
| occurrences (all) | 5 | 7 | 0 |
| Depressed mood | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 42 (0.00%) | 2 / 12 (16.67%) |
| occurrences (all) | 1 | 0 | 2 |
| Depression | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 4 / 42 (9.52%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 12 | 0 |

| | | | |
|--|------------------------|------------------------|-----------------------|
| Insomnia subjects affected / exposed occurrences (all) | 6 / 56 (10.71%) 6 | 6 / 42 (14.29%) 14 | 0 / 12 (0.00%) 0 |
| Investigations | | | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 9 / 56 (16.07%) 15 | 24 / 42 (57.14%) 53 | 2 / 12 (16.67%) 11 |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 13 / 56 (23.21%) 15 | 22 / 42 (52.38%) 40 | 2 / 12 (16.67%) 3 |
| Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) | 8 / 56 (14.29%) 9 | 10 / 42 (23.81%) 16 | 1 / 12 (8.33%) 1 |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 2 / 56 (3.57%) 2 | 3 / 42 (7.14%) 8 | 1 / 12 (8.33%) 2 |
| Blood cholesterol increased subjects affected / exposed occurrences (all) | 5 / 56 (8.93%) 7 | 3 / 42 (7.14%) 5 | 2 / 12 (16.67%) 3 |
| Blood creatinine increased subjects affected / exposed occurrences (all) | 5 / 56 (8.93%) 6 | 15 / 42 (35.71%) 34 | 6 / 12 (50.00%) 16 |
| Blood potassium increased subjects affected / exposed occurrences (all) | 0 / 56 (0.00%) 0 | 0 / 42 (0.00%) 0 | 1 / 12 (8.33%) 1 |
| Blood urea increased subjects affected / exposed occurrences (all) | 3 / 56 (5.36%) 3 | 3 / 42 (7.14%) 3 | 0 / 12 (0.00%) 0 |
| Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all) | 0 / 56 (0.00%) 0 | 2 / 42 (4.76%) 2 | 1 / 12 (8.33%) 1 |
| Lymphocyte count decreased subjects affected / exposed occurrences (all) | 0 / 56 (0.00%) 0 | 0 / 42 (0.00%) 0 | 1 / 12 (8.33%) 1 |
| Neutrophil count decreased | | | |

| | | | |
|--|------------------|------------------|-----------------|
| subjects affected / exposed | 6 / 56 (10.71%) | 3 / 42 (7.14%) | 0 / 12 (0.00%) |
| occurrences (all) | 11 | 15 | 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 4 / 56 (7.14%) | 7 / 42 (16.67%) | 2 / 12 (16.67%) |
| occurrences (all) | 5 | 18 | 2 |
| Transaminases increased | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 2 / 42 (4.76%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Weight decreased | | | |
| subjects affected / exposed | 3 / 56 (5.36%) | 8 / 42 (19.05%) | 1 / 12 (8.33%) |
| occurrences (all) | 3 | 11 | 1 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 5 / 56 (8.93%) | 5 / 42 (11.90%) | 0 / 12 (0.00%) |
| occurrences (all) | 12 | 20 | 0 |
| Injury, poisoning and procedural complications | | | |
| Arthropod bite | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 42 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Limb injury | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 42 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Cardiac disorders | | | |
| Tachycardia | | | |
| subjects affected / exposed | 4 / 56 (7.14%) | 0 / 42 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 9 / 56 (16.07%) | 9 / 42 (21.43%) | 1 / 12 (8.33%) |
| occurrences (all) | 11 | 15 | 1 |
| Dysgeusia | | | |
| subjects affected / exposed | 8 / 56 (14.29%) | 17 / 42 (40.48%) | 2 / 12 (16.67%) |
| occurrences (all) | 10 | 34 | 2 |
| Headache | | | |
| subjects affected / exposed | 11 / 56 (19.64%) | 20 / 42 (47.62%) | 2 / 12 (16.67%) |
| occurrences (all) | 13 | 38 | 3 |
| Lethargy | | | |

| | | | |
|--|------------------------|-------------------------|-----------------------|
| subjects affected / exposed occurrences (all) | 0 / 56 (0.00%) 0 | 0 / 42 (0.00%) 0 | 3 / 12 (25.00%) 6 |
| Neuropathy peripheral subjects affected / exposed occurrences (all) | 2 / 56 (3.57%) 2 | 1 / 42 (2.38%) 1 | 1 / 12 (8.33%) 1 |
| Paraesthesia subjects affected / exposed occurrences (all) | 3 / 56 (5.36%) 3 | 2 / 42 (4.76%) 3 | 0 / 12 (0.00%) 0 |
| Restless legs syndrome subjects affected / exposed occurrences (all) | 0 / 56 (0.00%) 0 | 0 / 42 (0.00%) 0 | 1 / 12 (8.33%) 1 |
| Tremor subjects affected / exposed occurrences (all) | 0 / 56 (0.00%) 0 | 3 / 42 (7.14%) 4 | 0 / 12 (0.00%) 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 18 / 56 (32.14%) 42 | 30 / 42 (71.43%) 149 | 8 / 12 (66.67%) 32 |
| Leukopenia subjects affected / exposed occurrences (all) | 1 / 56 (1.79%) 1 | 3 / 42 (7.14%) 3 | 1 / 12 (8.33%) 2 |
| Lymphopenia subjects affected / exposed occurrences (all) | 0 / 56 (0.00%) 0 | 1 / 42 (2.38%) 1 | 2 / 12 (16.67%) 3 |
| Neutropenia subjects affected / exposed occurrences (all) | 6 / 56 (10.71%) 14 | 9 / 42 (21.43%) 22 | 2 / 12 (16.67%) 5 |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 4 / 56 (7.14%) 8 | 8 / 42 (19.05%) 22 | 4 / 12 (33.33%) 13 |
| Ear and labyrinth disorders | | | |
| Ear pain subjects affected / exposed occurrences (all) | 0 / 56 (0.00%) 0 | 2 / 42 (4.76%) 4 | 2 / 12 (16.67%) 2 |
| Eye disorders | | | |

| | | | |
|---|------------------------|------------------------|-----------------------|
| Conjunctival hyperaemia subjects affected / exposed occurrences (all) | 0 / 56 (0.00%) 0 | 0 / 42 (0.00%) 0 | 1 / 12 (8.33%) 1 |
| Vision blurred subjects affected / exposed occurrences (all) | 4 / 56 (7.14%) 4 | 3 / 42 (7.14%) 3 | 1 / 12 (8.33%) 1 |
| Gastrointestinal disorders | | | |
| Abdominal discomfort subjects affected / exposed occurrences (all) | 3 / 56 (5.36%) 3 | 1 / 42 (2.38%) 1 | 0 / 12 (0.00%) 0 |
| Abdominal distension subjects affected / exposed occurrences (all) | 8 / 56 (14.29%) 9 | 11 / 42 (26.19%) 18 | 0 / 12 (0.00%) 0 |
| Abdominal pain subjects affected / exposed occurrences (all) | 14 / 56 (25.00%) 22 | 20 / 42 (47.62%) 51 | 5 / 12 (41.67%) 7 |
| Abdominal pain lower subjects affected / exposed occurrences (all) | 2 / 56 (3.57%) 2 | 6 / 42 (14.29%) 7 | 2 / 12 (16.67%) 2 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 7 / 56 (12.50%) 9 | 5 / 42 (11.90%) 9 | 2 / 12 (16.67%) 2 |
| Aphthous ulcer subjects affected / exposed occurrences (all) | 0 / 56 (0.00%) 0 | 0 / 42 (0.00%) 0 | 2 / 12 (16.67%) 2 |
| Ascites subjects affected / exposed occurrences (all) | 3 / 56 (5.36%) 4 | 2 / 42 (4.76%) 3 | 0 / 12 (0.00%) 0 |
| Constipation subjects affected / exposed occurrences (all) | 14 / 56 (25.00%) 16 | 22 / 42 (52.38%) 33 | 7 / 12 (58.33%) 11 |
| Diarrhoea subjects affected / exposed occurrences (all) | 13 / 56 (23.21%) 19 | 17 / 42 (40.48%) 35 | 3 / 12 (25.00%) 4 |
| Dry mouth | | | |

| | | | |
|--|------------------|------------------|------------------|
| subjects affected / exposed | 4 / 56 (7.14%) | 3 / 42 (7.14%) | 1 / 12 (8.33%) |
| occurrences (all) | 6 | 3 | 1 |
| Dyspepsia | | | |
| subjects affected / exposed | 5 / 56 (8.93%) | 3 / 42 (7.14%) | 2 / 12 (16.67%) |
| occurrences (all) | 7 | 3 | 3 |
| Flatulence | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 5 / 42 (11.90%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 8 | 1 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 4 / 56 (7.14%) | 2 / 42 (4.76%) | 2 / 12 (16.67%) |
| occurrences (all) | 5 | 2 | 2 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 3 / 42 (7.14%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Mouth ulceration | | | |
| subjects affected / exposed | 3 / 56 (5.36%) | 0 / 42 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Nausea | | | |
| subjects affected / exposed | 30 / 56 (53.57%) | 35 / 42 (83.33%) | 11 / 12 (91.67%) |
| occurrences (all) | 48 | 92 | 26 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 4 / 42 (9.52%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 5 | 0 |
| Stomatitis | | | |
| subjects affected / exposed | 4 / 56 (7.14%) | 7 / 42 (16.67%) | 1 / 12 (8.33%) |
| occurrences (all) | 4 | 11 | 1 |
| Tooth disorder | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 42 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Vomiting | | | |
| subjects affected / exposed | 24 / 56 (42.86%) | 24 / 42 (57.14%) | 9 / 12 (75.00%) |
| occurrences (all) | 41 | 67 | 22 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 8 / 42 (19.05%) | 1 / 12 (8.33%) |
| occurrences (all) | 2 | 8 | 1 |

| | | | |
|-----------------------------|-----------------|-----------------|----------------|
| Blister | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 42 (2.38%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 | 3 |
| Dry skin | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 6 / 42 (14.29%) | 1 / 12 (8.33%) |
| occurrences (all) | 2 | 8 | 1 |
| Erythema | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 2 / 42 (4.76%) | 1 / 12 (8.33%) |
| occurrences (all) | 2 | 3 | 1 |
| Nail discolouration | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 3 / 42 (7.14%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Photosensitivity reaction | | | |
| subjects affected / exposed | 6 / 56 (10.71%) | 5 / 42 (11.90%) | 1 / 12 (8.33%) |
| occurrences (all) | 6 | 6 | 1 |
| Pruritus | | | |
| subjects affected / exposed | 4 / 56 (7.14%) | 6 / 42 (14.29%) | 1 / 12 (8.33%) |
| occurrences (all) | 6 | 9 | 1 |
| Rash | | | |
| subjects affected / exposed | 3 / 56 (5.36%) | 8 / 42 (19.05%) | 1 / 12 (8.33%) |
| occurrences (all) | 3 | 18 | 2 |
| Rash macular | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 42 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 3 / 42 (7.14%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 7 | 0 |
| Skin lesion | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 42 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 42 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 56 (1.79%) | 1 / 42 (2.38%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 1 | 1 |
| Dysuria | | | |
| subjects affected / exposed | 3 / 56 (5.36%) | 3 / 42 (7.14%) | 0 / 12 (0.00%) |
| occurrences (all) | 3 | 3 | 0 |
| Micturition urgency | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 0 / 42 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 2 | 0 | 2 |
| Proteinuria | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 3 / 42 (7.14%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 8 | 0 |
| Urinary incontinence | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 3 / 42 (7.14%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 3 | 1 |
| Pollakiuria | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 42 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 9 / 42 (21.43%) | 3 / 12 (25.00%) |
| occurrences (all) | 2 | 16 | 5 |
| Back pain | | | |
| subjects affected / exposed | 5 / 56 (8.93%) | 7 / 42 (16.67%) | 2 / 12 (16.67%) |
| occurrences (all) | 5 | 11 | 3 |
| Bone pain | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 3 / 42 (7.14%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Joint swelling | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 3 / 42 (7.14%) | 2 / 12 (16.67%) |
| occurrences (all) | 1 | 3 | 3 |
| Muscle spasms | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 2 / 42 (4.76%) | 1 / 12 (8.33%) |
| occurrences (all) | 3 | 3 | 1 |
| Musculoskeletal chest pain | | | |

| | | | |
|-----------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed | 4 / 56 (7.14%) | 0 / 42 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 3 / 56 (5.36%) | 2 / 42 (4.76%) | 1 / 12 (8.33%) |
| occurrences (all) | 5 | 2 | 1 |
| Musculoskeletal stiffness | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 0 / 42 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 2 | 0 | 1 |
| Myalgia | | | |
| subjects affected / exposed | 3 / 56 (5.36%) | 3 / 42 (7.14%) | 0 / 12 (0.00%) |
| occurrences (all) | 3 | 4 | 0 |
| Neck pain | | | |
| subjects affected / exposed | 3 / 56 (5.36%) | 0 / 42 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 3 | 0 | 1 |
| Pain in extremity | | | |
| subjects affected / exposed | 3 / 56 (5.36%) | 5 / 42 (11.90%) | 1 / 12 (8.33%) |
| occurrences (all) | 3 | 9 | 1 |
| Infections and infestations | | | |
| Ear infection | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 42 (0.00%) | 2 / 12 (16.67%) |
| occurrences (all) | 0 | 0 | 2 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 2 / 42 (4.76%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 2 | 1 |
| Gingivitis | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 42 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Herpes simplex | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 42 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 4 / 56 (7.14%) | 0 / 42 (0.00%) | 4 / 12 (33.33%) |
| occurrences (all) | 5 | 0 | 5 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 5 / 42 (11.90%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 6 | 0 |

| | | | |
|---|------------------|------------------|-----------------|
| Pneumonia | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 4 / 42 (9.52%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 5 | 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 42 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Tooth infection | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 0 / 42 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 56 (3.57%) | 12 / 42 (28.57%) | 2 / 12 (16.67%) |
| occurrences (all) | 4 | 16 | 2 |
| Urinary tract infection | | | |
| subjects affected / exposed | 5 / 56 (8.93%) | 8 / 42 (19.05%) | 3 / 12 (25.00%) |
| occurrences (all) | 6 | 10 | 6 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 42 (2.38%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 16 / 56 (28.57%) | 12 / 42 (28.57%) | 3 / 12 (25.00%) |
| occurrences (all) | 18 | 19 | 3 |
| Dehydration | | | |
| subjects affected / exposed | 7 / 56 (12.50%) | 3 / 42 (7.14%) | 1 / 12 (8.33%) |
| occurrences (all) | 9 | 4 | 1 |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 56 (0.00%) | 1 / 42 (2.38%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Hypercholesterolaemia | | | |
| subjects affected / exposed | 4 / 56 (7.14%) | 4 / 42 (9.52%) | 1 / 12 (8.33%) |
| occurrences (all) | 4 | 10 | 1 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 7 / 56 (12.50%) | 1 / 42 (2.38%) | 1 / 12 (8.33%) |
| occurrences (all) | 15 | 2 | 1 |
| Hyperkalaemia | | | |

| | | | |
|-----------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 56 (1.79%) | 1 / 42 (2.38%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 4 | 3 |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 1 / 56 (1.79%) | 0 / 42 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 3 / 56 (5.36%) | 2 / 42 (4.76%) | 0 / 12 (0.00%) |
| occurrences (all) | 4 | 3 | 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 4 / 56 (7.14%) | 4 / 42 (9.52%) | 1 / 12 (8.33%) |
| occurrences (all) | 5 | 6 | 1 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 4 / 56 (7.14%) | 7 / 42 (16.67%) | 1 / 12 (8.33%) |
| occurrences (all) | 5 | 15 | 3 |
| Hyponatraemia | | | |
| subjects affected / exposed | 5 / 56 (8.93%) | 5 / 42 (11.90%) | 2 / 12 (16.67%) |
| occurrences (all) | 6 | 7 | 2 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 4 / 56 (7.14%) | 3 / 42 (7.14%) | 1 / 12 (8.33%) |
| occurrences (all) | 6 | 5 | 1 |

| | | | |
|---|-------------------|--|--|
| Non-serious adverse events | Part 3 (Phase 2) | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 26 / 26 (100.00%) | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 4 / 26 (15.38%) | | |
| occurrences (all) | 4 | | |
| Myelodysplastic syndrome | | | |
| subjects affected / exposed | 2 / 26 (7.69%) | | |
| occurrences (all) | 2 | | |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypertension | | | |

| | | | |
|--|------------------|--|--|
| subjects affected / exposed | 1 / 26 (3.85%) | | |
| occurrences (all) | 1 | | |
| Lymphoedema | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 2 / 26 (7.69%) | | |
| occurrences (all) | 3 | | |
| Axillary pain | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Chills | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Early satiety | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Fatigue | | | |
| subjects affected / exposed | 14 / 26 (53.85%) | | |
| occurrences (all) | 29 | | |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Injection site bruising | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Malaise | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Mucosal inflammation | | | |

| | | | |
|--|--|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Non-cardiac chest pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Oedema peripheral</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Peripheral swelling</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pyrexia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>2 / 26 (7.69%)</p> <p>2</p> <p>0 / 26 (0.00%)</p> <p>0</p> <p>5 / 26 (19.23%)</p> <p>6</p> <p>2 / 26 (7.69%)</p> <p>2</p> <p>3 / 26 (11.54%)</p> <p>4</p> | | |
| <p>Immune system disorders</p> <p>Allergy to arthropod bite</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>0 / 26 (0.00%)</p> <p>0</p> | | |
| <p>Reproductive system and breast disorders</p> <p>Pelvic pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vaginal discharge</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vaginal haemorrhage</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>0 / 26 (0.00%)</p> <p>0</p> <p>0 / 26 (0.00%)</p> <p>0</p> <p>0 / 26 (0.00%)</p> <p>0</p> | | |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dysphonia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dyspnoea</p> | <p>4 / 26 (15.38%)</p> <p>5</p> <p>0 / 26 (0.00%)</p> <p>0</p> | | |

| | | | |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 4 / 26 (15.38%) | | |
| occurrences (all) | 4 | | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 3 / 26 (11.54%) | | |
| occurrences (all) | 3 | | |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nasal discomfort | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | | |
| occurrences (all) | 1 | | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | | |
| occurrences (all) | 1 | | |
| Psychiatric disorders | | | |
| Agitation | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Anxiety | | | |
| subjects affected / exposed | 2 / 26 (7.69%) | | |
| occurrences (all) | 2 | | |
| Depressed mood | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Depression | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|--------------------------------------|-----------------|--|--|
| Insomnia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 6 / 26 (23.08%) | | |
| occurrences (all) | 18 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 6 / 26 (23.08%) | | |
| occurrences (all) | 9 | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood cholesterol increased | | | |
| subjects affected / exposed | 3 / 26 (11.54%) | | |
| occurrences (all) | 3 | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 3 / 26 (11.54%) | | |
| occurrences (all) | 4 | | |
| Blood potassium increased | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood urea increased | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Neutrophil count decreased | | | |

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|--|---|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Platelet count decreased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Transaminases increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Weight decreased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>White blood cell count decreased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>3 / 26 (11.54%)</p> <p>9</p> <p>2 / 26 (7.69%)</p> <p>7</p> <p>2 / 26 (7.69%)</p> <p>2</p> <p>1 / 26 (3.85%)</p> <p>2</p> <p>1 / 26 (3.85%)</p> <p>2</p> | | |
| <p>Injury, poisoning and procedural complications</p> <p>Arthropod bite</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Limb injury</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>0 / 26 (0.00%)</p> <p>0</p> <p>0 / 26 (0.00%)</p> <p>0</p> | | |
| <p>Cardiac disorders</p> <p>Tachycardia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>0 / 26 (0.00%)</p> <p>0</p> | | |
| <p>Nervous system disorders</p> <p>Dizziness</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dysgeusia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Headache</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Lethargy</p> | <p>6 / 26 (23.08%)</p> <p>6</p> <p>5 / 26 (19.23%)</p> <p>7</p> <p>2 / 26 (7.69%)</p> <p>2</p> | | |

| | | | |
|--------------------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 26 (3.85%) | | |
| occurrences (all) | 1 | | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Paraesthesia | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | | |
| occurrences (all) | 1 | | |
| Restless legs syndrome | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Tremor | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 6 / 26 (23.08%) | | |
| occurrences (all) | 38 | | |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Lymphopenia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Neutropenia | | | |
| subjects affected / exposed | 3 / 26 (11.54%) | | |
| occurrences (all) | 8 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 3 / 26 (11.54%) | | |
| occurrences (all) | 14 | | |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Eye disorders | | | |

| | | | |
|---|----------------------|--|--|
| Conjunctival hyperaemia subjects affected / exposed occurrences (all) | 0 / 26 (0.00%) 0 | | |
| Vision blurred subjects affected / exposed occurrences (all) | 0 / 26 (0.00%) 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort subjects affected / exposed occurrences (all) | 2 / 26 (7.69%) 2 | | |
| Abdominal distension subjects affected / exposed occurrences (all) | 4 / 26 (15.38%) 5 | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 4 / 26 (15.38%) 6 | | |
| Abdominal pain lower subjects affected / exposed occurrences (all) | 0 / 26 (0.00%) 0 | | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 0 / 26 (0.00%) 0 | | |
| Aphthous ulcer subjects affected / exposed occurrences (all) | 0 / 26 (0.00%) 0 | | |
| Ascites subjects affected / exposed occurrences (all) | 1 / 26 (3.85%) 1 | | |
| Constipation subjects affected / exposed occurrences (all) | 7 / 26 (26.92%) 9 | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 4 / 26 (15.38%) 4 | | |
| Dry mouth | | | |

| | | | |
|--|------------------|--|--|
| subjects affected / exposed | 2 / 26 (7.69%) | | |
| occurrences (all) | 2 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 6 / 26 (23.08%) | | |
| occurrences (all) | 6 | | |
| Flatulence | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 2 / 26 (7.69%) | | |
| occurrences (all) | 2 | | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Mouth ulceration | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nausea | | | |
| subjects affected / exposed | 11 / 26 (42.31%) | | |
| occurrences (all) | 20 | | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | | |
| occurrences (all) | 2 | | |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Tooth disorder | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 9 / 26 (34.62%) | | |
| occurrences (all) | 18 | | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | | |
| occurrences (all) | 1 | | |

| | | | |
|-----------------------------|-----------------|--|--|
| Blister | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dry skin | | | |
| subjects affected / exposed | 2 / 26 (7.69%) | | |
| occurrences (all) | 3 | | |
| Erythema | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nail discolouration | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | | |
| occurrences (all) | 1 | | |
| Photosensitivity reaction | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | | |
| occurrences (all) | 1 | | |
| Pruritus | | | |
| subjects affected / exposed | 3 / 26 (11.54%) | | |
| occurrences (all) | 3 | | |
| Rash | | | |
| subjects affected / exposed | 3 / 26 (11.54%) | | |
| occurrences (all) | 5 | | |
| Rash macular | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Skin lesion | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dysuria | | | |
| subjects affected / exposed | 2 / 26 (7.69%) | | |
| occurrences (all) | 2 | | |
| Micturition urgency | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Proteinuria | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Urinary incontinence | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | | |
| occurrences (all) | 1 | | |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 3 / 26 (11.54%) | | |
| occurrences (all) | 3 | | |
| Back pain | | | |
| subjects affected / exposed | 4 / 26 (15.38%) | | |
| occurrences (all) | 4 | | |
| Bone pain | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Joint swelling | | | |
| subjects affected / exposed | 3 / 26 (11.54%) | | |
| occurrences (all) | 3 | | |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal chest pain | | | |

| | | | |
|-----------------------------------|----------------|--|--|
| subjects affected / exposed | 1 / 26 (3.85%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal stiffness | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Myalgia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Neck pain | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 2 / 26 (7.69%) | | |
| occurrences (all) | 2 | | |
| Infections and infestations | | | |
| Ear infection | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gingivitis | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Herpes simplex | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | | |
| occurrences (all) | 1 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|---|------------------|--|--|
| Pneumonia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | | |
| occurrences (all) | 1 | | |
| Tooth infection | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 26 (7.69%) | | |
| occurrences (all) | 5 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 6 / 26 (23.08%) | | |
| occurrences (all) | 7 | | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 26 (7.69%) | | |
| occurrences (all) | 2 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 10 / 26 (38.46%) | | |
| occurrences (all) | 17 | | |
| Dehydration | | | |
| subjects affected / exposed | 2 / 26 (7.69%) | | |
| occurrences (all) | 6 | | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypercholesterolaemia | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | | |
| occurrences (all) | 1 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 2 / 26 (7.69%) | | |
| occurrences (all) | 2 | | |
| Hyperkalaemia | | | |

| | | | |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 2 / 26 (7.69%) | | |
| occurrences (all) | 3 | | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | | |
| occurrences (all) | 1 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | | |
| occurrences (all) | 1 | | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | | |
| occurrences (all) | 0 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 12 January 2012 | Exclusion criteria were revised to apply exclusion for history of clinically significant abnormal ECG to patients in both Parts 1 and 2 of the study. Withdrawal criteria were revised to include absolute QTc measurement > 500 msec as reason for withdrawal. |
| 23 April 2012 | The study design was revised to include an ovarian cancer arm in Part 2 of the study. An optional collection of a fresh or archival tumor tissue sample was added for patients who consented to provide a biopsy sample. Secondary objectives were revised to include an objective for evaluation of antitumor activity in patients with solid tumors enrolling into Part 1 of the study. |
| 02 October 2012 | The dose escalation plan was revised to include evaluation of BID, and possibly TID dosing. The study population for the RP2D expansion cohort was revised to include patients with a solid tumor and a deleterious gBRCA mutation, and the size was increased to up to 15 patients. Health-related quality of life (HRQoL) assessment was added to Part 2 of the study. The option for inpatient dose escalation was added to Part 1 of the study so that patients may have their dose escalated to a potentially therapeutic level. |
| 27 November 2013 | The RP2D was determined to be 600 mg BID based on safety, PK, and efficacy data from the Phase 1 portion of the study. The breast cancer arm was removed to prioritize development of rucaparib in ovarian cancer patients. Changes to inclusion and exclusion criteria. |
| 02 February 2015 | Part 3 was added to further evaluate the PK of, and the effect of food on, higher dose strength tablets at the RP2D in patients with any advanced solid tumor, inclusive of lymphoma, with evidence of a BRCA mutation. |
| 27 April 2015 | An additional cohort of patients with relapsed, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, with evidence of a deleterious BRCA mutation (germline or somatic) who have received at least 3, but no more than 4, prior chemotherapy regimens was included in the Phase 2 part of the study. Initial Part 2 became Part 2A, and the new cohort of patients was enrolled into Part 2B. |
| 29 June 2016 | The protocol was amended to implement more stringent pregnancy testing requirements, birth control measures including criteria for defining females of childbearing potential and to update adverse events of special interest for patient safety. Restrictions regarding concomitant use of medications that are CYP substrates were updated based on nonclinical data. Dose modification criteria were updated to provide management guideline in the event of Grade 3 or Grade 4 ALT/AST elevations. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported