



## 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 |
|------------------------------|-----|

|                  |                 |
|------------------|-----------------|
| <b>Arm title</b> | 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.

|                  |                 |
|------------------|-----------------|
| <b>Arm title</b> | 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.

| <b>Number of subjects in period 1</b> | 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<br>Units: Participants                |                 |                 |       |
| In utero  | 0               | 0               | 0     |
| Preterm new born infants<br>(gestational age <37 wks) | 0               | 0               | 0     |
| Newborns (0-27 days)                                  | 0               | 0               | 0     |
| Infants and toddlers (28 days-23<br>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<br>Units: years                        |                 |                 |       |
| arithmetic mean                                       | 44.7            | 44.7            |       |
| standard deviation                                    | ± 11.99         | ± 9.55          | -     |
| Gender Categorical<br>Units: Participants             |                 |                 |       |
| Female  | 27              | 27              | 54    |
| Male  | 0               | 0               | 0     |
| Race<br>Units: Subjects                               |                 |                 |       |
| White   | 25              | 26              | 51    |
| Black or African American                             | 1               | 0               | 1     |
| Asian   | 1               | 1               | 2     |
| Native Hawaiian or Other Pacific<br>Islander          | 0               | 0               | 0     |
| American Indian or Alaska Native                      | 0               | 0               | 0     |
| Other   | 0               | 0               | 0     |
| Ethnicity<br>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:<br>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:<br>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 <sup>[1]</sup> |
| End point description:<br>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:<br>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:<br>[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.<br>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:<br>The CBR is defined as the percentage of participants with a RECIST tumour response of confirmed CR, |                             |



PR or stable disease (SD) for  $\geq 8$  weeks  $\pm 1$  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  $100 \times 1 - (\text{sum of all target lesion diameters at visit} / \text{sum of all target lesion diameters at baseline})$ . 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 <sup>[2]</sup> | 27 <sup>[3]</sup> |  |  |
| 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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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**

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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 %

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

|   |                      |                        |  |
|---|----------------------|------------------------|--|
| subjects affected / exposed<br>occurrences (all)  | 9 / 27 (33.33%)<br>9 | 1 / 27 (3.70%)<br>1    |  |
| Cough<br>subjects affected / exposed<br>occurrences (all)                                   | 8 / 27 (29.63%)<br>8 | 4 / 27 (14.81%)<br>5   |  |
| Psychiatric disorders   |                      |                        |  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                                | 7 / 27 (25.93%)<br>7 | 2 / 27 (7.41%)<br>2    |  |
| Depression<br>subjects affected / exposed<br>occurrences (all)                              | 3 / 27 (11.11%)<br>3 | 1 / 27 (3.70%)<br>1    |  |
| Investigations  |                      |                        |  |
| Aspartate aminotransferase<br>increased<br>subjects affected / exposed<br>occurrences (all) | 3 / 27 (11.11%)<br>3 | 0 / 27 (0.00%)<br>0    |  |
| Weight increased<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 27 (0.00%)<br>0  | 3 / 27 (11.11%)<br>3   |  |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)      | 2 / 27 (7.41%)<br>2  | 0 / 27 (0.00%)<br>0    |  |
| Nervous system disorders  |                      |                        |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)                                | 6 / 27 (22.22%)<br>9 | 10 / 27 (37.04%)<br>23 |  |
| Peripheral sensory neuropathy<br>subjects affected / exposed<br>occurrences (all)           | 3 / 27 (11.11%)<br>3 | 0 / 27 (0.00%)<br>0    |  |
| Hypoaesthesia<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 27 (0.00%)<br>0  | 2 / 27 (7.41%)<br>2    |  |
| Lethargy<br>subjects affected / exposed<br>occurrences (all)                                | 0 / 27 (0.00%)<br>0  | 2 / 27 (7.41%)<br>2    |  |
| Migraine  |                      |                        |  |

|  |                     |                      |  |
|--|---------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all) | 1 / 27 (3.70%)<br>1 | 3 / 27 (11.11%)<br>5 |  |
| 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                       |                     |                      |  |
| Nausea   |                     |                      |  |
| subjects affected / exposed                      | 15 / 27 (55.56%)    | 14 / 27 (51.85%)     |  |
| occurrences (all)                                | 19                  | 17                   |  |
| Dyspepsia  |                     |                      |  |
| subjects affected / exposed                      | 2 / 27 (7.41%)      | 5 / 27 (18.52%)      |  |
| occurrences (all)                                | 2                   | 5                    |  |
| Abdominal pain                                   |                     |                      |  |
| subjects affected / exposed                      | 2 / 27 (7.41%)      | 5 / 27 (18.52%)      |  |
| occurrences (all)                                | 2                   | 5                    |  |
| Diarrhoea  |                     |                      |  |
| subjects affected / exposed                      | 4 / 27 (14.81%)     | 8 / 27 (29.63%)      |  |
| occurrences (all)                                | 5                   | 10                   |  |
| Constipation                                     |                     |                      |  |
| subjects affected / exposed                      | 8 / 27 (29.63%)     | 6 / 27 (22.22%)      |  |
| occurrences (all)                                | 8                   | 6                    |  |
| Vomiting   |                     |                      |  |
| subjects affected / exposed                      | 6 / 27 (22.22%)     | 10 / 27 (37.04%)     |  |
| occurrences (all)                                | 8                   | 16                   |  |
| 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<br>occurrences (all)   | 2 / 27 (7.41%)<br>2  | 0 / 27 (0.00%)<br>0 |  |
| Toothache<br>subjects affected / exposed<br>occurrences (all)  | 2 / 27 (7.41%)<br>2  | 1 / 27 (3.70%)<br>1 |  |
| Stomatitis<br>subjects affected / exposed<br>occurrences (all)   | 3 / 27 (11.11%)<br>3 | 1 / 27 (3.70%)<br>1 |  |
| Gastrooesophageal reflux disease<br>subjects affected / exposed<br>occurrences (all)                                     | 1 / 27 (3.70%)<br>1  | 2 / 27 (7.41%)<br>2 |  |
| Skin and subcutaneous tissue disorders<br>Rash<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 27 (3.70%)<br>1  | 2 / 27 (7.41%)<br>2 |  |
| Skin lesion<br>subjects affected / exposed<br>occurrences (all)  | 0 / 27 (0.00%)<br>0  | 2 / 27 (7.41%)<br>2 |  |
| Renal and urinary disorders<br>Urinary tract pain<br>subjects affected / exposed<br>occurrences (all)                    | 2 / 27 (7.41%)<br>2  | 1 / 27 (3.70%)<br>1 |  |
| Musculoskeletal and connective tissue disorders<br>Pain in extremity<br>subjects affected / exposed<br>occurrences (all) | 7 / 27 (25.93%)<br>7 | 2 / 27 (7.41%)<br>2 |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)  | 6 / 27 (22.22%)<br>6 | 1 / 27 (3.70%)<br>1 |  |
| Musculoskeletal chest pain<br>subjects affected / exposed<br>occurrences (all)   | 2 / 27 (7.41%)<br>2  | 2 / 27 (7.41%)<br>3 |  |
| Bone pain<br>subjects affected / exposed<br>occurrences (all)  | 1 / 27 (3.70%)<br>2  | 2 / 27 (7.41%)<br>2 |  |
| Muscular weakness  |                      |                     |  |

|                                    |                 |                 |  |
|------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed        | 2 / 27 (7.41%)  | 0 / 27 (0.00%)  |  |
| occurrences (all)                  | 2               | 0               |  |
| Arthralgia                         |                 |                 |  |
| subjects affected / exposed        | 6 / 27 (22.22%) | 4 / 27 (14.81%) |  |
| occurrences (all)                  | 7               | 4               |  |
| Infections and infestations        |                 |                 |  |
| Nasopharyngitis                    |                 |                 |  |
| subjects affected / exposed        | 0 / 27 (0.00%)  | 2 / 27 (7.41%)  |  |
| occurrences (all)                  | 0               | 4               |  |
| Sinusitis                          |                 |                 |  |
| subjects affected / exposed        | 2 / 27 (7.41%)  | 0 / 27 (0.00%)  |  |
| occurrences (all)                  | 2               | 0               |  |
| 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 |                 |                 |  |
| Anorexia                           |                 |                 |  |
| subjects affected / exposed        | 5 / 27 (18.52%) | 3 / 27 (11.11%) |  |
| occurrences (all)                  | 5               | 3               |  |
| Hypokalaemia                       |                 |                 |  |
| subjects affected / exposed        | 0 / 27 (0.00%)  | 2 / 27 (7.41%)  |  |
| occurrences (all)                  | 0               | 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 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.<br>2. The sponsor project manager was changed. The protocol was updated accordingly.<br>3. Removed text specific to the previous protocol amendment (number 4) regarding visits done before the protocol was approved.<br>4. Updated the exclusion criteria to include 2 methods of contraception in combination rather than 1.<br>5. Updated the summary of Phase I data.  |

|              |  |
|--------------|--|
| 26 July 2021 | <p>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.</p> |
|--------------|--|

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: