Clinical trial results:
A Phase II, Open-Label, Non-Comparative, International, Multicentre Study To Assess The Efficacy And Safety Of KU-0059436 Given Orally Twice Daily In Patients With Advanced BRCA1- Or BRCA2-Associated Ovarian Cancer

Summary

EudraCT number	2006-006459-10
Trial protocol	DE SE ES GB
Global end of trial date	24 July 2009

Results information

Result version number	v1 (current)
This version publication date	20 July 2018
First version publication date	20 July 2018

Trial information

Trial identification

Sponsor protocol code	D0810C00009 (KU36-58)

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	1 Francis Crick Avenue, Cambridge Biomedical Campus, United Kingdom, CB2 1AA
Public contact	Gerard Lynch, AstraZeneca, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	Gerard Lynch, AstraZeneca, ClinicalTrialTransparency@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	24 July 2009
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 July 2009
Global end of trial reached?	Yes
Global end of trial date	24 July 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of olaparib (also known as AZD2281 and KU-0059436) at two dose levels in terms of objective tumour response rate when administered orally to patients with advanced BRCA1 or BRCA2-associated ovarian cancer.

Protection of trial subjects:

Patients could discontinue the IP at any time at the discretion of the Investigator. Patients were free to withdraw without prejudice to further treatment.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 June 2007
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	Australia: 12
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	United States: 42
Worldwide total number of subjects	57
EEA total number of subjects	3

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)	42

From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was enrolled on June 11, 2007 and efficacy and safety data were collected up to the data cut-off of March 17, 2009. Patients were enrolled at 12 centres in 5 countries: Australia, Germany, Spain, Sweden and the USA.

Pre-assignment

Screening details:

Two cohorts of women with Breast Cancer gene 1 (BRCA1)- or BRCA2-associated ovarian cancer who had failed at least one prior chemotherapy in the advanced/metastatic setting, were planned to receive olaparib 100 mg bd (n= up to 24) or 400 mg bd (n= up to 40). Enrolment to 2 cohorts was sequential with the 400 mg bd cohort being recruited first.

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	olaparib 100 mg bd

Arm description:

olaparib (KU-0059436; AZD2281) 100 mg oral capsules, twice daily

Arm type	Experimental
Investigational medicinal product name	olaparib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

olaparib (KU-0059436; AZD2281) 100 mg oral capsules, twice daily

Arm title	olaparib 400 mg bd

Arm description:

olaparib (KU-0059436; AZD2281) 400 mg oral capsules, twice daily

Arm type	Experimental
Investigational medicinal product name	olaparib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

olaparib (KU-0059436; AZD2281) 400 mg oral capsules, twice daily

Number of subjects in period 1	olaparib 100 mg bd	olaparib 400 mg bd
Started	24	33
Completed	7	17
Not completed	17	16
Adverse event, serious fatal	1	1
Physician decision	-	1
Adverse event, non-fatal	-	2
Non-compliance	-	1
Intercurrent illness	-	1
Lack of efficacy	16	10

Baseline characteristics

Reporting groups	
Reporting group title	olaparib 100 mg bd
Reporting group description:	
olaparib (KU-0059436; AZD2281) 100 mg oral capsules, twice daily	
Reporting group title	olaparib 400 mg bd
Reporting group description:	
olaparib (KU-0059436; AZD2281) 400 mg oral capsules, twice daily	

Reporting group values	olaparib 100 mg bd	olaparib 400 mg bd	Total
Number of subjects	24	33	57
Age categorical			
Units: Subjects			
Adults (18-64 years)	19	23	42
From 65-84 years	5	10	15
Age Continuous			
Units: Years			
arithmetic mean	55.6	56.8	
standard deviation	± 8.02	± 10.49	-
Sex: Female, Male			
Units: Subjects			
Female	24	33	57
Male	0	0	0
BRCA mutation			
BRCA1 or BRCA2 mutations known to cause loss of gene function (clinical deleterious or suspected deleterious mutations).			
Units: Subjects			
BRCA1	19	21	40
BRCA2	5	12	17

End points

End points reporting groups

Reporting group title	olaparib 100 mg bd
Reporting group description:	
olaparib (KU-0059436; AZD2281) 100 mg oral capsules, twice daily	
Reporting group title	olaparib 400 mg bd
Reporting group description:	
olaparib (KU-0059436; AZD2281) 400 mg oral capsules, twice daily	

Primary: Confirmed objective tumour response (according to Response Evaluation Criteria In Solid Tumors (RECIST)

End point title	Confirmed objective tumour response (according to Response Evaluation Criteria In Solid Tumors (RECIST)[1]
End point description:	
Per Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.0) for target lesions and assessed by CT/MRI: Complete Response (CR), Disappearance of all target lesions; Partial Response (PR), >=30% decrease from baseline in the sum of the longest diameter of target lesions; Overall Response (OR) = CR + PR.	
End point type	Primary
End point timeframe:	
Baseline, every 8 also at study termination or initiation of confounding anti-cancer therapy.	

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: There are no statistical analyses in this study as it was exploratory.

End point values	olaparib 100 mg bd	olaparib 400 mg bd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22[2]	31[3]		
Units: Participants				
PP Analysis Set	3	11		
ITT Analysis Set	3	11		

Notes:

[2] - Number analysed refers to PP Analysis Set

[3] - Number analysed refers to PP Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit (CB)

End point title	Clinical Benefit (CB)
End point description:	
Clinical Benefit (CB) is defined as the percentage of patients with a RECIST tumour response of confirmed complete response, partial response or stable disease for ≥8 weeks)	
End point type	Secondary
End point timeframe:	
End of study	

End point values	olaparib 100 mg bd	olaparib 400 mg bd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	31		
Units: Percentage of participants				
number (confidence interval 95%)				
PP Analysis Set	45.5 (26.9 to 65.3)	71.0 (53.4 to 83.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response

End point title	Duration of response
End point description:	
Duration of response to olaparib	
End point type	Secondary
End point timeframe:	
End of study	

End point values	olaparib 100 mg bd	olaparib 400 mg bd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	31		
Units: Days				
median (full range (min-max))				
PP Analysis Set	242 (169 to 288)	301 (126 to 506)		

Statistical analyses

No statistical analyses for this end point

Secondary: Best percentage change in tumour size

End point title	Best percentage change in tumour size
End point description:	
The best % change (reduction) from baseline in tumour size (defined as the sum of the longest diameters as measured among all target lesions).	
End point type	Secondary
End point timeframe:	
End of study	

End point values	olaparib 100 mg bd	olaparib 400 mg bd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	31		
Units: Percent change				
median (full range (min-max))				
PP Analysis Set	-5.1 (-85.7 to 66.1)	-25.8 (-100.0 to 150.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)

End point description:

Progression-Free Survival (PFS) is defined as the time from first dose to the earlier date of radiologic progression (as per RECIST criteria) or death by any cause in the absence of objective progression.

End point type	Secondary

End point timeframe:

End of study

End point values	olaparib 100 mg bd	olaparib 400 mg bd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	31		
Units: Days				
median (confidence interval 95%)				
PP Analysis Set	62.5 (56 to 113)	226 (105 to 338)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From baseline, every visit until 30 days after last dose.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups	
Reporting group title	olaparib 100 mg bd
Reporting group description: olaparib (KU-0059436; AZD2281) 100 mg oral capsules, twice daily	
Reporting group title	olaparib 400 mg bd
Reporting group description: olaparib (KU-0059436; AZD2281) 400 mg oral capsules, twice daily	

Serious adverse events	olaparib 100 mg bd	olaparib 400 mg bd	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 24 (29.17%)	12 / 33 (36.36%)	
number of deaths (all causes)	10	11	
number of deaths resulting from adverse events			
Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	0 / 24 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Oedema Peripheral			
subjects affected / exposed	0 / 24 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary Embolism			
subjects affected / exposed	1 / 24 (4.17%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Failure			

subjects affected / exposed	1 / 24 (4.17%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mental Status Changes			
subjects affected / exposed	1 / 24 (4.17%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Humerus Fracture			
subjects affected / exposed	0 / 24 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood Pressure Increased			
subjects affected / exposed	1 / 24 (4.17%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac Failure Congestive			
subjects affected / exposed	1 / 24 (4.17%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	1 / 24 (4.17%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	0 / 24 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			

subjects affected / exposed	1 / 24 (4.17%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal Obstruction			
subjects affected / exposed	0 / 24 (0.00%)	2 / 33 (6.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 24 (4.17%)	2 / 33 (6.06%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 24 (4.17%)	2 / 33 (6.06%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Pain			
subjects affected / exposed	1 / 24 (4.17%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large Intestinal Obstruction			
subjects affected / exposed	1 / 24 (4.17%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Obstruction			
subjects affected / exposed	0 / 24 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			

subjects affected / exposed	0 / 24 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal Perforation			
subjects affected / exposed	0 / 24 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small Intestinal Obstruction			
subjects affected / exposed	0 / 24 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile Duct Stone			
subjects affected / exposed	0 / 24 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal Failure			
subjects affected / exposed	1 / 24 (4.17%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Failure Acute			
subjects affected / exposed	0 / 24 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			

subjects affected / exposed	1 / 24 (4.17%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 24 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	olaparib 100 mg bd	olaparib 400 mg bd	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 24 (95.83%)	33 / 33 (100.00%)	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	13 / 24 (54.17%)	17 / 33 (51.52%)	
occurrences (all)	13	17	
Oedema Peripheral			
subjects affected / exposed	1 / 24 (4.17%)	6 / 33 (18.18%)	
occurrences (all)	1	6	
Pyrexia			
subjects affected / exposed	2 / 24 (8.33%)	2 / 33 (6.06%)	
occurrences (all)	2	2	
Asthenia			
subjects affected / exposed	0 / 24 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Reproductive system and breast disorders			
Pelvic Pain			
subjects affected / exposed	2 / 24 (8.33%)	2 / 33 (6.06%)	
occurrences (all)	2	2	

Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	4 / 24 (16.67%)	0 / 33 (0.00%)	
occurrences (all)	4	0	
Cough			
subjects affected / exposed	3 / 24 (12.50%)	1 / 33 (3.03%)	
occurrences (all)	3	1	
Dyspnoea Exertional			
subjects affected / exposed	0 / 24 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Oropharyngeal Pain			
subjects affected / exposed	1 / 24 (4.17%)	2 / 33 (6.06%)	
occurrences (all)	1	2	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 24 (4.17%)	4 / 33 (12.12%)	
occurrences (all)	1	4	
Depression			
subjects affected / exposed	2 / 24 (8.33%)	3 / 33 (9.09%)	
occurrences (all)	2	3	
Anxiety			
subjects affected / exposed	1 / 24 (4.17%)	2 / 33 (6.06%)	
occurrences (all)	1	2	
Investigations			
Waist Circumference Increased			
subjects affected / exposed	4 / 24 (16.67%)	0 / 33 (0.00%)	
occurrences (all)	4	0	
Haemoglobin Urine			
subjects affected / exposed	3 / 24 (12.50%)	0 / 33 (0.00%)	
occurrences (all)	3	0	
Blood Urine Present			
subjects affected / exposed	2 / 24 (8.33%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	0 / 24 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	

Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 24 (4.17%)	4 / 33 (12.12%)	
occurrences (all)	1	4	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 24 (16.67%)	7 / 33 (21.21%)	
occurrences (all)	4	7	
Neuropathy Peripheral			
subjects affected / exposed	4 / 24 (16.67%)	1 / 33 (3.03%)	
occurrences (all)	4	1	
Dizziness			
subjects affected / exposed	2 / 24 (8.33%)	3 / 33 (9.09%)	
occurrences (all)	2	3	
Dysgeusia			
subjects affected / exposed	2 / 24 (8.33%)	1 / 33 (3.03%)	
occurrences (all)	2	1	
Sinus Headache			
subjects affected / exposed	1 / 24 (4.17%)	2 / 33 (6.06%)	
occurrences (all)	1	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 24 (12.50%)	7 / 33 (21.21%)	
occurrences (all)	3	7	
Lymphopenia			
subjects affected / exposed	2 / 24 (8.33%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Thrombocytopenia			
subjects affected / exposed	3 / 24 (12.50%)	1 / 33 (3.03%)	
occurrences (all)	3	1	
Neutropenia			
subjects affected / exposed	2 / 24 (8.33%)	3 / 33 (9.09%)	
occurrences (all)	2	3	
Gastrointestinal disorders			
Nausea			

subjects affected / exposed	15 / 24 (62.50%)	21 / 33 (63.64%)	
occurrences (all)	15	21	
Diarrhoea			
subjects affected / exposed	7 / 24 (29.17%)	12 / 33 (36.36%)	
occurrences (all)	7	12	
Abdominal Pain			
subjects affected / exposed	4 / 24 (16.67%)	9 / 33 (27.27%)	
occurrences (all)	4	9	
Vomiting			
subjects affected / exposed	6 / 24 (25.00%)	11 / 33 (33.33%)	
occurrences (all)	6	11	
Constipation			
subjects affected / exposed	6 / 24 (25.00%)	4 / 33 (12.12%)	
occurrences (all)	6	4	
Abdominal Distension			
subjects affected / exposed	4 / 24 (16.67%)	6 / 33 (18.18%)	
occurrences (all)	4	6	
Dyspepsia			
subjects affected / exposed	4 / 24 (16.67%)	4 / 33 (12.12%)	
occurrences (all)	4	4	
Abdominal Pain Upper			
subjects affected / exposed	3 / 24 (12.50%)	3 / 33 (9.09%)	
occurrences (all)	3	3	
Abdominal Discomfort			
subjects affected / exposed	1 / 24 (4.17%)	3 / 33 (9.09%)	
occurrences (all)	1	3	
Abdominal Pain Lower			
subjects affected / exposed	0 / 24 (0.00%)	3 / 33 (9.09%)	
occurrences (all)	0	3	
Gastrooesophageal Reflux Disease			
subjects affected / exposed	1 / 24 (4.17%)	3 / 33 (9.09%)	
occurrences (all)	1	3	
Gastrointestinal Pain			
subjects affected / exposed	2 / 24 (8.33%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Ascites			

subjects affected / exposed	0 / 24 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Gastritis			
subjects affected / exposed	0 / 24 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Rectal Haemorrhage			
subjects affected / exposed	0 / 24 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Salivary Hypersecretion			
subjects affected / exposed	0 / 24 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Stomatitis			
subjects affected / exposed	1 / 24 (4.17%)	2 / 33 (6.06%)	
occurrences (all)	1	2	
Intestinal obstruction			
subjects affected / exposed	0 / 24 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	5 / 24 (20.83%)	5 / 33 (15.15%)	
occurrences (all)	5	5	
Dry Skin			
subjects affected / exposed	2 / 24 (8.33%)	1 / 33 (3.03%)	
occurrences (all)	2	1	
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	2 / 24 (8.33%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 24 (16.67%)	2 / 33 (6.06%)	
occurrences (all)	4	2	
Back Pain			
subjects affected / exposed	4 / 24 (16.67%)	2 / 33 (6.06%)	
occurrences (all)	4	2	
Muscle Spasms			

subjects affected / exposed	0 / 24 (0.00%)	4 / 33 (12.12%)	
occurrences (all)	0	4	
Pain In Extremity			
subjects affected / exposed	0 / 24 (0.00%)	3 / 33 (9.09%)	
occurrences (all)	0	3	
Flank Pain			
subjects affected / exposed	0 / 24 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Joint Swelling			
subjects affected / exposed	0 / 24 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Myalgia			
subjects affected / exposed	1 / 24 (4.17%)	2 / 33 (6.06%)	
occurrences (all)	1	2	
Infections and infestations			
Urinary Tract Infection			
subjects affected / exposed	5 / 24 (20.83%)	2 / 33 (6.06%)	
occurrences (all)	5	2	
Upper Respiratory Tract Infection			
subjects affected / exposed	2 / 24 (8.33%)	3 / 33 (9.09%)	
occurrences (all)	2	3	
Oral Herpes			
subjects affected / exposed	2 / 24 (8.33%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Cellulitis			
subjects affected / exposed	0 / 24 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Herpes Zoster			
subjects affected / exposed	0 / 24 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Nasopharyngitis			
subjects affected / exposed	0 / 24 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Sinusitis			
subjects affected / exposed	0 / 24 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	

Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	2 / 24 (8.33%)	4 / 33 (12.12%)	
occurrences (all)	2	4	
Hypomagnesaemia			
subjects affected / exposed	1 / 24 (4.17%)	4 / 33 (12.12%)	
occurrences (all)	1	4	
Anorexia			
subjects affected / exposed	1 / 24 (4.17%)	3 / 33 (9.09%)	
occurrences (all)	1	3	
Hyperkalaemia			
subjects affected / exposed	2 / 24 (8.33%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Decreased Appetite			
subjects affected / exposed	1 / 24 (4.17%)	2 / 33 (6.06%)	
occurrences (all)	1	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 September 2007	Section 4 Objectives. A second dose group (100 mg bd) was introduced. After completion of the 400 mg bd dose group (40 patients), up to 24 patients (at least 6 of each BRCA type) were to be treated with 100 mg bd. The statistics section (5.7.3) was changed to provide justification for the amended sample size with the addition of the new cohort of patients. Section 5.3.1 Inclusion criteria. Inclusion criteria 2, 3 and 7 were each expanded for clarification. Section 5.3.2 Exclusion criteria. Exclusion criteria 4, 5 and 6 were each expanded for clarification. Section 5.3.2 Exclusion criteria. Exclusion criterion 2 was modified. This criterion cross-refers to the section concerning restrictions in concomitant medication which was also changed. Some previously restricted drugs were to be allowed (specifically, fluvoxamine, fluconazole, fluoxetine, amiodarone, paroxetine, quinidine). Section 5.3.4 Discontinuation of patients from treatment. The original protocol stated that patients were to be discontinued from treatment if they had significant disease progression. The amendment clarified that the definition of progressive disease should be based on imaging / RECIST criteria and not mainly on tumour markers (if possible). Section 2.3.1.1 Independent Data Monitoring Committee. An IDMC was introduced. The original protocol stated that ineligible patients would not be replaced. This was revised to state that ineligible patients who gave informed consent but never received study drug (screening failures) would be replaced.
20 March 2008	Section 4.2 Secondary objectives. The secondary endpoint Time to progression (TTP) was changed to progression-free survival (PFS). Section 5.1 Study Design. Design was revised such that after cycle 6 all patients who were benefiting from treatment with olaparib were to continue on treatment and return to site for visits every 2 months. Another column was added to Table 2 to specify data to be collected at these visits. Section 5.1 Study Design. Blood sampling for peripheral blood mononuclear cells (PBMCs) was discontinued for new patients entering the study. The section “procedures in case of pregnancy” was updated.
22 May 2008	All ongoing patients in the 100 mg bd dose group were offered the option to move to the 400 mg bd dose immediately or when the investigator considered that disease progression had occurred.
11 February 2009	This amendment defined the end of study as 12 months post-LPI, or after approval of amendment 4, whichever was the later.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported