Clinical trial results:
A Phase I, Open Label, Multi-centre Study of AZD2281 Administered Orally in Combination with Cisplatin, to Assess the Safety and Tolerability in Patients with Advanced Solid Tumours

Summary

EudraCT number	2008-000062-24
Trial protocol	ES
Global end of trial date	07 December 2023

Results information

Result version number	v1 (current)
This version publication date	25 December 2024
First version publication date	25 December 2024

Trial information

Trial identification

Sponsor protocol code	D0810C00021

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00782574
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	151 85, Sodertalje, Sweden,
Public contact	Global Clinical Lead, AstraZeneca, +1 8772409479, information.center@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca, +1 8772409479, information.center@astrazeneca.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	01 February 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 December 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to determine the safety and tolerability of twice daily oral doses of AZD2281 when administered in combination with cisplatin to participants with advanced solid tumours.

Protection of trial subjects:

The conduct of this clinical study met all local and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization guideline: Good Clinical Practice, and applicable regulatory requirements. Participants signed an informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 November 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 22
Country: Number of subjects enrolled	United States: 32
Worldwide total number of subjects	54
EEA total number of subjects	22

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)	48
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 4 sites in 2 countries (the United States and Spain).

Pre-assignment

Screening details:

A total of 59 participants were enrolled in the study, out of which only 54 participants received treatment. Out of 59 enrolled, four participants were incorrectly enrolled and one participant was excluded due to the investigator's decision.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1: Continuous Dosing

Arm description:

Participants received oral olaparib capsule 50 mg once on Study Day 1 and thereafter received combination therapy of oral olaparib capsule 50 mg twice daily (BID) and intravenous (IV) cisplatin infusion 75 mg/m^2 on Day 1 (Study Day 8) of 21-day cycle. Participants continued receiving oral olaparib 50 mg BID until Day 21 of the cycle. Participants continued receiving combination therapy until Cycle 6 or until they received benefit and were free from significant toxicity. Post cisplatin discontinuation after Cycle 6, participants continued receiving oral olaparib capsule 400 mg BID (monotherapy phase) at the investigator's discretion until participants received benefit or not met disease progression or any other discontinuation criteria.

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

Dosage and administration details:

Intravenous (IV) cisplatin infusion 75 mg/m^2 on Day 1 (Study Day 8) of 21-day cycle as combination therapy. Participants continued receiving combination therapy until Cycle 6 or until they received benefit and were free from significant toxicity.

Investigational medicinal product name	Olaparib
Investigational medicinal product code	AZD2281
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Oral olaparib capsule 50 mg once on Study Day 1 and thereafter twice daily (BID) as combination therapy on Day 1 (Study Day 8) of 21-day cycle until Day 21 of the cycle. Participants continued receiving combination therapy until Cycle 6 or until they received benefit and were free from significant toxicity. Post discontinuation of combination therapy after Cycle 6, participants continued receiving oral olaparib capsule 400 mg BID (monotherapy phase) at the investigator's discretion until participants received benefit or not met disease progression or any other discontinuation criteria.

Arm title	Cohort 2: Continuous Dosing

Arm description:

Participants received oral olaparib capsule 100 mg once on Study Day 1 and thereafter received combination therapy of oral olaparib capsule 100 mg twice daily (BID) and intravenous (IV) cisplatin infusion 75 mg/m^2 on Day 1 (Study Day 8) of 21-day cycle. Participants continued receiving oral

olaparib 100 mg BID until Day 21 of the cycle. Participants continued receiving combination therapy until Cycle 6 or until they received benefit and were free from significant toxicity. Post cisplatin discontinuation after Cycle 6, participants continued receiving oral olaparib capsule 400 mg BID (monotherapy phase) at the investigator's discretion until participants received benefit or not met disease progression or any other discontinuation criteria.

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

Dosage and administration details:

The IV cisplatin infusion 75 mg/m^2 on Day 1 (Study Day 8) of 21-day cycle as combination therapy. Participants continued receiving combination therapy until Cycle 6 or until they received benefit and were free from significant toxicity.

Investigational medicinal product name	Olaparib
Investigational medicinal product code	AZD2281
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Oral olaparib capsule 100 mg once on Study Day 1 and thereafter BID as combination therapy on Day 1 (Study Day 8) of 21-day cycle until Day 21 of the cycle. Participants continued receiving combination therapy until Cycle 6 or until they received benefit and were free from significant toxicity. Post discontinuation of combination therapy after Cycle 6, participants continued receiving oral olaparib capsule 400 mg BID (monotherapy phase) at the investigator's discretion until participants received benefit or not met disease progression or any other discontinuation criteria.

Arm title	Cohort 3: Continuous Dosing

Arm description:

Participants received oral olaparib capsule 200 mg once on Study Day 1 and thereafter received combination therapy of oral olaparib capsule 200 mg twice daily (BID) and intravenous (IV) cisplatin infusion 75 mg/m^2 on Day 1 (Study Day 8) of 21-day cycle. Participants continued receiving oral olaparib 200 mg BID until Day 21 of the cycle. Participants continued receiving combination therapy until Cycle 6 or until they received benefit and were free from significant toxicity. Post cisplatin discontinuation after Cycle 6, participants continued receiving oral olaparib capsule 400 mg BID (monotherapy phase) at the investigator's discretion until participants received benefit or not met disease progression or any other discontinuation criteria.

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

Dosage and administration details:

The IV cisplatin infusion 75 mg/m^2 on Day 1 (Study Day 8) of 21-day cycle as combination therapy. Participants continued receiving combination therapy until Cycle 6 or until they received benefit and were free from significant toxicity.

Investigational medicinal product name	Olaparib
Investigational medicinal product code	AZD2281
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Oral olaparib capsule 200 mg once on Study Day 1 and thereafter BID as combination therapy on Day 1 (Study Day 8) of 21-day cycle until Day 21 of the cycle. Participants continued receiving combination therapy until Cycle 6 or until they received benefit and were free from significant toxicity. Post discontinuation of combination therapy after Cycle 6, participants continued receiving oral olaparib capsule 400 mg BID (monotherapy phase) at the investigator's discretion until participants received

benefit or not met disease progression or any other discontinuation criteria.

Arm title	Cohort 4: Intermittent Dosing

Arm description:

Participants received oral olaparib capsule 100 mg BID on Days 1 to 10 and IV cisplatin infusion 75 mg/m^2 on Day 1 of 21-day cycle. Participants continued receiving combination therapy until Cycle 6 or until they received benefit and were free from significant toxicity. Post cisplatin discontinuation after Cycle 6, participants continued receiving oral olaparib capsule 400 mg BID (monotherapy phase) at the investigator's discretion until participants received benefit or not met disease progression or any other discontinuation criteria.

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

Dosage and administration details:

The IV cisplatin infusion 75 mg/m^2 on Day 1 of 21-day cycle as combination therapy. Participants continued receiving combination therapy until Cycle 6 or until they received benefit and were free from significant toxicity.

Investigational medicinal product name	Olaparib
Investigational medicinal product code	AZD2281
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Oral olaparib capsule 100 mg BID on Days 1 to 10 of 21-day cycle. Participants continued receiving combination therapy until Cycle 6 or until they received benefit and were free from significant toxicity. Post discontinuation of combination therapy after Cycle 6, participants continued receiving oral olaparib capsule 400 mg BID (monotherapy phase) at the investigator's discretion until participants received benefit or not met disease progression or any other discontinuation criteria.

Arm title	Cohort 5: Intermittent Dosing

Arm description:

Participants received oral olaparib capsule 50 mg BID on Days 1 to 10 and IV cisplatin infusion 75 mg/m^2 on Day 1 of 21-day cycle. Participants continued receiving combination therapy until Cycle 6 or until they received benefit and were free from significant toxicity. Post cisplatin discontinuation after Cycle 6, participants continued receiving oral olaparib capsule 400 mg BID (monotherapy phase) at the investigator's discretion until participants received benefit or not met disease progression or any other discontinuation criteria.

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

Dosage and administration details:

The IV cisplatin infusion 75 mg/m^2 on Day 1 of 21-day cycle as combination therapy. Participants continued receiving combination therapy until Cycle 6 or until they received benefit and were free from significant toxicity.

Investigational medicinal product name	Olaparib
Investigational medicinal product code	AZD2281
Other name	
Pharmaceutical forms	Capsule

Routes of administration	Oral use

Dosage and administration details:

Oral olaparib capsule 50 mg BID on Days 1 to 10 of 21-day cycle. Participants continued receiving combination therapy until Cycle 6 or until they received benefit and were free from significant toxicity. Post discontinuation of combination therapy after Cycle 6, participants continued receiving oral olaparib capsule 400 mg BID (monotherapy phase) at the investigator's discretion until participants received benefit or not met disease progression or any other discontinuation criteria.

Arm title	Cohort 6: Intermittent Dosing

Arm description:

Participants received oral olaparib capsule 50 mg BID on Days 1 to 10 and IV cisplatin infusion 60 mg/m^2 on Day 1 of 21-day cycle. Participants continued receiving combination therapy until Cycle 6 or until they received benefit and were free from significant toxicity. Post cisplatin discontinuation after Cycle 6, participants continued receiving oral olaparib capsule 400 mg BID (monotherapy phase) at the investigator's discretion until participants received benefit or not met disease progression or any other discontinuation criteria.

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

Dosage and administration details:

The IV cisplatin infusion 60 mg/m^2 on Day 1 of 21-day cycle as combination therapy. Participants continued receiving combination therapy until Cycle 6 or until they received benefit and were free from significant toxicity.

Investigational medicinal product name	Olaparib
Investigational medicinal product code	AZD2281
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Oral olaparib capsule 50 mg BID on Days 1 to 10 of 21-day cycle. Participants continued receiving combination therapy until Cycle 6 or until they received benefit and were free from significant toxicity. Post discontinuation of combination therapy after Cycle 6, participants continued receiving oral olaparib capsule 400 mg BID (monotherapy phase) at the investigator's discretion until participants received benefit or not met disease progression or any other discontinuation criteria.

Number of subjects in period 1	Cohort 1: Continuous Dosing	Cohort 2: Continuous Dosing	Cohort 3: Continuous Dosing
Started	3	13	6
Completed	0	0	0
Not completed	3	13	6
Ongoing study at data cutoff	2	-	-
Adverse event, non-fatal	-	2	2
Condition under investigation worsened	1	11	4
Not specified	-	-	-

Number of subjects in period 1	Cohort 4: Intermittent Dosing	Cohort 5: Intermittent Dosing	Cohort 6: Intermittent Dosing
Started	14	6	12
Completed	0	0	0
Not completed	14	6	12

Ongoing study at data cutoff	1	1	6
Adverse event, non-fatal	-	-	-
Condition under investigation worsened	12	5	6
Not specified	1	-	-

Baseline characteristics

Reporting groups

Reporting group title	Cohort 1: Continuous Dosing

Reporting group description:

Participants received oral olaparib capsule 50 mg once on Study Day 1 and thereafter received combination therapy of oral olaparib capsule 50 mg twice daily (BID) and intravenous (IV) cisplatin infusion 75 mg/m^2 on Day 1 (Study Day 8) of 21-day cycle. Participants continued receiving oral olaparib 50 mg BID until Day 21 of the cycle. Participants continued receiving combination therapy until Cycle 6 or until they received benefit and were free from significant toxicity. Post cisplatin discontinuation after Cycle 6, participants continued receiving oral olaparib capsule 400 mg BID (monotherapy phase) at the investigator's discretion until participants received benefit or not met disease progression or any other discontinuation criteria.

Reporting group title	Cohort 2: Continuous Dosing

Reporting group description:

Participants received oral olaparib capsule 100 mg once on Study Day 1 and thereafter received combination therapy of oral olaparib capsule 100 mg twice daily (BID) and intravenous (IV) cisplatin infusion 75 mg/m^2 on Day 1 (Study Day 8) of 21-day cycle. Participants continued receiving oral olaparib 100 mg BID until Day 21 of the cycle. Participants continued receiving combination therapy until Cycle 6 or until they received benefit and were free from significant toxicity. Post cisplatin discontinuation after Cycle 6, participants continued receiving oral olaparib capsule 400 mg BID (monotherapy phase) at the investigator's discretion until participants received benefit or not met disease progression or any other discontinuation criteria.

Reporting group title	Cohort 3: Continuous Dosing

Reporting group description:

Participants received oral olaparib capsule 200 mg once on Study Day 1 and thereafter received combination therapy of oral olaparib capsule 200 mg twice daily (BID) and intravenous (IV) cisplatin infusion 75 mg/m^2 on Day 1 (Study Day 8) of 21-day cycle. Participants continued receiving oral olaparib 200 mg BID until Day 21 of the cycle. Participants continued receiving combination therapy until Cycle 6 or until they received benefit and were free from significant toxicity. Post cisplatin discontinuation after Cycle 6, participants continued receiving oral olaparib capsule 400 mg BID (monotherapy phase) at the investigator's discretion until participants received benefit or not met disease progression or any other discontinuation criteria.

Reporting group title	Cohort 4: Intermittent Dosing

Reporting group description:

Participants received oral olaparib capsule 100 mg BID on Days 1 to 10 and IV cisplatin infusion 75 mg/m^2 on Day 1 of 21-day cycle. Participants continued receiving combination therapy until Cycle 6 or until they received benefit and were free from significant toxicity. Post cisplatin discontinuation after Cycle 6, participants continued receiving oral olaparib capsule 400 mg BID (monotherapy phase) at the investigator's discretion until participants received benefit or not met disease progression or any other discontinuation criteria.

Reporting group title	Cohort 5: Intermittent Dosing

Reporting group description:

Participants received oral olaparib capsule 50 mg BID on Days 1 to 10 and IV cisplatin infusion 75 mg/m^2 on Day 1 of 21-day cycle. Participants continued receiving combination therapy until Cycle 6 or until they received benefit and were free from significant toxicity. Post cisplatin discontinuation after Cycle 6, participants continued receiving oral olaparib capsule 400 mg BID (monotherapy phase) at the investigator's discretion until participants received benefit or not met disease progression or any other discontinuation criteria.

Reporting group title	Cohort 6: Intermittent Dosing

Reporting group description:

Participants received oral olaparib capsule 50 mg BID on Days 1 to 10 and IV cisplatin infusion 60 mg/m^2 on Day 1 of 21-day cycle. Participants continued receiving combination therapy until Cycle 6 or until they received benefit and were free from significant toxicity. Post cisplatin discontinuation after Cycle 6, participants continued receiving oral olaparib capsule 400 mg BID (monotherapy phase) at the investigator's discretion until participants received benefit or not met disease progression or any other discontinuation criteria.

Reporting group values	Cohort 1: Continuous Dosing	Cohort 2: Continuous Dosing	Cohort 3: Continuous Dosing
Number of subjects	3	13	6
Age categorical Units: Participants			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	3	12	4
From 65-84 years	0	1	2
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	50.7	49.2	53.2
standard deviation	± 12.0	± 10.8	± 14.9
Sex: Female, Male Units: Participants			
Female	3	13	6
Male	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	1	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	3	12	6
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	0	0	0
Unknown or Not Reported	3	13	6

Reporting group values	Cohort 4: Intermittent Dosing	Cohort 5: Intermittent Dosing	Cohort 6: Intermittent Dosing
Number of subjects	14	6	12
Age categorical Units: Participants			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	13	6	10

From 65-84 years	1	0	2
85 years and over	0	0	0

Age Continuous			
Units: Years			
arithmetic mean	47.7	49.7	48.3
standard deviation	± 9.3	± 9.6	± 11.0
Sex: Female, Male			
Units: Participants			
Female	14	6	10
Male	0	0	2
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	14	6	12
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	0	0	0
Unknown or Not Reported	14	6	12

Reporting group values	Total		
Number of subjects	54		
Age categorical			
Units: Participants			
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)	48		
From 65-84 years	6		
85 years and over	0		
Age Continuous			
Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: Participants			
Female	52		
Male	2		

Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	1		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	0		
White	53		
More than one race	0		
Unknown or Not Reported	0		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0		
Not Hispanic or Latino	0		
Unknown or Not Reported	54		

End points

End points reporting groups

Reporting group title	Cohort 1: Continuous Dosing

Reporting group description:

Participants received oral olaparib capsule 50 mg once on Study Day 1 and thereafter received combination therapy of oral olaparib capsule 50 mg twice daily (BID) and intravenous (IV) cisplatin infusion 75 mg/m^2 on Day 1 (Study Day 8) of 21-day cycle. Participants continued receiving oral olaparib 50 mg BID until Day 21 of the cycle. Participants continued receiving combination therapy until Cycle 6 or until they received benefit and were free from significant toxicity. Post cisplatin discontinuation after Cycle 6, participants continued receiving oral olaparib capsule 400 mg BID (monotherapy phase) at the investigator’s discretion until participants received benefit or not met disease progression or any other discontinuation criteria.

Reporting group title	Cohort 2: Continuous Dosing

Reporting group description:

Participants received oral olaparib capsule 100 mg once on Study Day 1 and thereafter received combination therapy of oral olaparib capsule 100 mg twice daily (BID) and intravenous (IV) cisplatin infusion 75 mg/m^2 on Day 1 (Study Day 8) of 21-day cycle. Participants continued receiving oral olaparib 100 mg BID until Day 21 of the cycle. Participants continued receiving combination therapy until Cycle 6 or until they received benefit and were free from significant toxicity. Post cisplatin discontinuation after Cycle 6, participants continued receiving oral olaparib capsule 400 mg BID (monotherapy phase) at the investigator’s discretion until participants received benefit or not met disease progression or any other discontinuation criteria.

Reporting group title	Cohort 3: Continuous Dosing

Reporting group description:

Participants received oral olaparib capsule 200 mg once on Study Day 1 and thereafter received combination therapy of oral olaparib capsule 200 mg twice daily (BID) and intravenous (IV) cisplatin infusion 75 mg/m^2 on Day 1 (Study Day 8) of 21-day cycle. Participants continued receiving oral olaparib 200 mg BID until Day 21 of the cycle. Participants continued receiving combination therapy until Cycle 6 or until they received benefit and were free from significant toxicity. Post cisplatin discontinuation after Cycle 6, participants continued receiving oral olaparib capsule 400 mg BID (monotherapy phase) at the investigator’s discretion until participants received benefit or not met disease progression or any other discontinuation criteria.

Reporting group title	Cohort 4: Intermittent Dosing

Reporting group description:

Participants received oral olaparib capsule 100 mg BID on Days 1 to 10 and IV cisplatin infusion 75 mg/m^2 on Day 1 of 21-day cycle. Participants continued receiving combination therapy until Cycle 6 or until they received benefit and were free from significant toxicity. Post cisplatin discontinuation after Cycle 6, participants continued receiving oral olaparib capsule 400 mg BID (monotherapy phase) at the investigator’s discretion until participants received benefit or not met disease progression or any other discontinuation criteria.

Reporting group title	Cohort 5: Intermittent Dosing

Reporting group description:

Participants received oral olaparib capsule 50 mg BID on Days 1 to 10 and IV cisplatin infusion 75 mg/m^2 on Day 1 of 21-day cycle. Participants continued receiving combination therapy until Cycle 6 or until they received benefit and were free from significant toxicity. Post cisplatin discontinuation after Cycle 6, participants continued receiving oral olaparib capsule 400 mg BID (monotherapy phase) at the investigator’s discretion until participants received benefit or not met disease progression or any other discontinuation criteria.

Reporting group title	Cohort 6: Intermittent Dosing

Reporting group description:

Participants received oral olaparib capsule 50 mg BID on Days 1 to 10 and IV cisplatin infusion 60 mg/m^2 on Day 1 of 21-day cycle. Participants continued receiving combination therapy until Cycle 6 or until they received benefit and were free from significant toxicity. Post cisplatin discontinuation after Cycle 6, participants continued receiving oral olaparib capsule 400 mg BID (monotherapy phase) at the investigator’s discretion until participants received benefit or not met disease progression or any other discontinuation criteria.

Primary: Number of Participants With Treatment Emergent Adverse Events (TEAEs) and Treatment Emergent Serious Adverse Events (TESAEs)

End point title	Number of Participants With Treatment Emergent Adverse Events (TEAEs) and Treatment Emergent Serious Adverse Events (TESAEs)[1]

End point description:

An adverse event (AE) is any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. A serious adverse event (SAE) is an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. The TEAEs are defined as events present at baseline that worsened in intensity after administration of study drug or events absent at baseline that emerged after administration of study drug. Safety analysis set included all participants who received at least one dose of olaparib.

End point type	Primary

End point timeframe:

Day 1 through Day 1181 (maximum observed duration)

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: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Cohort 1: Continuous Dosing	Cohort 2: Continuous Dosing	Cohort 3: Continuous Dosing	Cohort 4: Intermittent Dosing
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	13	6	14
Units: Participants				
TEAEs	3	13	6	14
TESAEs	0	3	2	2

End point values	Cohort 5: Intermittent Dosing	Cohort 6: Intermittent Dosing		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	12		
Units: Participants				
TEAEs	6	12		
TESAEs	4	5		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Clinically Significant Abnormalities in Vital Signs

End point title	Number of Participants With Clinically Significant Abnormalities in Vital Signs[2]

End point description:

Number of participants with clinically significant abnormalities in vital signs are reported. Clinically significant abnormal vital signs are defined as any significant abnormal finding in the vital sign

parameters (blood pressure, pulse rate, and body temperature). Safety analysis set included all participants who received at least one dose of olaparib.

End point type	Primary

End point timeframe:

Day 1 through Day 1181 (maximum observed duration)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Cohort 1: Continuous Dosing	Cohort 2: Continuous Dosing	Cohort 3: Continuous Dosing	Cohort 4: Intermittent Dosing
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	13	6	14
Units: Participants	0	0	0	0

End point values	Cohort 5: Intermittent Dosing	Cohort 6: Intermittent Dosing		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	12		
Units: Participants	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Abnormal Electrocardiogram (ECG) Reported as TEAEs

End point title	Number of Participants With Abnormal Electrocardiogram (ECG) Reported as TEAEs[3]

End point description:

Number of participants with abnormal ECG reported as TEAEs are reported. Safety analysis set included all participants who received at least one dose of olaparib.

End point type	Primary

End point timeframe:

Day 1 through Day 1181 (maximum observed duration)

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 analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Cohort 1: Continuous Dosing	Cohort 2: Continuous Dosing	Cohort 3: Continuous Dosing	Cohort 4: Intermittent Dosing
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	13	6	14
Units: Participants	0	0	0	0

End point values	Cohort 5: Intermittent Dosing	Cohort 6: Intermittent Dosing		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	12		
Units: Participants	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Abnormal Clinical Laboratory Parameters Reported as TEAEs

End point title	Number of Participants With Abnormal Clinical Laboratory Parameters Reported as TEAEs[4]

End point description:

Number of participants with abnormal clinical laboratory parameters reported as TEAEs are reported. Abnormal clinical laboratory parameters defined as any abnormal finding during analysis of haematology, clinical chemistry, and urinalysis. Safety analysis set included all participants who received at least one dose of olaparib.

End point type	Primary

End point timeframe:

Day 1 through Day 1181 (maximum observed duration)

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 analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Cohort 1: Continuous Dosing	Cohort 2: Continuous Dosing	Cohort 3: Continuous Dosing	Cohort 4: Intermittent Dosing
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	13	6	14
Units: Participants				
Anaemia	1	6	4	3
Hypoglobulinaemia	0	0	0	0
Leukocytosis	0	0	0	1
Leukopenia	1	6	0	5
Lymphopenia	1	1	0	3
Macrocytosis	0	0	1	0
Neutropenia	3	5	4	6
Thrombocytopenia	2	4	3	2
Thrombocytosis	0	1	0	0

Ketonuria	1	0	0	0
Proteinuria	1	1	0	1
Activated partial thromboplastin time prolonged	0	1	0	0
Activated partial thromboplastin time shortened	0	1	0	1
Alanine aminotransferase increased	1	3	0	1
Aspartate aminotransferase increased	0	1	0	0
Blood alkaline phosphatase increased	2	2	1	1
Blood amylase increased	1	0	0	1
Blood chloride decreased	0	0	0	1
Blood creatinine increased	0	1	0	0
Blood glucose increased	0	0	0	2
Blood lactate dehydrogenase increased	0	3	0	1
Blood phosphorus decreased	0	0	0	0
Blood potassium decreased	0	0	0	0
Blood urea increased	0	1	0	1
Blood urine present	0	0	0	1
Gamma-glutamyltransferase increased	0	3	0	0
Globulin	0	1	0	0
Globulins decreased	0	0	0	1
Glucose urine	0	0	0	1
Glucose urine present	0	0	0	0
International normalised ratio increased	0	1	0	0
Lipase	0	0	0	0
Lipase increased	0	0	1	2
Low density lipoprotein increased	0	0	0	1
Neutrophil count decreased	0	1	0	0
Neutrophil count increased	0	0	0	1
Protein total decreased	0	0	0	1
Protein urine present	0	0	0	2
Prothrombin time prolonged	0	1	0	0
Red blood cells urine	0	0	0	1
Red blood cells urine positive	0	0	0	1
Urinary sediment present	0	0	0	1
White blood cell count decreased	0	0	0	0
White blood cell count increased	0	2	0	1
White blood cells urine positive	0	1	0	2
Hypercholesterolaemia	0	1	0	1
Hyperglycaemia	0	3	1	1
Hyperkalaemia	1	0	0	0
Hyperphosphataemia	0	1	0	0
Hypertriglyceridaemia	0	1	0	0
Hypoalbuminaemia	0	0	0	1
Hypocalcaemia	0	0	0	1
Hypochloraemia	1	0	0	0
Hypokalaemia	1	0	1	1
Hypomagnesaemia	1	3	2	1
Hyponatraemia	1	0	0	1
Hypophosphataemia	0	0	1	0

End point values	Cohort 5: Intermittent Dosing	Cohort 6: Intermittent Dosing		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	12		
Units: Participants				
Anaemia	3	3		
Hypoglobulinaemia	0	1		
Leukocytosis	0	0		
Leukopenia	0	0		
Lymphopenia	0	1		
Macrocytosis	0	0		
Neutropenia	1	3		
Thrombocytopenia	0	0		
Thrombocytosis	0	0		
Ketonuria	0	0		
Proteinuria	0	0		
Activated partial thromboplastin time prolonged	0	0		
Activated partial thromboplastin time shortened	0	0		
Alanine aminotransferase increased	1	3		
Aspartate aminotransferase increased	0	1		
Blood alkaline phosphatase increased	0	1		
Blood amylase increased	0	0		
Blood chloride decreased	0	0		
Blood creatinine increased	1	0		
Blood glucose increased	0	0		
Blood lactate dehydrogenase increased	0	0		
Blood phosphorus decreased	0	1		
Blood potassium decreased	0	1		
Blood urea increased	0	1		
Blood urine present	0	0		
Gamma-glutamyltransferase increased	0	1		
Globulin	0	0		
Globulins decreased	0	0		
Glucose urine	0	0		
Glucose urine present	0	1		
International normalised ratio increased	0	0		
Lipase	0	1		
Lipase increased	0	0		
Low density lipoprotein increased	0	0		
Neutrophil count decreased	0	1		
Neutrophil count increased	0	0		
Protein total decreased	0	0		
Protein urine present	0	0		
Prothrombin time prolonged	0	0		
Red blood cells urine	0	0		
Red blood cells urine positive	0	0		

Urinary sediment present	0	0		
White blood cell count decreased	0	1		
White blood cell count increased	0	1		
White blood cells urine positive	0	0		
Hypercholesterolaemia	0	0		
Hyperglycaemia	0	1		
Hyperkalaemia	0	0		
Hyperphosphataemia	0	0		
Hypertriglyceridaemia	0	0		
Hypoalbuminaemia	0	0		
Hypocalcaemia	0	0		
Hypochloraemia	0	1		
Hypokalaemia	0	0		
Hypomagnesaemia	0	0		
Hyponatraemia	0	1		
Hypophosphataemia	0	1		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Abnormality or Aggravation in Physical Examination

End point title	Number of Participants With Abnormality or Aggravation in Physical Examination[5]

End point description:

Number of participants with abnormality or aggravation in physical examination are reported. Safety analysis set included all participants who received at least one dose of olaparib.

End point type	Primary

End point timeframe:

Baseline (screening), at Weeks 2, 5, and 8, every week following Week 8, and at withdrawal, and 30-day follow-up; for olaparib monotherapy on Days, 1, 43, then every 6 weeks, at olaparib discontinuation

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Cohort 1: Continuous Dosing	Cohort 2: Continuous Dosing	Cohort 3: Continuous Dosing	Cohort 4: Intermittent Dosing
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	13	6	14
Units: Participants	0	0	0	0

End point values	Cohort 5: Intermittent Dosing	Cohort 6: Intermittent Dosing		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	12		

Units: Participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Objective Response by Response Evaluation Criteria in Solid Tumors (RECIST)

End point title	Percentage of Participants With Objective Response by Response Evaluation Criteria in Solid Tumors (RECIST)

End point description:

Objective response was defined as participants with a best response of complete response (CR) or partial response (PR) based on RECIST assessment response. The CR is defined as disappearance of all target and non-target lesions and no new lesions. The PR is defined as >=30% decrease in the sum of the diameters of target lesions compared to baseline and no new non-target lesion. Percentage of participants with objective response was reported. Full analysis set included all participants who received at least one dose of study drug. Here, number of participants analyzed denotes those participants who had target tumour at baseline and were evaluable for RECIST response. The arbitrary numbers 9.9999 and 99999 signified low and high value of confidence interval (CI) was not calculated as cohort size was less than 10.

End point type	Secondary

End point timeframe:

Baseline (within 28 days pre-dose), end of every 2 cycles of treatment, at study withdrawal; for olaparib monotherapy at Weeks 9, 18, then every 12 weeks relative to Cycle 1 Day 1 of combination therapy until disease progression (approx. 15.1 years)

End point values	Cohort 1: Continuous Dosing	Cohort 2: Continuous Dosing	Cohort 3: Continuous Dosing	Cohort 4: Intermittent Dosing
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	12	4	10
Units: Percentage of Participants				
number (confidence interval 95%)	100 (9.9999 to 99999)	0 (0.0 to 24.2)	75.0 (9.9999 to 99999)	50.0 (23.7 to 76.3)

End point values	Cohort 5: Intermittent Dosing	Cohort 6: Intermittent Dosing		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	11		
Units: Percentage of Participants				
number (confidence interval 95%)	50.0 (9.9999 to 99999)	45.5 (21.3 to 72.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Objective Response

End point title	Duration of Objective Response

End point description:

Duration of objective response was defined as the time from the initial assessment prior of PR or CR (the assessment prior to being a confirmed response), until the earliest date of objective disease progression or death. The median duration of response was derived from Kaplan Meier analysis. Full analysis set included all participants who received at least one dose of study drug. The arbitrary number 999.99 signified the median was not calculated due to insufficient number to calculate. Here, number of participants analyzed denotes those participants who had objective response. Responses were still ongoing in Cohorts 1, 4, 5, and 6 at data cut-off.

End point type	Secondary

End point timeframe:

Baseline (within 28 days pre-dose), end of every 2 cycles of treatment, at study withdrawal; for olaparib monotherapy at Weeks 9, 18, then every 12 weeks relative to Cycle 1 Day 1 of combination therapy until disease progression (approx. 15.1 years)

End point values	Cohort 1: Continuous Dosing	Cohort 2: Continuous Dosing	Cohort 3: Continuous Dosing	Cohort 4: Intermittent Dosing
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	0[6]	3	5
Units: Days				
median (full range (min-max))	999.99 (88 to 1092)	(to)	316 (41 to 887)	133 (91 to 694)

Notes:

[6] - Number of subjects analyzed is zero as for this cohort, zero participant had objective response.

End point values	Cohort 5: Intermittent Dosing	Cohort 6: Intermittent Dosing		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	5		
Units: Days				
median (full range (min-max))	307 (179 to 388)	162 (83 to 245)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Onset of Objective Response

End point title	Time to Onset of Objective Response

End point description:

Onset of response was defined as the time interval from first taking study drug to the assessment when CR or PR was first observed, providing it was subsequently confirmed. The median time to onset response was derived from Kaplan Meier analysis. Full analysis set included all participants who received at least one dose of study drug. Here, number of participants analyzed those participants who had

objective response.

End point type	Secondary

End point timeframe:

Baseline (within 28 days pre-dose), end of every 2 cycles of treatment, at study withdrawal; for olaparib monotherapy at Weeks 9, 18, then every 12 weeks relative to Cycle 1 Day 1 of combination therapy until disease progression (approx. 15.1 years)

End point values	Cohort 1: Continuous Dosing	Cohort 2: Continuous Dosing	Cohort 3: Continuous Dosing	Cohort 4: Intermittent Dosing
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	0[7]	3	5
Units: Days				
median (full range (min-max))	128 (41 to 172)	(to)	46 (35 to 48)	49 (44 to 101)

Notes:

[7] - Number of subjects analyzed is zero as for this cohort, zero participant had objective response.

End point values	Cohort 5: Intermittent Dosing	Cohort 6: Intermittent Dosing		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	5		
Units: Days				
median (full range (min-max))	40 (38 to 84)	56 (35 to 96)		

Statistical analyses

No statistical analyses for this end point

Secondary: Best Percentage Change From Baseline in Target Lesion Size

End point title	Best Percentage Change From Baseline in Target Lesion Size

End point description:

The total tumor size was defined as the sum of the longest diameter of the target lesions. Best change in target lesion size is the maximum reduction from baseline or minimum increase in the absence of a reduction. The percentage change in total tumor (target lesion) size at each scheduled visit was calculated as the [(visit sum target lesions – baseline sum of target lesions)/baseline sum target lesions]*100. A negative change denotes a reduction in target lesion size. Full analysis set included all participants who received at least one dose of study drug. Here, number of participants analyzed denotes the number of participants evaluated for this outcome measure.

End point type	Secondary

End point timeframe:

For combination therapy at baseline (up to 28 days prior to Study Day 1), Day 50, and at time of withdrawal; for olaparib monotherapy at Weeks 9, 18, thereafter every 12 weeks relative to Cycle 1 Day 1 of combination therapy until disease progression

End point values	Cohort 1: Continuous Dosing	Cohort 2: Continuous Dosing	Cohort 3: Continuous Dosing	Cohort 4: Intermittent Dosing
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	12	4	10
Units: Percent Change in Lesion Size				
arithmetic mean (standard deviation)	-56.9 (± 16.34)	-6.1 (± 21.95)	-52.2 (± 31.21)	-32.5 (± 27.32)

End point values	Cohort 5: Intermittent Dosing	Cohort 6: Intermittent Dosing		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	11		
Units: Percent Change in Lesion Size				
arithmetic mean (standard deviation)	-39.3 (± 29.48)	-21.0 (± 36.94)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of Olaparib

End point title	Plasma Concentration of Olaparib[8]

End point description:

Plasma concentration of olaparib at Visit (V) 2 (Study Day 1) and 3 (Study Day 8) is reported. Pharmacokinetic (PK) analysis set included subset of safety analysis set including participants who had reportable PK data for olaparib both alone at Visit 2 and in combination with cisplatin at Visit 3. Number analyzed (n) denotes those participants who were evaluable at the specified time point. The arbitrary numbers 9.9999 and 99999 signified geometric mean and geometric CV%, respectively, not reported as the geometric mean and geometric CV% were not calculated due to insufficient number to calculate.

End point type	Secondary

End point timeframe:

Predose, 1, 2, 3, 4, 6, 8, and 12 hours post dose on V2 (Study Day 1) and V3 (Study Day 8)

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	Cohort 1: Continuous Dosing	Cohort 2: Continuous Dosing	Cohort 3: Continuous Dosing	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	12	6	
Units: µg/mL				
geometric mean (geometric coefficient of variation)				
V2: 1 hour (n=3,12,6)	0.591 (± 176.200)	1.404 (± 198.200)	1.640 (± 86.440)	
V2: 2 hours (n=3,12,6)	1.168 (± 150.200)	2.439 (± 91.100)	3.080 (± 29.990)	

V2: 3 hours (n=3,12,6)	0.669 (± 169.400)	2.213 (± 104.400)	2.769 (± 36.610)	
V2: 4 hours (n=3,12,6)	0.430 (± 161.500)	1.864 (± 128.200)	2.113 (± 47.280)	
V2: 6 hours (n=3,12,6)	0.222 (± 110.300)	1.208 (± 176.200)	1.277 (± 54.360)	
V2: 8 hours (n=3,12,6)	0.117 (± 111.100)	0.754 (± 200.400)	0.771 (± 45.770)	
V2: 12 hours (n=3,11,6)	0.057 (± 123.900)	0.451 (± 197.500)	0.455 (± 41.040)	
V3: 1 hour (n=3,11,6)	2.895 (± 26.430)	1.607 (± 133.800)	1.481 (± 136.600)	
V3: 2 hours (n=3,12,6)	1.059 (± 71.460)	2.349 (± 81.450)	2.546 (± 36.230)	
V3: 3 hours (n=3,12,6)	0.738 (± 123.900)	2.376 (± 102.800)	2.321 (± 40.360)	
V3: 4 hours (n=3,12,6)	0.502 (± 158.300)	1.921 (± 125.900)	1.836 (± 44.910)	
V3: 6 hours (n=3,12,6)	0.250 (± 210.700)	1.400 (± 162.300)	1.130 (± 59.780)	
V3: 8 hours (n=3,11,6)	0.163 (± 287.500)	0.889 (± 218.100)	0.670 (± 70.100)	
V3: 12 hours (n=2,12,5)	9.9999 (± 99999)	0.629 (± 254.300)	0.356 (± 99.260)	

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Concentration (Cmax) of Olaparib

End point title	Maximum Observed Concentration (Cmax) of Olaparib[9]

End point description:

The Cmax of olaparib at V2 (Study Day 1) and V3 (Study Day 8) is reported. The PK analysis set included subset of safety analysis set including participants who had reportable PK data for olaparib both alone at V2 and in combination with cisplatin at V3.

End point type	Secondary

End point timeframe:

Predose, 1, 2, 3, 4, 6, 8, and 12 hours post dose on V2 (Study Day 1) and V3 (Study Day 8)

Notes:

[9] - 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: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	Cohort 1: Continuous Dosing	Cohort 2: Continuous Dosing	Cohort 3: Continuous Dosing	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	12	6	
Units: µg/mL				
geometric mean (geometric coefficient of variation)				
V2	1.581 (± 117.900)	3.272 (± 56.600)	3.557 (± 13.620)	
V3	2.895 (± 26.430)	3.185 (± 68.180)	3.020 (± 37.560)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum Observed Serum Concentration (Tmax) of Olaparib

End point title	Time to Reach Maximum Observed Serum Concentration (Tmax) of Olaparib[10]

End point description:

The Tmax of olaparib at V2 (Study Day 1) and V3 (Study Day 8) is reported. The PK analysis set included subset of safety analysis set including participants who had reportable PK data for olaparib both alone at V2 and in combination with cisplatin at V3.

End point type	Secondary

End point timeframe:

Predose, 1, 2, 3, 4, 6, 8, and 12 hours post dose on V2 (Study Day 1) and V3 (Study Day 8)

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	Cohort 1: Continuous Dosing	Cohort 2: Continuous Dosing	Cohort 3: Continuous Dosing	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	12	6	
Units: Hour				
median (full range (min-max))				
V2	1.000 (1.000 to 2.000)	2.000 (1.000 to 4.000)	2.000 (1.000 to 3.000)	
V3	1.000 (1.000 to 1.000)	2.000 (1.000 to 6.000)	1.500 (1.000 to 3.000)	

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-time Curve From Time Zero to the Last Measurable Concentration (AUC0-t) of Olaparib

End point title	Area Under the Concentration-time Curve From Time Zero to the Last Measurable Concentration (AUC0-t) of Olaparib[11]

End point description:

The AUC0-t of olaparib at V2 (Study Day 1) and V3 (Study Day 8) is reported. The PK analysis set included subset of safety analysis set including participants who had reportable PK data for olaparib both alone at V2 and in combination with cisplatin at V3.

End point type	Secondary

End point timeframe:

Predose, 1, 2, 3, 4, 6, 8, and 12 hours post dose on V2 (Study Day 1) and V3 (Study Day 8)

Notes:

[11] - 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: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	Cohort 1: Continuous Dosing	Cohort 2: Continuous Dosing	Cohort 3: Continuous Dosing	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	12	6	
Units: µg.h/mL				
geometric mean (geometric coefficient of variation)				
V2	4.433 (± 109.800)	15.310 (± 103.500)	16.520 (± 25.470)	
V3	7.401 (± 40.560)	16.210 (± 113.600)	14.380 (± 35.230)	

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

Day 1 through Day 1181 (maximum observed duration)

Adverse event reporting additional description:

Safety analysis set included all participants who received at least one dose of olaparib.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	Cohort 1: Continuous Dosing

Reporting group description:

Participants received oral olaparib capsule 50 mg once on Study Day 1 and thereafter received combination therapy of oral olaparib capsule 50 mg twice daily (BID) and intravenous (IV) cisplatin infusion 75 mg/m^2 on Day 1 (Study Day 8) of 21-day cycle. Participants continued receiving oral olaparib 50 mg BID until Day 21 of the cycle. Participants continued receiving combination therapy until Cycle 6 or until they received benefit and were free from significant toxicity. Post cisplatin discontinuation after Cycle 6, participants continued receiving oral olaparib capsule 400 mg BID (monotherapy phase) at the investigator’s discretion until participants received benefit or not met disease progression or any other discontinuation criteria.

Reporting group title	Cohort 2: Continuous Dosing

Reporting group description:

Participants received oral olaparib capsule 100 mg once on Study Day 1 and thereafter received combination therapy of oral olaparib capsule 100 mg twice daily (BID) and intravenous (IV) cisplatin infusion 75 mg/m^2 on Day 1 (Study Day 8) of 21-day cycle. Participants continued receiving oral olaparib 100 mg BID until Day 21 of the cycle. Participants continued receiving combination therapy until Cycle 6 or until they received benefit and were free from significant toxicity. Post cisplatin discontinuation after Cycle 6, participants continued receiving oral olaparib capsule 400 mg BID (monotherapy phase) at the investigator’s discretion until participants received benefit or not met disease progression or any other discontinuation criteria.

Reporting group title	Cohort 6: Intermittent Dosing

Reporting group description:

Participants received oral olaparib capsule 50 mg BID on Days 1 to 10 and IV cisplatin infusion 60 mg/m^2 on Day 1 of 21-day cycle. Participants continued receiving combination therapy until Cycle 6 or until they received benefit and were free from significant toxicity. Post cisplatin discontinuation after Cycle 6, participants continued receiving oral olaparib capsule 400 mg BID (monotherapy phase) at the investigator’s discretion until participants received benefit or not met disease progression or any other discontinuation criteria.

Reporting group title	Cohort 4: Intermittent Dosing

Reporting group description:

Participants received oral olaparib capsule 100 mg BID on Days 1 to 10 and IV cisplatin infusion 75 mg/m^2 on Day 1 of 21-day cycle. Participants continued receiving combination therapy until Cycle 6 or until they received benefit and were free from significant toxicity. Post cisplatin discontinuation after Cycle 6, participants continued receiving oral olaparib capsule 400 mg BID (monotherapy phase) at the investigator’s discretion until participants received benefit or not met disease progression or any other discontinuation criteria.

Reporting group title	Cohort 5: Intermittent Dosing

Reporting group description:

Participants received oral olaparib capsule 50 mg BID on Days 1 to 10 and IV cisplatin infusion 75 mg/m^2 on Day 1 of 21-day cycle. Participants continued receiving combination therapy until Cycle 6 or until they received benefit and were free from significant toxicity. Post cisplatin discontinuation after Cycle 6, participants continued receiving oral olaparib capsule 400 mg BID (monotherapy phase) at the investigator’s discretion until participants received benefit or not met disease progression or any other discontinuation criteria.

Reporting group title	Cohort 3: Continuous Dosing

Reporting group description:

Participants received oral olaparib capsule 200 mg once on Study Day 1 and thereafter received combination therapy of oral olaparib capsule 200 mg twice daily (BID) and intravenous (IV) cisplatin infusion 75 mg/m^2 on Day 1 (Study Day 8) of 21-day cycle. Participants continued receiving oral olaparib 200 mg BID until Day 21 of the cycle. Participants continued receiving combination therapy until Cycle 6 or until they received benefit and were free from significant toxicity. Post cisplatin discontinuation after Cycle 6, participants continued receiving oral olaparib capsule 400 mg BID (monotherapy phase) at the investigator's discretion until participants received benefit or not met disease progression or any other discontinuation criteria.

Serious adverse events	Cohort 1: Continuous Dosing	Cohort 2: Continuous Dosing	Cohort 6: Intermittent Dosing
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	3 / 13 (23.08%)	5 / 12 (41.67%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Toxicity to various agents			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (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
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (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
Nervous system disorders			
Migraine			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (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
Neuralgia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (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
Blood and lymphatic system disorders			
Thrombocytopenia			

subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	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
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (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
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (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
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (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
Small intestinal obstruction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (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
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	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
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (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
Psychiatric disorders			
Depression			

subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	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
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (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 vein thrombosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (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
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (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
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (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
Bronchitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (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
Cellulitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (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

Device related infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (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
Metabolism and nutrition disorders			
Electrolyte imbalance			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (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
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (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

Serious adverse events	Cohort 4: Intermittent Dosing	Cohort 5: Intermittent Dosing	Cohort 3: Continuous Dosing
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 14 (14.29%)	4 / 6 (66.67%)	2 / 6 (33.33%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Toxicity to various agents			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 6 (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
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 6 (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
Nervous system disorders			
Migraine			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuralgia			

subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (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
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (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
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (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
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (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
Vomiting			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (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
Small intestinal obstruction			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (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, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 6 (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
Dyspnoea			

subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (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			
Renal failure acute			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 6 (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
Renal vein thrombosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (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
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (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
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (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
Bronchitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 6 (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
Upper respiratory tract infection			

subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 6 (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
Cellulitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 6 (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
Device related infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (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
Metabolism and nutrition disorders			
Electrolyte imbalance			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 6 (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
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 6 (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

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

Non-serious adverse events	Cohort 1: Continuous Dosing	Cohort 2: Continuous Dosing	Cohort 6: Intermittent Dosing
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	13 / 13 (100.00%)	12 / 12 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant muscle neoplasm			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Tumour associated fever			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			

Flushing			
subjects affected / exposed	1 / 3 (33.33%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Hot flush			
subjects affected / exposed	1 / 3 (33.33%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Lymphoedema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Catheter site pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Asthenia			
subjects affected / exposed	1 / 3 (33.33%)	6 / 13 (46.15%)	2 / 12 (16.67%)
occurrences (all)	1	10	7
Atrophy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Axillary pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Chest pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	2 / 3 (66.67%)	6 / 13 (46.15%)	7 / 12 (58.33%)
occurrences (all)	2	6	7
Feeling jittery			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			

subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Localised oedema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Malaise			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	1 / 3 (33.33%)	1 / 13 (7.69%)	1 / 12 (8.33%)
occurrences (all)	1	2	1
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Thrombosis in device			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Mucosal inflammation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Breast discomfort			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			

Dysphonia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Cough			
subjects affected / exposed	0 / 3 (0.00%)	3 / 13 (23.08%)	4 / 12 (33.33%)
occurrences (all)	0	3	4
Bronchial secretion retention			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Bronchial hyperreactivity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	1 / 3 (33.33%)	2 / 13 (15.38%)	1 / 12 (8.33%)
occurrences (all)	1	2	1
Hypoxia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	3	0
Nasal congestion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	4 / 12 (33.33%)
occurrences (all)	0	0	4
Rhinorrhoea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Rhinitis allergic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Pulmonary embolism			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Productive cough			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0

Pneumothorax			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Pleuritic pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Pharyngeal inflammation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Orthopnoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 3 (0.00%)	2 / 13 (15.38%)	1 / 12 (8.33%)
occurrences (all)	0	2	1
Wheezing			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Nightmare			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Nervousness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	2 / 12 (16.67%)
occurrences (all)	0	1	2
Depression			
subjects affected / exposed	1 / 3 (33.33%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Depressed mood			

subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Anxiety			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 3 (33.33%)	3 / 13 (23.08%)	3 / 12 (25.00%)
occurrences (all)	1	3	3
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Activated partial thromboplastin time shortened			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Bacterial test			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Bacterial test positive			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 3 (66.67%)	2 / 13 (15.38%)	1 / 12 (8.33%)
occurrences (all)	2	2	1
Blood amylase increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Blood chloride decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Blood urine present			

subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Blood glucose increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 3 (0.00%)	3 / 13 (23.08%)	0 / 12 (0.00%)
occurrences (all)	0	6	0
Blood phosphorus decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Blood potassium decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Blood urea increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Blood creatinine increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	3 / 13 (23.08%)	1 / 12 (8.33%)
occurrences (all)	0	4	1
Globulin			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Globulins decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Glucose urine			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Glucose urine present			

subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
International normalised ratio increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Lipase			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Lipase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Low density lipoprotein increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Neutrophil count decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Neutrophil count increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Protein total decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Red blood cells urine			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Prothrombin time prolonged			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
White blood cells urine positive			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
White blood cell count increased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 13 (15.38%)	1 / 12 (8.33%)
occurrences (all)	0	2	1

White blood cell count decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Weight decreased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 13 (15.38%)	1 / 12 (8.33%)
occurrences (all)	0	2	1
Urinary sediment present			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Red blood cells urine positive			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Protein urine present			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Foot fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Humerus fracture			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Thermal burn			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Tooth injury			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Urinary anastomotic leak			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Sunburn			

subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Sinus tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Nervous system disorders			
Hyperaesthesia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	1 / 3 (33.33%)	1 / 13 (7.69%)	4 / 12 (33.33%)
occurrences (all)	1	1	6
Dysgeusia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	3 / 12 (25.00%)
occurrences (all)	0	0	6
Dizziness			
subjects affected / exposed	0 / 3 (0.00%)	4 / 13 (30.77%)	2 / 12 (16.67%)
occurrences (all)	0	5	2
Disturbance in attention			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Coordination abnormal			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Burning sensation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Amnesia			

subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Aphasia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Neurotoxicity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	1 / 12 (8.33%)
occurrences (all)	0	1	2
Post-traumatic headache			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Hypoaesthesia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Hypokinesia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Neuropathy peripheral			
subjects affected / exposed	2 / 3 (66.67%)	1 / 13 (7.69%)	3 / 12 (25.00%)
occurrences (all)	2	1	3
Sinus headache			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Tension headache			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	0 / 3 (0.00%)	4 / 13 (30.77%)	0 / 12 (0.00%)
occurrences (all)	0	4	0
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	1 / 3 (33.33%)	6 / 13 (46.15%)	3 / 12 (25.00%)
occurrences (all)	1	7	3
Leukopenia			
subjects affected / exposed	1 / 3 (33.33%)	6 / 13 (46.15%)	0 / 12 (0.00%)
occurrences (all)	1	7	0
Leukocytosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Hypoglobulinaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Lymphopenia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 13 (7.69%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
Macrocytosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	3 / 3 (100.00%)	5 / 13 (38.46%)	3 / 12 (25.00%)
occurrences (all)	3	5	4
Thrombocytopenia			
subjects affected / exposed	2 / 3 (66.67%)	3 / 13 (23.08%)	0 / 12 (0.00%)
occurrences (all)	2	3	0
Thrombocytosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Ear and labyrinth disorders			
Ototoxicity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Deafness			
subjects affected / exposed	3 / 3 (100.00%)	1 / 13 (7.69%)	1 / 12 (8.33%)
occurrences (all)	3	1	1
Deafness unilateral			

subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Ear pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Hearing impaired			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Tinnitus			
subjects affected / exposed	1 / 3 (33.33%)	4 / 13 (30.77%)	4 / 12 (33.33%)
occurrences (all)	1	4	9
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Dry eye			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Eye pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Miosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Scotoma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Visual acuity reduced			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Macular degeneration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0

Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Abdominal discomfort			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	2 / 12 (16.67%)
occurrences (all)	0	1	4
Abdominal pain upper			
subjects affected / exposed	1 / 3 (33.33%)	2 / 13 (15.38%)	1 / 12 (8.33%)
occurrences (all)	1	2	3
Aerophagia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Anal pruritus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Ascites			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	1 / 3 (33.33%)	7 / 13 (53.85%)	7 / 12 (58.33%)
occurrences (all)	1	9	12
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Dysphagia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Flatulence			

subjects affected / exposed	1 / 3 (33.33%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Gastric ulcer			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Gastritis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	4 / 13 (30.77%)	6 / 12 (50.00%)
occurrences (all)	0	4	11
Gingival pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Glossodynia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	2 / 3 (66.67%)	9 / 13 (69.23%)	9 / 12 (75.00%)
occurrences (all)	2	16	16
Oral pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Pancreatitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	2 / 3 (66.67%)	8 / 13 (61.54%)	4 / 12 (33.33%)
occurrences (all)	2	14	9
Stomatitis			

subjects affected / exposed	0 / 3 (0.00%)	3 / 13 (23.08%)	2 / 12 (16.67%)
occurrences (all)	0	3	2
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 13 (0.00%)	3 / 12 (25.00%)
occurrences (all)	1	0	3
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Photosensitivity reaction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	1 / 3 (33.33%)	0 / 13 (0.00%)	2 / 12 (16.67%)
occurrences (all)	1	0	2
Onychoclasis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Erythema nodosum			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Cold sweat			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Dermatitis acneiform			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Dry skin			

subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Ecchymosis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Erythema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Swelling face			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Rash papular			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Nephropathy toxic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Ketonuria			
subjects affected / exposed	1 / 3 (33.33%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Dysuria			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Bladder pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Nocturia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Urinary tract pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1

Urinary retention			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Urinary incontinence			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Proteinuria			
subjects affected / exposed	1 / 3 (33.33%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	2	1	0
Pollakiuria			
subjects affected / exposed	1 / 3 (33.33%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Endocrine disorders			
Cushingoid			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Arthralgia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 13 (0.00%)	3 / 12 (25.00%)
occurrences (all)	2	0	4
Bone pain			
subjects affected / exposed	0 / 3 (0.00%)	2 / 13 (15.38%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Pain in extremity			
subjects affected / exposed	1 / 3 (33.33%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Neck pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Myalgia			
subjects affected / exposed	2 / 3 (66.67%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	3	0	0
Musculoskeletal pain			

subjects affected / exposed	1 / 3 (33.33%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Musculoskeletal chest pain			
subjects affected / exposed	0 / 3 (0.00%)	4 / 13 (30.77%)	0 / 12 (0.00%)
occurrences (all)	0	4	0
Muscular weakness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Muscle contracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Groin pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Pain in jaw			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Tendon pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Infections and infestations			
Bacterial infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Bronchitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Candidiasis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Cystitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0

Gastroenteritis viral			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Infected bites			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Onychomycosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Respiratory tract infection			
subjects affected / exposed	1 / 3 (33.33%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Herpes zoster			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Urinary tract infection			
subjects affected / exposed	1 / 3 (33.33%)	5 / 13 (38.46%)	2 / 12 (16.67%)
occurrences (all)	4	5	3
Metabolism and nutrition disorders			
Diabetes mellitus			

subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Dehydration			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	3 / 12 (25.00%)
occurrences (all)	0	1	3
Decreased appetite			
subjects affected / exposed	0 / 3 (0.00%)	7 / 13 (53.85%)	3 / 12 (25.00%)
occurrences (all)	0	9	5
Acidosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Hypomagnesaemia			
subjects affected / exposed	1 / 3 (33.33%)	3 / 13 (23.08%)	0 / 12 (0.00%)
occurrences (all)	1	5	0
Hypokalaemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Hypochloraemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Hypocalcaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Hyponatraemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Hyperphosphataemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Hyperkalaemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Hyperglycaemia			

subjects affected / exposed	0 / 3 (0.00%)	3 / 13 (23.08%)	1 / 12 (8.33%)
occurrences (all)	0	5	1
Hypercholesterolaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Gout			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Hypertriglyceridaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Hypophosphataemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1

Non-serious adverse events	Cohort 4: Intermittent Dosing	Cohort 5: Intermittent Dosing	Cohort 3: Continuous Dosing
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 14 (100.00%)	6 / 6 (100.00%)	6 / 6 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant muscle neoplasm			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Tumour associated fever			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hot flush			
subjects affected / exposed	0 / 14 (0.00%)	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences (all)	0	2	1
Hypertension			
subjects affected / exposed	1 / 14 (7.14%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Lymphoedema			

subjects affected / exposed	1 / 14 (7.14%)	1 / 6 (16.67%)	2 / 6 (33.33%)
occurrences (all)	1	1	3
General disorders and administration site conditions			
Catheter site pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Asthenia			
subjects affected / exposed	6 / 14 (42.86%)	4 / 6 (66.67%)	3 / 6 (50.00%)
occurrences (all)	17	14	17
Atrophy			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Axillary pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Chest pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	5 / 14 (35.71%)	1 / 6 (16.67%)	3 / 6 (50.00%)
occurrences (all)	6	1	4
Feeling jittery			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Influenza like illness			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Localised oedema			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	0 / 14 (0.00%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Non-cardiac chest pain			

subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Oedema peripheral			
subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	2
Pyrexia			
subjects affected / exposed	3 / 14 (21.43%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Thrombosis in device			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Mucosal inflammation			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	1
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Breast discomfort			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	4 / 14 (28.57%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	5	2	0
Bronchial secretion retention			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Bronchial hyperreactivity			

subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Dyspnoea			
subjects affected / exposed	2 / 14 (14.29%)	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences (all)	2	2	1
Hypoxia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Epistaxis			
subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Nasal congestion			
subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rhinitis allergic			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Pulmonary embolism			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Productive cough			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pneumothorax			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pleuritic pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pharyngeal inflammation			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Orthopnoea			

subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Oropharyngeal pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Wheezing			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Nightmare			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Nervousness			
subjects affected / exposed	0 / 14 (0.00%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Insomnia			
subjects affected / exposed	5 / 14 (35.71%)	2 / 6 (33.33%)	2 / 6 (33.33%)
occurrences (all)	5	2	4
Depression			
subjects affected / exposed	3 / 14 (21.43%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	3	1	0
Depressed mood			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Anxiety			
subjects affected / exposed	2 / 14 (14.29%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	2	1	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 14 (7.14%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	2	1	0
Activated partial thromboplastin time prolonged			

subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Activated partial thromboplastin time shortened			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Bacterial test			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Bacterial test positive			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Blood amylase increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Blood chloride decreased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Blood urine present			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Blood glucose increased			
subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Blood phosphorus decreased			

subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood potassium decreased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood urea increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Blood creatinine increased			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Globulin			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Globulins decreased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Glucose urine			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Glucose urine present			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
International normalised ratio increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Lipase			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Lipase increased			

subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	1
Low density lipoprotein increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Neutrophil count decreased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Neutrophil count increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Protein total decreased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Red blood cells urine			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Prothrombin time prolonged			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
White blood cells urine positive			
subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
White blood cell count increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
White blood cell count decreased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Urinary sediment present			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Red blood cells urine positive			

subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Protein urine present			
subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Foot fracture			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Humerus fracture			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Thermal burn			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Tooth injury			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Urinary anastomotic leak			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Sunburn			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Tachycardia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Sinus tachycardia			

subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Hyperaesthesia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	4 / 14 (28.57%)	3 / 6 (50.00%)	3 / 6 (50.00%)
occurrences (all)	6	4	4
Dysgeusia			
subjects affected / exposed	5 / 14 (35.71%)	3 / 6 (50.00%)	1 / 6 (16.67%)
occurrences (all)	8	3	2
Dizziness			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	2 / 6 (33.33%)
occurrences (all)	0	1	3
Disturbance in attention			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Coordination abnormal			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Burning sensation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Amnesia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Aphasia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Neurotoxicity			
subjects affected / exposed	3 / 14 (21.43%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	4	0	0
Paraesthesia			
subjects affected / exposed	3 / 14 (21.43%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	3	0	1

Peripheral sensory neuropathy			
subjects affected / exposed	3 / 14 (21.43%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	3	0	1
Post-traumatic headache			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Hypoaesthesia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Hypokinesia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Neuropathy peripheral			
subjects affected / exposed	1 / 14 (7.14%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Sinus headache			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tension headache			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Somnolence			
subjects affected / exposed	0 / 14 (0.00%)	3 / 6 (50.00%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 14 (21.43%)	3 / 6 (50.00%)	4 / 6 (66.67%)
occurrences (all)	3	3	4
Leukopenia			
subjects affected / exposed	5 / 14 (35.71%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	5	0	0
Leukocytosis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Hypoglobulinaemia			

subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Lymphopenia			
subjects affected / exposed	3 / 14 (21.43%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Macrocytosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Neutropenia			
subjects affected / exposed	6 / 14 (42.86%)	1 / 6 (16.67%)	4 / 6 (66.67%)
occurrences (all)	6	1	4
Thrombocytopenia			
subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	3 / 6 (50.00%)
occurrences (all)	2	0	3
Thrombocytosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Ototoxicity			
subjects affected / exposed	0 / 14 (0.00%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Deafness			
subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	2	0	2
Deafness unilateral			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ear pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hearing impaired			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tinnitus			
subjects affected / exposed	7 / 14 (50.00%)	3 / 6 (50.00%)	4 / 6 (66.67%)
occurrences (all)	10	5	4

Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dry eye			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Eye pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Miosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Scotoma			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Vision blurred			
subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Visual acuity reduced			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Macular degeneration			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Abdominal discomfort			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Abdominal pain			
subjects affected / exposed	2 / 14 (14.29%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	2	3	0
Abdominal pain upper			

subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	2	0	2
Aerophagia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Anal pruritus			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Ascites			
subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Constipation			
subjects affected / exposed	5 / 14 (35.71%)	1 / 6 (16.67%)	3 / 6 (50.00%)
occurrences (all)	6	2	6
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Dyspepsia			
subjects affected / exposed	3 / 14 (21.43%)	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences (all)	4	2	1
Dysphagia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Flatulence			
subjects affected / exposed	1 / 14 (7.14%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	1	1	2
Gastric ulcer			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Gastritis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Diarrhoea			
subjects affected / exposed	4 / 14 (28.57%)	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences (all)	5	4	1
Gingival pain			

subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Glossodynia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Haemorrhoids			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	12 / 14 (85.71%)	4 / 6 (66.67%)	4 / 6 (66.67%)
occurrences (all)	23	18	13
Oral pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pancreatitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	7 / 14 (50.00%)	4 / 6 (66.67%)	2 / 6 (33.33%)
occurrences (all)	12	10	2
Stomatitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Palmar-plantar erythrodysaesthesia syndrome			

subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Photosensitivity reaction			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	2 / 14 (14.29%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	2	3	0
Onychoclasis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Hyperhidrosis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Erythema nodosum			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Cold sweat			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dermatitis acneiform			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Dry skin			
subjects affected / exposed	1 / 14 (7.14%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	2	1	0
Ecchymosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	1 / 14 (7.14%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	3	1	0
Swelling face			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rash			

subjects affected / exposed	3 / 14 (21.43%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	3	1	0
Rash papular			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Nephropathy toxic			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Ketonuria			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dysuria			
subjects affected / exposed	3 / 14 (21.43%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Bladder pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Nocturia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Urinary tract pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Urinary retention			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Urinary incontinence			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Proteinuria			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Pollakiuria			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Endocrine disorders			
Cushingoid			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 14 (21.43%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	3	1	1
Arthralgia			
subjects affected / exposed	3 / 14 (21.43%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	3	0	2
Bone pain			
subjects affected / exposed	1 / 14 (7.14%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	1	3	1
Pain in extremity			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Neck pain			
subjects affected / exposed	2 / 14 (14.29%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	2	1	0
Myalgia			
subjects affected / exposed	0 / 14 (0.00%)	2 / 6 (33.33%)	2 / 6 (33.33%)
occurrences (all)	0	2	2
Musculoskeletal pain			
subjects affected / exposed	2 / 14 (14.29%)	2 / 6 (33.33%)	2 / 6 (33.33%)
occurrences (all)	3	2	3
Musculoskeletal chest pain			
subjects affected / exposed	3 / 14 (21.43%)	1 / 6 (16.67%)	2 / 6 (33.33%)
occurrences (all)	4	1	2
Muscular weakness			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Muscle contracture			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Groin pain			

subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pain in jaw			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tendon pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bacterial infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Bronchitis			
subjects affected / exposed	0 / 14 (0.00%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Candidiasis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Cystitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis viral			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Infected bites			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 14 (7.14%)	2 / 6 (33.33%)	2 / 6 (33.33%)
occurrences (all)	2	3	2

Onychomycosis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Pneumonia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Herpes zoster			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	2 / 14 (14.29%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	3	2	0
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dehydration			
subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	2	0	2
Decreased appetite			
subjects affected / exposed	2 / 14 (14.29%)	2 / 6 (33.33%)	2 / 6 (33.33%)
occurrences (all)	3	2	2
Acidosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypomagnesaemia			

subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	1	0	2
Hypokalaemia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Hypochloraemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Hypoalbuminaemia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Hyponatraemia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Hyperphosphataemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hyperkalaemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Hypercholesterolaemia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Gout			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypertriglyceridaemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypophosphataemia			

subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 September 2008	Added inclusion criteria # 2 and 7; creatinine clearance and histological confirmation of metastatic cancer, Management of toxicity due to cisplatin: additional paragraph entitled ototoxicity and clarifications to other paragraphs.
27 May 2009	Synopsis/Section 4.1.1.1 of clinical study protocol (CSP): study design/stopping criteria for dose escalation (Part A/Phase I): additional details on the last cohort; once the desired doses or maximum tolerated dose (MTD) of the combination therapy had been determined (or the highest dose level had been explored) the cohort was expanded to a minimum of 6 participants and a maximum of 12 participants in order to ensure that there were 6 evaluable participants who had completed 4 cycles of treatment. Synopsis/Sections 4.1.1 and 4.4.6.2 of CSP and Section 5.1.5.3 of clinical study report (CSR): duration of treatment; olaparib monotherapy dose (Synopsis of CSP). Sections 4.4.3 and 4.4.5 of CSP and Section 5.3.1 of CSR: Exclusion criteria, # 7, # 16; pregnancy exclusion and prior use of any polyadenosine 5'-diphosphoribose polymerase (PARP) inhibitor and section on contraception. Sections 4.5.2.2 and 4.4.5 of CSP and Section 5.4.2.2 of CSR; cisplatin preparation. Sections 4.5.4 of CSP and Section 5.4.2.2 of CSR; management of toxicity due to cisplatin. Section 7.5.2 of CSP and Section 5.1.1 of CSR; description of variables in relation to hypotheses.
29 October 2009	Synopsis of CSP: Study Design, Table 2, Figure 2, Part A/Phase I; addition of a new intermittent dosing schedule in Part A/Phase I. Section 4.5.3 of the CSP: management of toxicity; the management of toxicity and additional management for intermittent dose schedule. Synopsis of CSP and page 88 of CSP: Study centre(s), type and number of participants planned; an increase in maximum number of participants in Part A/Phase I. Synopsis of CSP and page 88, Section 4.1.4 of CSP: Study centre(s), type and number of participants planned; reduction of participant number in Part B/ Phase II.
01 July 2010	Synopsis of CSP: study centre(s), type and number of participants planned; removal of the Phase II/Part B part of the study - Triple Negative Breast Cancer part of the study. Section 6.5 of CSP: duration of treatment; increase in timelines of the study. Synopsis of CSP/Figure 3: addition of further participant cohorts to explore intermittent dosing schedules. Synopsis of CSP/Section 4.1 overall study design: increase in the number of participants in the Phase I/Part A part of the study; increased to 60 participants. Synopsis of CSP/Study Design: reduction in the overall number of sites. Removal of the Central nervous system function from baseline assessments. Section 4.1.3 of the CSP: maximum tolerated dose; allowed for exploration of different combination dosing regimens to provide a tolerated dose of Olaparib combined with cisplatin which can be investigated in further studies, however the highest dose explored was set as 400 mg BID (the MTD established in a monotherapy Phase I study). Sections 4.5.3.2, 4.5.3.4, 4.5.3.4.1, 4.5.3.7, and 4.5.3.5 of CSP: management of neutropenic events and non-haematological toxicity attributable to olaparib; clarification on the management of toxicity and additional management for intermittent dose schedule.
11 March 2011	Clarifications to Amendment 4 affecting several sections of CSP: Amendment 4 was written to allow an initial dose level option of olaparib with a reduced dose of cisplatin at 60 mg/m^2 (Further reductions of cisplatin due to toxicity needed to be clarified for participants that started on the low dose cisplatin dosing schedule.)

06 January 2012	Removal of Appendices related to study design that are not required after Amendment 4, renumbering of appendices, and addition of Appendix C i.e. an AstraZeneca standard to be included in protocols (List of Appendices). Inclusion of breast cancer antigen (BRCA) mutation status as part of screening assessment. Added a separate table to detail assessments and visit schedule when a participant moves to olaparib monotherapy. Added details of olaparib monotherapy in case cisplatin was discontinued due to cisplatin related toxicity. Expansion and clarification of list of allowed concomitant medications to include anticoagulant therapy and anti-emetics, and clarification on use of granulocyte colony stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and erythropoietin. Clarified that live virus and bacterial vaccines should not be administered while receiving study medication and during 30-day follow-up period and further expanded list of prohibited medications with clarifications. Updated information on laboratory safety measurements to specify which measurements will be performed. Section on adverse events modified and updated. Clarification to range of absolute neutrophil count (ANC) in management of neutropenic events. Updates to section on ethics review in accordance with the current guidelines followed by AstraZeneca on ethical conduct of study and following regulatory guidelines. Updated guidelines in obtaining informed consent to clarify that any incentives to participants as well as provisions for participants harmed as consequence of study participation are described in the informed consent form (ICF). Added sections on procedures in case pregnancy, related to maternal and paternal exposure and updated section on procedures in case of overdose. Change in information on identity of investigational product to clarify that olaparib was manufactured by Patheon Inc on behalf of AstraZeneca.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported