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
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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	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cytomegalovirus infection			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Epiglottitis			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	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	1 / 56 (1.79%)	4 / 42 (9.52%)	2 / 12 (16.67%)
occurrences (all)	1	8	3
Lymphoedema			
subjects affected / exposed	2 / 56 (3.57%)	1 / 42 (2.38%)	2 / 12 (16.67%)
occurrences (all)	3	7	2
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 56 (3.57%)	13 / 42 (30.95%)	1 / 12 (8.33%)
occurrences (all)	2	49	2
Axillary pain			
subjects affected / exposed	0 / 56 (0.00%)	1 / 42 (2.38%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Chest pain			
subjects affected / exposed	3 / 56 (5.36%)	1 / 42 (2.38%)	0 / 12 (0.00%)
occurrences (all)	3	1	0
Chills			
subjects affected / exposed	1 / 56 (1.79%)	5 / 42 (11.90%)	1 / 12 (8.33%)
occurrences (all)	1	5	1
Early satiety			
subjects affected / exposed	1 / 56 (1.79%)	3 / 42 (7.14%)	0 / 12 (0.00%)
occurrences (all)	1	3	0
Fatigue			
subjects affected / exposed	28 / 56 (50.00%)	30 / 42 (71.43%)	6 / 12 (50.00%)
occurrences (all)	48	85	8
Influenza like illness			
subjects affected / exposed	2 / 56 (3.57%)	5 / 42 (11.90%)	1 / 12 (8.33%)
occurrences (all)	2	8	2
Injection site bruising			
subjects affected / exposed	0 / 56 (0.00%)	0 / 42 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Malaise			
subjects affected / exposed	2 / 56 (3.57%)	1 / 42 (2.38%)	1 / 12 (8.33%)
occurrences (all)	2	2	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	6 / 56 (10.71%)	6 / 42 (14.29%)	0 / 12 (0.00%)
occurrences (all)	6	14	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	9 / 56 (16.07%)	24 / 42 (57.14%)	2 / 12 (16.67%)
occurrences (all)	15	53	11
Aspartate aminotransferase increased			
subjects affected / exposed	13 / 56 (23.21%)	22 / 42 (52.38%)	2 / 12 (16.67%)
occurrences (all)	15	40	3
Blood alkaline phosphatase increased			
subjects affected / exposed	8 / 56 (14.29%)	10 / 42 (23.81%)	1 / 12 (8.33%)
occurrences (all)	9	16	1
Blood bilirubin increased			
subjects affected / exposed	2 / 56 (3.57%)	3 / 42 (7.14%)	1 / 12 (8.33%)
occurrences (all)	2	8	2
Blood cholesterol increased			
subjects affected / exposed	5 / 56 (8.93%)	3 / 42 (7.14%)	2 / 12 (16.67%)
occurrences (all)	7	5	3
Blood creatinine increased			
subjects affected / exposed	5 / 56 (8.93%)	15 / 42 (35.71%)	6 / 12 (50.00%)
occurrences (all)	6	34	16
Blood potassium increased			
subjects affected / exposed	0 / 56 (0.00%)	0 / 42 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Blood urea increased			
subjects affected / exposed	3 / 56 (5.36%)	3 / 42 (7.14%)	0 / 12 (0.00%)
occurrences (all)	3	3	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 56 (0.00%)	2 / 42 (4.76%)	1 / 12 (8.33%)
occurrences (all)	0	2	1
Lymphocyte count decreased			
subjects affected / exposed	0 / 56 (0.00%)	0 / 42 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	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	0 / 56 (0.00%)	0 / 42 (0.00%)	3 / 12 (25.00%)
occurrences (all)	0	0	6
Neuropathy peripheral			
subjects affected / exposed	2 / 56 (3.57%)	1 / 42 (2.38%)	1 / 12 (8.33%)
occurrences (all)	2	1	1
Paraesthesia			
subjects affected / exposed	3 / 56 (5.36%)	2 / 42 (4.76%)	0 / 12 (0.00%)
occurrences (all)	3	3	0
Restless legs syndrome			
subjects affected / exposed	0 / 56 (0.00%)	0 / 42 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Tremor			
subjects affected / exposed	0 / 56 (0.00%)	3 / 42 (7.14%)	0 / 12 (0.00%)
occurrences (all)	0	4	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	18 / 56 (32.14%)	30 / 42 (71.43%)	8 / 12 (66.67%)
occurrences (all)	42	149	32
Leukopenia			
subjects affected / exposed	1 / 56 (1.79%)	3 / 42 (7.14%)	1 / 12 (8.33%)
occurrences (all)	1	3	2
Lymphopenia			
subjects affected / exposed	0 / 56 (0.00%)	1 / 42 (2.38%)	2 / 12 (16.67%)
occurrences (all)	0	1	3
Neutropenia			
subjects affected / exposed	6 / 56 (10.71%)	9 / 42 (21.43%)	2 / 12 (16.67%)
occurrences (all)	14	22	5
Thrombocytopenia			
subjects affected / exposed	4 / 56 (7.14%)	8 / 42 (19.05%)	4 / 12 (33.33%)
occurrences (all)	8	22	13
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 56 (0.00%)	2 / 42 (4.76%)	2 / 12 (16.67%)
occurrences (all)	0	4	2
Eye disorders			

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

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

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			

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

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

Conjunctival hyperaemia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Vision blurred			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Abdominal distension			
subjects affected / exposed	4 / 26 (15.38%)		
occurrences (all)	5		
Abdominal pain			
subjects affected / exposed	4 / 26 (15.38%)		
occurrences (all)	6		
Abdominal pain lower			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Aphthous ulcer			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Ascites			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	7 / 26 (26.92%)		
occurrences (all)	9		
Diarrhoea			
subjects affected / exposed	4 / 26 (15.38%)		
occurrences (all)	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 occurrences (all)	0 / 26 (0.00%) 0		
Sepsis subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Tooth infection subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 5		
Urinary tract infection subjects affected / exposed occurrences (all)	6 / 26 (23.08%) 7		
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	10 / 26 (38.46%) 17		
Dehydration subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 6		
Hypercalcaemia subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0		
Hypercholesterolaemia subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Hyperglycaemia subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 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 included 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 intrapatient 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