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 Breast Cancer

Summary

EudraCT number	2006-006458-91
Trial protocol	SE ES DE GB
Global end of trial date	21 December 2022

Results information

Result version number	v1 (current)
This version publication date	31 December 2023
First version publication date	31 December 2023

Trial information

Trial identification

Sponsor protocol code	D0810C00008 (KU36-44)

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00494234
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca ClinicalStudy Information Center
Sponsor organisation address	One MedImmune Way, Gaithersburg, Maryland, United States, 20878
Public contact	Global Clinical Lead, AstraZeneca Clinical Study Information Center, +1 8772409479, information.center@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca Clinical Study Information Center, +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	02 July 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 December 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study 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 participants with advanced BRCA1- or BRCA2-associated breast cancer.

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	15 June 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	14 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	United States: 34
Country: Number of subjects enrolled	United Kingdom: 7
Worldwide total number of subjects	54
EEA total number of subjects	6

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)	50
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 13 centers in 5 countries (Australia, Germany, Sweden, UK and the USA).

Pre-assignment

Screening details:

A total of 54 participants were enrolled and received at least one dose of study drug.

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

Arm description:

Participants received two 50 mg capsules in the morning and two 50 mg capsules in the evening in 28-days cycle until confirmed disease progression, continuous treatment interruption, unacceptable toxicity or any other discontinuation criterion was met.

Arm type	Experimental
Investigational medicinal product name	Olaparib
Investigational medicinal product code	KU-0059436
Other name	Lynparza
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Two 50 mg capsules in the morning and two 50 mg capsules in the evening administered orally, without interruption each day.

Arm title	Olaparib 400 mg

Arm description:

Participants received eight 50 mg capsules in the morning and eight 50 mg capsules in the evening in 28-days cycle until confirmed disease progression, continuous treatment interruption, unacceptable toxicity or any other discontinuation criterion was met.

Arm type	Experimental
Investigational medicinal product name	Olaparib
Investigational medicinal product code	KU-0059436
Other name	Lynparza
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Eight 50 mg capsules in the morning and eight 50 mg capsules in the evening administered orally, without interruption each day.

Number of subjects in period 1	Olaparib 100 mg	Olaparib 400 mg
Started	27	27
Completed	13	18
Not completed	14	9
Consent withdrawn by subject	1	-
Disease progression	11	8
Death	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Olaparib 100 mg
Reporting group description:	
Participants received two 50 mg capsules in the morning and two 50 mg capsules in the evening in 28-days cycle until confirmed disease progression, continuous treatment interruption, unacceptable toxicity or any other discontinuation criterion was met.	
Reporting group title	Olaparib 400 mg
Reporting group description:	
Participants received eight 50 mg capsules in the morning and eight 50 mg capsules in the evening in 28-days cycle until confirmed disease progression, continuous treatment interruption, unacceptable toxicity or any other discontinuation criterion was met.	

Reporting group values	Olaparib 100 mg	Olaparib 400 mg	Total
Number of subjects	27	27	54
Age Categorical Units: Participants			
In utero	0	0	0
Preterm new born 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)	24	26	50
From 65-84 years	3	1	4
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	44.7	44.7	
standard deviation	± 11.99	± 9.55	-
Gender Categorical Units: Participants			
Female	27	27	54
Male	0	0	0
Race Units: Subjects			
White	25	26	51
Black or African American	1	0	1
Asian	1	1	2
Native Hawaiian or Other Pacific Islander	0	0	0
American Indian or Alaska Native	0	0	0
Other	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	2	2	4
Not Hispanic or Latino	4	6	10
Unknown or not reported	21	19	40

End points

End points reporting groups

Reporting group title	Olaparib 100 mg

Reporting group description:

Participants received two 50 mg capsules in the morning and two 50 mg capsules in the evening in 28-days cycle until confirmed disease progression, continuous treatment interruption, unacceptable toxicity or any other discontinuation criterion was met.

Reporting group title	Olaparib 400 mg

Reporting group description:

Participants received eight 50 mg capsules in the morning and eight 50 mg capsules in the evening in 28-days cycle until confirmed disease progression, continuous treatment interruption, unacceptable toxicity or any other discontinuation criterion was met.

Primary: Confirmed Objective Response Rate (ORR) According to Response Evaluation Criteria in Solid Tumors (RECIST) Criteria

End point title	Confirmed Objective Response Rate (ORR) According to Response Evaluation Criteria in Solid Tumors (RECIST) Criteria[1]

End point description:

The ORR is the percentage of participants whose best tumour response is either complete response (CR) or partial response (PR), according to the RECIST v1.0 criteria. The CR is defined as disappearance of all target lesions (TLs). The PR is defined as at least a 30% decrease in the sum of longest diameters (LD) taking as reference the baseline sum of LD. Percentage of participants with ORR is reported. The per-protocol (PP) population included all enrolled participants who completed the trial schedule and medication regime without any major deviations to the protocol.

End point type	Primary

End point timeframe:

Baseline (Days -28 to 0), Day 1 of Cycle 3, thereafter every alternate cycles until study termination or withdrawal (approximately up to 2 years)

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. NB. This must have been written by stat

End point values	Olaparib 100 mg	Olaparib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	26		
Units: Percentage of participants				
number (not applicable)	25.0	42.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR)

End point title	Clinical Benefit Rate (CBR)

End point description:

The CBR is defined as the percentage of participants with a RECIST tumour response of confirmed CR,

PR or stable disease (SD) for ≥ 8 weeks +/- 1 week visit window. The CR is defined as disappearance of all TLs. The PR is defined as at least a 30% decrease in the sum of LD taking as reference the baseline sum of LD. Stable disease is neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum of LD since the treatment started. The PP population included all enrolled participants who completed the trial schedule and medication regime without any major deviations to the protocol.

End point type	Secondary

End point timeframe:

From Day 1 of Cycle 3 through study withdrawal (approximately up to 2 years)

End point values	Olaparib 100 mg	Olaparib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	26		
Units: Percentage of Participants				
number (confidence interval 95%)	70.8 (50.8 to 85.1)	84.6 (66.5 to 93.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)

End point description:

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. Those participants who were withdrawn from the study without disease progression were regarded as censored at their last evaluable RECIST assessment. Where participants had not progressed at the termination of the study, they were also regarded as censored at their last evaluable RECIST assessment. PFS was analyzed using Kaplan-Meier estimate. The PP population included all enrolled participants who completed the trial schedule and medication regime without any major deviations to the protocol.

End point type	Secondary

End point timeframe:

Baseline (Days -28 to 0), Day 1 of Cycle 3, thereafter every alternate cycles until study termination or withdrawal (approximately up to 2 years)

End point values	Olaparib 100 mg	Olaparib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	26		
Units: Days				
median (confidence interval 95%)	122 (67 to 167)	193.5 (140 to 226)		

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 tumour size is defined as the sum of the longest diameters as measured among all target lesions. At each assessment, the percentage change in tumour size is defined as 100 × 1 - (sum of all target lesion diameters at visit/sum of all target lesion diameters at baseline). The PP population included all enrolled participants who completed the trial schedule and medication regime without any major deviations to the protocol.

End point type	Secondary

End point timeframe:

Baseline (Days -28 to 0) through study withdrawal (approximately up to 2 years)

End point values	Olaparib 100 mg	Olaparib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	26		
Units: Best percentage change in tumour size				
median (confidence interval 95%)	-10.14 (-68.9 to 286.7)	-29.43 (-100.0 to 26.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR) to Olaparib

End point title	Duration of Response (DoR) to Olaparib

End point description:

Duration of response is defined as the date of progression per RECIST criteria – the date when CR or PR [whichever is earliest] is confirmed + 1. The CR is defined as disappearance of all TLs. The PR is defined as at least a 30% decrease in the sum of LD taking as reference the baseline sum of LD. The PP population included all enrolled participants who completed the trial schedule and medication regime without any major deviations to the protocol. Duration of response was analyzed for those participants who had OR.

End point type	Secondary

End point timeframe:

Baseline (Days -28 to 0), Day 1 of Cycle 3, thereafter every alternate cycles until study termination or withdrawal (approximately up to 2 years)

End point values	Olaparib 100 mg	Olaparib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	11		
Units: Days				
median (full range (min-max))	140.5 (55 to 175)	144.0 (92 to 393)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Improvement in Eastern Co-operative Oncology Group (ECOG) Performance Status Total Score From Baseline

End point title	Number of Participants With Improvement in Eastern Co-operative Oncology Group (ECOG) Performance Status Total Score From Baseline

End point description:

ECOG performance status is used by researchers to assess how a participant's disease is progressing. The scores are: 0=Fully Active, able to carry out work without restrictions; 1=Restricted activity and able to carry out light work or sedentary nature; 2=capable of self-care but unable to carry out work activities; 3=Capable of only limited self-care, confined to bed or chair more than 50% of waking hours; 4=Completely Disabled, and totally confined to bed or chair; 5=Dead. Change in ECOG performance status was defined as improved (less than the baseline value), no change (same as at baseline), worsened (greater than the baseline value) or missing (score is missing or was not recorded at baseline). If no measurement was recorded at Cycle 1 Day 1, the change was calculated in relation to the last recorded ECOG value prior to Day 1. The PP population included all enrolled participants who completed the trial schedule and medication regime without any major deviations to the protocol.

End point type	Secondary

End point timeframe:

Screening (Days -7 to 0), Day 1 Cycle 7 (ie, after completing 6 cycles of treatment) and study withdrawal (approximately up to 2 years).

End point values	Olaparib 100 mg	Olaparib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[2]	27[3]		
Units: Participants				
number (not applicable)				
Cycle 7 Day 1 (n=11; n=15)	1	6		
Withdrawal visit (n=14; n=22)	0	2		

Notes:

[2] - Number of subjects analyzed is included in the category title

[3] - Number of subjects analyzed is included in the category title

Statistical analyses

No statistical analyses for this end point

Secondary: 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)

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 population included all participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Day 1 through Day 480 (maximum observed duration)

End point values	Olaparib 100 mg	Olaparib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	27		
Units: Participants				
Any TEAE	27	27		
Any TESAE	5	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Clinically Significant Changes in Vital Signs from Baseline

End point title	Number of Participants With Clinically Significant Changes in Vital Signs from Baseline

End point description:

Number of participants with clinically significant changes in vital signs are reported. Vital sign parameters included body temperature, blood pressure, and pulse rate. Safety population included all participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Day 1 through Day 480 (maximum observed duration)

End point values	Olaparib 100 mg	Olaparib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	27		
Units: Participants				
Tachycardia	1	0		
Supraventricular arrhythmia	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With at Least 2-Grade Change from Baseline to Worst Toxicity Grade in Clinical Laboratory Parameters

End point title	Number of Participants With at Least 2-Grade Change from Baseline to Worst Toxicity Grade in Clinical Laboratory Parameters

End point description:

Number of participants with at least 2-grade change from baseline to worst toxicity grade in clinical laboratory parameters are reported. Laboratory parameters included hematology, clinical chemistry, and urinalysis. Safety population included all participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Day 1 through Day 480 (maximum observed duration)

End point values	Olaparib 100 mg	Olaparib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	27		
Units: Participants				
Haemoglobin	2	3		
White blood cells	5	11		
Absolute neutrophil count	3	6		
Lymphocytes	3	2		
Platelets	0	2		
Activated partial thromboplastin time	1	2		
Alanine aminotransferase	2	3		
Aspartate aminotransferase	3	1		
Alkaline phosphatase	1	0		
Gamma glutamyl transferase	4	2		
Albumin	1	0		
Total bilirubin	0	4		
Sodium (decrease)	1	0		
Potassium (increase)	0	1		
Creatinine	0	2		
Glucose (increase)	2	2		
Glucose (decrease)	3	3		
Calcium (decrease)	3	3		
Amylase	1	0		
Lipase	2	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 to 480 (maximum observed duration)

Adverse event reporting additional description:

The safety population included all participants who received at least one dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups

Reporting group title	Olaparib 100 mg

Reporting group description:

Participants received two 50 mg capsules in the morning and two 50 mg capsules in the evening in 28-days cycle until confirmed disease progression, continuous treatment interruption, unacceptable toxicity or any other discontinuation criterion was met.

Reporting group title	Olaparib 400 mg

Reporting group description:

Participants received eight 50 mg capsules in the morning and eight 50 mg capsules in the evening in 28-days cycle until confirmed disease progression, continuous treatment interruption, unacceptable toxicity or any other discontinuation criterion was met.

Serious adverse events	Olaparib 100 mg	Olaparib 400 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 27 (18.52%)	9 / 27 (33.33%)	
number of deaths (all causes)	3	6	
number of deaths resulting from adverse events	0	0	
Investigations			
Haemoglobin decreased			
subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Allergic transfusion reaction			
subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			

subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 27 (3.70%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 27 (3.70%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	1 / 27 (3.70%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 27 (0.00%)	3 / 27 (11.11%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 27 (0.00%)	2 / 27 (7.41%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 27 (3.70%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			

subjects affected / exposed	2 / 27 (7.41%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory disorder			
subjects affected / exposed	1 / 27 (3.70%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Purpura			
subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	
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 acute			
subjects affected / exposed	1 / 27 (3.70%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	1 / 27 (3.70%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
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	Olaparib 400 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 27 (100.00%)	26 / 27 (96.30%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Cancer pain			
subjects affected / exposed	4 / 27 (14.81%)	1 / 27 (3.70%)	
occurrences (all)	4	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	17 / 27 (62.96%)	19 / 27 (70.37%)	
occurrences (all)	19	25	
Oedema peripheral			
subjects affected / exposed	4 / 27 (14.81%)	6 / 27 (22.22%)	
occurrences (all)	4	6	
Influenza like illness			
subjects affected / exposed	0 / 27 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Asthenia			
subjects affected / exposed	0 / 27 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Chest pain			
subjects affected / exposed	1 / 27 (3.70%)	2 / 27 (7.41%)	
occurrences (all)	1	2	
Pyrexia			
subjects affected / exposed	2 / 27 (7.41%)	3 / 27 (11.11%)	
occurrences (all)	2	3	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	2 / 27 (7.41%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea exertional			
subjects affected / exposed	0 / 27 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Pleural effusion			
subjects affected / exposed	2 / 27 (7.41%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
Dyspnoea			

subjects affected / exposed	9 / 27 (33.33%)	1 / 27 (3.70%)	
occurrences (all)	9	1	
Cough			
subjects affected / exposed	8 / 27 (29.63%)	4 / 27 (14.81%)	
occurrences (all)	8	5	
Psychiatric disorders			
Depression			
subjects affected / exposed	3 / 27 (11.11%)	1 / 27 (3.70%)	
occurrences (all)	3	1	
Insomnia			
subjects affected / exposed	7 / 27 (25.93%)	2 / 27 (7.41%)	
occurrences (all)	7	2	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 27 (11.11%)	0 / 27 (0.00%)	
occurrences (all)	3	0	
Alanine aminotransferase increased			
subjects affected / exposed	2 / 27 (7.41%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
Weight increased			
subjects affected / exposed	0 / 27 (0.00%)	3 / 27 (11.11%)	
occurrences (all)	0	3	
Nervous system disorders			
Migraine			
subjects affected / exposed	1 / 27 (3.70%)	3 / 27 (11.11%)	
occurrences (all)	1	5	
Peripheral sensory neuropathy			
subjects affected / exposed	3 / 27 (11.11%)	0 / 27 (0.00%)	
occurrences (all)	3	0	
Hypoaesthesia			
subjects affected / exposed	0 / 27 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Lethargy			
subjects affected / exposed	0 / 27 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Headache			

subjects affected / exposed	6 / 27 (22.22%)	10 / 27 (37.04%)	
occurrences (all)	9	23	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 27 (11.11%)	5 / 27 (18.52%)	
occurrences (all)	3	5	
Neutropenia			
subjects affected / exposed	0 / 27 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	6 / 27 (22.22%)	10 / 27 (37.04%)	
occurrences (all)	8	16	
Constipation			
subjects affected / exposed	8 / 27 (29.63%)	6 / 27 (22.22%)	
occurrences (all)	8	6	
Diarrhoea			
subjects affected / exposed	4 / 27 (14.81%)	8 / 27 (29.63%)	
occurrences (all)	5	10	
Abdominal pain			
subjects affected / exposed	2 / 27 (7.41%)	5 / 27 (18.52%)	
occurrences (all)	2	5	
Dyspepsia			
subjects affected / exposed	2 / 27 (7.41%)	5 / 27 (18.52%)	
occurrences (all)	2	5	
Nausea			
subjects affected / exposed	15 / 27 (55.56%)	14 / 27 (51.85%)	
occurrences (all)	19	17	
Flatulence			
subjects affected / exposed	0 / 27 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	3	
Abdominal pain upper			
subjects affected / exposed	0 / 27 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	3	
Abdominal pain lower			

subjects affected / exposed	2 / 27 (7.41%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
Toothache			
subjects affected / exposed	2 / 27 (7.41%)	1 / 27 (3.70%)	
occurrences (all)	2	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 27 (3.70%)	2 / 27 (7.41%)	
occurrences (all)	1	2	
Stomatitis			
subjects affected / exposed	3 / 27 (11.11%)	1 / 27 (3.70%)	
occurrences (all)	3	1	
Skin and subcutaneous tissue disorders			
Skin lesion			
subjects affected / exposed	0 / 27 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Rash			
subjects affected / exposed	1 / 27 (3.70%)	2 / 27 (7.41%)	
occurrences (all)	1	2	
Renal and urinary disorders			
Urinary tract pain			
subjects affected / exposed	2 / 27 (7.41%)	1 / 27 (3.70%)	
occurrences (all)	2	1	
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	2 / 27 (7.41%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
Bone pain			
subjects affected / exposed	1 / 27 (3.70%)	2 / 27 (7.41%)	
occurrences (all)	2	2	
Musculoskeletal chest pain			
subjects affected / exposed	2 / 27 (7.41%)	2 / 27 (7.41%)	
occurrences (all)	2	3	
Back pain			
subjects affected / exposed	6 / 27 (22.22%)	1 / 27 (3.70%)	
occurrences (all)	6	1	
Pain in extremity			

subjects affected / exposed	7 / 27 (25.93%)	2 / 27 (7.41%)	
occurrences (all)	7	2	
Arthralgia			
subjects affected / exposed	6 / 27 (22.22%)	4 / 27 (14.81%)	
occurrences (all)	7	4	
Infections and infestations			
Sinusitis			
subjects affected / exposed	2 / 27 (7.41%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
Nasopharyngitis			
subjects affected / exposed	0 / 27 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	4	
Bronchitis			
subjects affected / exposed	0 / 27 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Oral candidiasis			
subjects affected / exposed	2 / 27 (7.41%)	1 / 27 (3.70%)	
occurrences (all)	2	1	
Urinary tract infection			
subjects affected / exposed	2 / 27 (7.41%)	3 / 27 (11.11%)	
occurrences (all)	2	3	
Upper respiratory tract infection			
subjects affected / exposed	4 / 27 (14.81%)	2 / 27 (7.41%)	
occurrences (all)	5	3	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 27 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Anorexia			
subjects affected / exposed	5 / 27 (18.52%)	3 / 27 (11.11%)	
occurrences (all)	5	3	

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 participants), up to 24 participants (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 participants. 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 1, 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 participants from treatment. The original protocol stated that participants 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.
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. Blood sampling for peripheral blood mononuclear cells (PBMCs) was discontinued for new participants entering the study. Section 5.1 Study Design. Biochemistry assessments for amylase and lipase were added. Section 5.3 Selection of study population. The participant number was reduced (64 to 52), sites were added, and the recruitment period was lengthened. The statistics section (5.7.3) was changed to provide justification for the amended sample size. Section 5.3.2 Exclusion criteria. Exclusion criterion 3 was modified.
04 June 2008	Section 5.3 Selection of study population. The sample size was increased from ‘up to 26’ to ‘up to 27’ per cohort. Section 5.3.4 Discontinuation of participants from treatment or assessment. Participants in the 100 mg bd dose cohort could move to 400 mg bd, at the investigator’s discretion, if they had clinically significant progressive disease. Section 5.7.4 Interim analyses. Flexibility was added to the protocol to allow for a potential increase in dose in cohort 2 (100 mg bd). Informal interim monthly reviews of withdrawal rates from each cohort were introduced and if a statistically significantly higher withdrawal rate in the 100 mg bd dose group was observed, then participants in the 100 mg bd dose group were to be allowed to move to the 400 mg bd dose, at the investigator’s discretion.
11 February 2009	This amendment defined the end of study as 6 months post-LPI, or after approval of amendment 4, whichever was the later.
19 August 2010	1. The sponsor of the study was changed from KuDOS Pharmaceuticals Ltd., to AstraZeneca AB, with a change of address. The protocol was updated accordingly. 2. The sponsor project manager was changed. The protocol was updated accordingly. 3. Removed text specific to the previous protocol amendment (number 4) regarding visits done before the protocol was approved. 4. Updated the exclusion criteria to include 2 methods of contraception in combination rather than 1. 5. Updated the summary of Phase I data.

26 July 2021	Synopsis, Sections 3.1.1 Presentation of KU-0059436, 3.1.3 Packaging/Labelling of KU-0059436, 3.2 Dose, Route and Schedule of KU-0059436 Administration, 5.3 Table 3 Schedule of Assessments, and 6.1.3.5 Overdose and NEW Sections 3.3.3 Dose Modifications During the Continued Access Phase and 5.3.5 Patients in the Continued Access Phase: Addition of language regarding transition from capsule form to tablet form for those participants in continued access phase, including labelling, follow up, overdose and recommended capsule doses to equivalent tablet doses. Section 3.1.2 Storage/Stability of KU-0059436 Removal of text regarding KU-0059436 needing to be protected from light. Section 3.5.1 Medications That May NOT be Administered: Updated language on live/bacterial vaccines not being permitted while taking KU-0059436 (olaparib). Section 3.5.4 Contraception: Added language on contraception and length of time on contraception. Section 6.1.3.7 KU-0059436 (Olaparib) Adverse Events of Special Interest: Updated safety language regarding adverse events of special interest.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The plasma concentration data was analysed using a population approach and polyadenosine 5’ diphosphoribose polymerase (PARP) inhibition data had already been obtained from Study D0810C00002. Hence no PK and PARP inhibition data are included.

Notes: