



## Clinical trial results:

### **OPINION - A Phase IIIb, Single-arm, Open-label Multicentre Study of Olaparib Maintenance Monotherapy in Platinum Sensitive Relapsed non-Germline BRCA Mutated Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum-based Chemotherapy**

#### **Summary**

|                          |   |
|--------------------------|---|
| EudraCT number           | 2017-002767-17                                  |
| Trial protocol           | CZ SI BG GB NL ES BE AT SE PT NO DK FI PL IT RO |
| Global end of trial date | 10 March 2022                                   |

#### **Results information**

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 15 December 2022 |
| First version publication date | 15 December 2022 |

#### **Trial information**

##### **Trial identification**

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | D0816C00020 |
|-----------------------|-------------|

##### **Additional study identifiers**

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03402841 |
| WHO universal trial number (UTN)   | -           |

Notes:

##### **Sponsors**

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | AstraZeneca AB   |
| Sponsor organisation address | Karlebyhusentren, B674 Astraallen, Södertälje, Sweden, 151 85                          |
| Public contact               | Global Clinical Lead, AstraZeneca, +1 877-240-9479, information.center@astrazeneca.com |
| Scientific contact           | Global Clinical Lead, AstraZeneca, +1 877-240-9479, 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                       | 10 March 2022 |
| Is this the analysis of the primary completion data? | No            |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 10 March 2022 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

To determine the efficacy by progression-free survival (PFS) (investigator-recorded assessments according to modified Response Evaluation Criteria In Solid Tumours version 1.1 (RECIST v1.1) of olaparib maintenance monotherapy in non-germline breast cancer susceptibility gene mutated (non-gBRCAm) platinum-sensitive relapsed (PSR) ovarian cancer.

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 06 February 2018 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Belgium: 7         |
| Country: Number of subjects enrolled | Bulgaria: 8        |
| Country: Number of subjects enrolled | Canada: 37         |
| Country: Number of subjects enrolled | Czechia: 22        |
| Country: Number of subjects enrolled | Denmark: 1         |
| Country: Number of subjects enrolled | Finland: 13        |
| Country: Number of subjects enrolled | Israel: 12         |
| Country: Number of subjects enrolled | Italy: 30          |
| Country: Number of subjects enrolled | Netherlands: 3     |
| Country: Number of subjects enrolled | Norway: 14         |
| Country: Number of subjects enrolled | Poland: 16         |
| Country: Number of subjects enrolled | Portugal: 9        |
| Country: Number of subjects enrolled | Slovenia: 17       |
| Country: Number of subjects enrolled | Spain: 52          |
| Country: Number of subjects enrolled | Sweden: 11         |
| Country: Number of subjects enrolled | Switzerland: 12    |
| Country: Number of subjects enrolled | United Kingdom: 15 |
| Worldwide total number of subjects   | 279                |
| EEA total number of subjects         | 203                |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| 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)                      | 132 |
| From 65 to 84 years                       | 146 |
| 85 years and over                         | 1   |

## Subject disposition

### Recruitment

Recruitment details:

This was a Phase IIIb, single-arm, open-label multicentre study to assess the efficacy and safety of single-agent olaparib as a maintenance treatment in eligible patients. A total of 279 patients were enrolled in this study.

### Pre-assignment

Screening details:

Olaparib was administered to all patients at a starting dose of 300 milligrams (mg) twice daily. Dose reductions were required in patients experiencing toxicities or due to concomitant medication (CM).

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Not applicable                 |
| Blinding used                | Not blinded                    |

### Arms

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

Arm description:

Olaparib was administered to all patients at a starting dose of 300 mg twice daily. Dose reductions were required in patients experiencing toxicities or due to CM. Patients continued with olaparib until documented disease progression as assessed by the Investigator or unacceptable toxicity or for as long as they did not meet any other discontinuation criteria.

|  |                     |
|--|---------------------|
| Arm type                               | Experimental        |
| Investigational medicinal product name | Olaparib            |
| Investigational medicinal product code | AZD2281, KU-0059436 |
| Other name                             |                     |
| Pharmaceutical forms                   | Tablet              |
| Routes of administration               | Oral use            |

Dosage and administration details:

Patients received 2\*150 mg olaparib tablets (i.e. total 300 mg) twice daily at the same time each day, approximately 12 hours apart with one glass of water. Olaparib tablets taken with or without food.

| <b>Number of subjects in period 1</b> | Olaparib |
|---------------------------------------|----------|
| Started                               | 279      |
| Completed                             | 128      |
| Not completed                         | 151      |
| Consent withdrawn by subject          | 3        |
| Death                                 | 146      |
| Lost to follow-up                     | 2        |

## Baseline characteristics

### Reporting groups

|                       |          |
|-----------------------|----------|
| Reporting group title | Olaparib |
|-----------------------|----------|

Reporting group description:

Olaparib was administered to all patients at a starting dose of 300 mg twice daily. Dose reductions were required in patients experiencing toxicities or due to CM. Patients continued with olaparib until documented disease progression as assessed by the Investigator or unacceptable toxicity or for as long as they did not meet any other discontinuation criteria.

| Reporting group values  | Olaparib       | Total |  |
|---|----------------|-------|--|
| Number of subjects  | 279            | 279   |  |
| Age Categorical<br>Units:   |                |       |  |
| Age Continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 64.0<br>± 9.19 | -     |  |
| Gender Categorical<br>Units: Patients                                   |                |       |  |
| Female  | 279            | 279   |  |
| Male  | 0              | 0     |  |
| Race<br>Units: Subjects   |                |       |  |
| White   | 273            | 273   |  |
| Black or African American   | 1              | 1     |  |
| Asian   | 2              | 2     |  |
| Unspecified   | 2              | 2     |  |
| Missing   | 1              | 1     |  |
| Ethnicity<br>Units: Subjects  |                |       |  |
| Hispanic or Latino  | 7              | 7     |  |
| Not Hispanic or Latino  | 271            | 271   |  |
| Missing   | 1              | 1     |  |

## End points

### End points reporting groups

|                       |          |
|-----------------------|----------|
| Reporting group title | Olaparib |
|-----------------------|----------|

Reporting group description:

Olaparib was administered to all patients at a starting dose of 300 mg twice daily. Dose reductions were required in patients experiencing toxicities or due to CM. Patients continued with olaparib until documented disease progression as assessed by the Investigator or unacceptable toxicity or for as long as they did not meet any other discontinuation criteria.

### Primary: Progression Free Survival (PFS)

|                 |  |
|-----------------|--|
| End point title | Progression Free Survival (PFS) <sup>[1]</sup> |
|-----------------|--|

End point description:

PFS is defined as the time from date of first dose until the date of objective radiological disease progression; assessed according to modified RECIST 1.1 or death (by any cause in the absence of progression). Progression was determined by investigator assessment, RECIST 1.1. Calculated using the Kaplan-Meier technique. Confidence intervals (CI) for median PFS was derived based on Brookmeyer-Crowley method. The Full Analysis Set (FAS) included all enrolled patients assigned to olaparib.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to maximum of 32 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: As this is a single arm study, the comparison analysis cannot be performed for this end point.

| End point values                 | Olaparib          |  |  |  |
|----------------------------------|-------------------|--|--|--|
| Subject group type               | Reporting group   |  |  |  |
| Number of subjects analysed      | 279               |  |  |  |
| Units: months                    |                   |  |  |  |
| median (confidence interval 95%) | 9.2 (7.6 to 10.9) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to First Subsequent Therapy or Death (TFST)

|                 |  |
|-----------------|--|
| End point title | Time to First Subsequent Therapy or Death (TFST) |
|-----------------|--|

End point description:

TFST is defined as the time from date of first dose to date of first subsequent treatment commencement or death due to any cause if this occurs before commencement of first subsequent treatment. Calculated using the Kaplan-Meier technique. CI for median TFST was derived based on Brookmeyer-Crowley method. The FAS included all enrolled patients assigned to olaparib.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to a maximum of 43 months

|                                  |                     |  |  |  |
|----------------------------------|---------------------|--|--|--|
| <b>End point values</b>          | Olaparib            |  |  |  |
| Subject group type               | Reporting group     |  |  |  |
| Number of subjects analysed      | 279                 |  |  |  |
| Units: months                    |                     |  |  |  |
| median (confidence interval 95%) | 13.9 (11.5 to 16.6) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Treatment Discontinuation or Death (TDT)

|  |  |
|--|--|
| End point title  | Time to Treatment Discontinuation or Death (TDT) |
| End point description:   |  |
| TDT is defined as the time from date of first dose to date of study drug discontinuation or death due to any cause if this occurs before study drug discontinuation. Calculated using the Kaplan-Meier technique. CI for median TDT was derived based on Brookmeyer-Crowley method. The FAS included all enrolled patients assigned to olaparib. |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| Up to a maximum of 43 months   |  |

|                                  |                   |  |  |  |
|----------------------------------|-------------------|--|--|--|
| <b>End point values</b>          | Olaparib          |  |  |  |
| Subject group type               | Reporting group   |  |  |  |
| Number of subjects analysed      | 279               |  |  |  |
| Units: months                    |                   |  |  |  |
| median (confidence interval 95%) | 9.6 (7.8 to 11.1) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: PFS by Homologous Recombination Deficiency (HRD)/ Breast Cancer Susceptibility Gene Mutation (Mutated) (BRCAm) Status

|  |   |
|--|---|
| End point title  | PFS by Homologous Recombination Deficiency (HRD)/ Breast Cancer Susceptibility Gene Mutation (Mutated) (BRCAm) Status |
| End point description:   |   |
| HRD/BRCAm status was based on the central blood and tumour assessments. Assessed according to modified RECIST 1.1 or death (by any cause in the absence of progression). Progression was determined by investigator assessment, RECIST 1.1. Calculated using the Kaplan-Meier technique. CI for median PFS was derived based on Brookmeyer-Crowley method. The FAS included all enrolled patients assigned |   |

to Olaparib. Only FAS patients with available central assessment are reported. Here, 99999=the upper CI was not calculable due to insufficient progression events.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to maximum of 32 months

| End point values                                   | Olaparib             |  |  |  |
|--|----------------------|--|--|--|
| Subject group type                                 | Reporting group      |  |  |  |
| Number of subjects analysed                        | 242                  |  |  |  |
| Units: months                                      |                      |  |  |  |
| median (confidence interval 95%)                   |                      |  |  |  |
| HRD status positive and/or sBRCAm subgroup (n=121) | 11.1 (9.2 to 14.6)   |  |  |  |
| HRD status positive, non-BRCAM subgroup (n=94)     | 9.7 (8.1 to 13.6)    |  |  |  |
| HRD status negative subgroup (n=115)               | 7.3 (5.5 to 9.0)     |  |  |  |
| sBRCAm subgroup (n=27)                             | 16.4 (12.8 to 99999) |  |  |  |
| gBRCAm subgroup (n=6)                              | 12.1 (3.7 to 99999)  |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival (OS)

|                 |                       |
|-----------------|-----------------------|
| End point title | Overall Survival (OS) |
|-----------------|-----------------------|

End point description:

OS is defined as the time from the date of first dose of olaparib to the date of death from any cause. Calculated using the Kaplan-Meier technique. CI for median OS was derived based on Brookmeyer-Crowley method. The FAS included all enrolled patients assigned to olaparib.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to a maximum of 43 months

| End point values                 | Olaparib            |  |  |  |
|----------------------------------|---------------------|--|--|--|
| Subject group type               | Reporting group     |  |  |  |
| Number of subjects analysed      | 279                 |  |  |  |
| Units: months                    |                     |  |  |  |
| median (confidence interval 95%) | 32.7 (29.5 to 35.3) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Chemotherapy-free Interval (CT-FI)

|                 |                                    |
|-----------------|------------------------------------|
| End point title | Chemotherapy-free Interval (CT-FI) |
|-----------------|------------------------------------|

End point description:

CT-FI is defined as the time from the date of the last dose of platinum chemotherapy prior to olaparib maintenance therapy until the date of initiation of the next anticancer therapy. Calculated using the Kaplan-Meier technique. CI for median CT-FI was derived based on Brookmeyer-Crowley method. The FAS included all enrolled patients assigned to olaparib.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to a maximum of 43 months

| End point values                 | Olaparib            |  |  |  |
|----------------------------------|---------------------|--|--|--|
| Subject group type               | Reporting group     |  |  |  |
| Number of subjects analysed      | 279                 |  |  |  |
| Units: months                    |                     |  |  |  |
| median (confidence interval 95%) | 17.9 (13.8 to 23.3) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Patients With a 10-Point Deterioration From Baseline in TOI Score at any Point During the Treatment Period

|                 |  |
|-----------------|--|
| End point title | Percentage of Patients With a 10-Point Deterioration From Baseline in TOI Score at any Point During the Treatment Period |
|-----------------|--|

End point description:

10-point deterioration was defined as a FACT-O TOI response of "10-point deterioration" at any time point over the course of treatment. The TOI is an established single targeted index composed of the following scales of the FACT-O: physical and functional well-being and additional concerns. The range of possible scores for the FACT-O TOI is 0-100, with a higher score indicating better HRQoL. A decrease in score of at least 10 points from baseline was defined as a clinically meaningful deterioration. The FACT-O set consisted of all FAS patients with at least a baseline and a post-baseline assessment (excluding the end of treatment and 30-day follow up assessments).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to a maximum of 32 months

|                                  |                     |  |  |  |
|----------------------------------|---------------------|--|--|--|
| <b>End point values</b>          | Olaparib            |  |  |  |
| Subject group type               | Reporting group     |  |  |  |
| Number of subjects analysed      | 249                 |  |  |  |
| Units: percentage of patients    |                     |  |  |  |
| number (confidence interval 95%) | 42.6 (36.3 to 49.0) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Patients With any Improvement From Baseline in Trial Outcome Index (TOI) Score at any Point During the Treatment Period

|                 |   |
|-----------------|---|
| End point title | Percentage of Patients With any Improvement From Baseline in Trial Outcome Index (TOI) Score at any Point During the Treatment Period |
|-----------------|---|

End point description:

Improvement was defined as a functional assessment of cancer therapy - ovarian (FACT-O) TOI response of "any improvement" at any time point over the course of treatment. The TOI is an established single targeted index composed of the following scales of the FACT-O: physical and functional well-being and additional concerns. The range of possible scores for the FACT-O TOI is 0-100, with a higher score indicating better health related quality of life (HRQoL). An increase in score from baseline indicates an improvement in HRQoL. The FACT-O set consisted of all FAS patients with at least a baseline and a post-baseline assessment (excluding the end of treatment and 30-day follow up assessments).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to a maximum of 32 months

|                                  |                     |  |  |  |
|----------------------------------|---------------------|--|--|--|
| <b>End point values</b>          | Olaparib            |  |  |  |
| Subject group type               | Reporting group     |  |  |  |
| Number of subjects analysed      | 249                 |  |  |  |
| Units: percentage of patients    |                     |  |  |  |
| number (confidence interval 95%) | 64.3 (58.0 to 70.2) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Includes adverse events with an onset date on or after the date of first dose and up to and including 30 days following the date of last dose of olaparib, up to a maximum of 43 months

Adverse event reporting additional description:

Safety Analysis set consisted of all patients in the FAS who received at least 1 dose of olaparib.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 24.1 |
|--------------------|------|

### Reporting groups

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Olaparib 300mg BID |
|-----------------------|--------------------|

Reporting group description:

Olaparib was administered to all patients at a starting dose of 300 mg twice daily. Dose reductions were required in patients experiencing toxicities or due to CM.

Patients continued with olaparib until documented disease progression as assessed by the Investigator or unacceptable toxicity or for as long as they did not meet any other discontinuation criteria.

| Reporting group title   | Olaparib 300mg BID |  |  |
|---|--------------------|--|--|
| <b>Serious adverse events</b>                                       | Olaparib 300mg BID |  |  |
| Total subjects affected by serious adverse events                   |                    |  |  |
| subjects affected / exposed   | 58 / 279 (20.79%)  |  |  |
| number of deaths (all causes)                                       | 146                |  |  |
| number of deaths resulting from adverse events                      | 2                  |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |  |  |
| Breast cancer   |                    |  |  |
| subjects affected / exposed   | 2 / 279 (0.72%)    |  |  |
| occurrences causally related to treatment / all                     | 0 / 2              |  |  |
| deaths causally related to treatment / all                          | 0 / 0              |  |  |
| Rectal adenocarcinoma   |                    |  |  |
| subjects affected / exposed   | 1 / 279 (0.36%)    |  |  |
| occurrences causally related to treatment / all                     | 0 / 1              |  |  |
| deaths causally related to treatment / all                          | 0 / 0              |  |  |
| Squamous cell carcinoma   |                    |  |  |
| subjects affected / exposed   | 1 / 279 (0.36%)    |  |  |
| occurrences causally related to treatment / all                     | 0 / 1              |  |  |
| deaths causally related to treatment / all                          | 0 / 0              |  |  |
| Vascular disorders  |                    |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Pelvic venous thrombosis                        |                 |  |  |
| subjects affected / exposed                     | 1 / 279 (0.36%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Aortic embolus                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 279 (0.36%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Haemorrhage                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 279 (0.36%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory, thoracic and mediastinal disorders |                 |  |  |
| Chronic obstructive pulmonary disease           |                 |  |  |
| subjects affected / exposed                     | 1 / 279 (0.36%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Chronic respiratory disease                     |                 |  |  |
| subjects affected / exposed                     | 1 / 279 (0.36%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumonitis                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 279 (0.36%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pulmonary embolism                              |                 |  |  |
| subjects affected / exposed                     | 3 / 279 (1.08%) |  |  |
| occurrences causally related to treatment / all | 1 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory failure                             |                 |  |  |
| subjects affected / exposed                     | 1 / 279 (0.36%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|  |                                   |  |  |
|--|-----------------------------------|--|--|
| Psychiatric disorders<br>Depression<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                    | 1 / 279 (0.36%)<br>1 / 1<br>0 / 0 |  |  |
| Investigations<br>Blood creatinine increased<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all           | 1 / 279 (0.36%)<br>1 / 1<br>0 / 0 |  |  |
| Injury, poisoning and procedural complications<br>Fall<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | 1 / 279 (0.36%)<br>0 / 1<br>0 / 0 |  |  |
| Lumbar vertebral fracture<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                              | 1 / 279 (0.36%)<br>0 / 2<br>0 / 0 |  |  |
| Femur fracture<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all   | 1 / 279 (0.36%)<br>0 / 1<br>0 / 0 |  |  |
| Toxicity to various agents<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                             | 1 / 279 (0.36%)<br>0 / 1<br>0 / 0 |  |  |
| Ankle fracture<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all   | 1 / 279 (0.36%)<br>0 / 1<br>0 / 0 |  |  |
| Cardiac disorders<br>Myocardial infarction   |                                   |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 279 (0.36%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| <b>Nervous system disorders</b>                 |                  |  |  |
| Epilepsy  |                  |  |  |
| subjects affected / exposed                     | 1 / 279 (0.36%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| <b>Blood and lymphatic system disorders</b>     |                  |  |  |
| Anaemia   |                  |  |  |
| subjects affected / exposed                     | 22 / 279 (7.89%) |  |  |
| occurrences causally related to treatment / all | 29 / 31          |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Thrombocytopenia                                |                  |  |  |
| subjects affected / exposed                     | 1 / 279 (0.36%)  |  |  |
| occurrences causally related to treatment / all | 2 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| <b>Gastrointestinal disorders</b>               |                  |  |  |
| Colitis ischaemic                               |                  |  |  |
| subjects affected / exposed                     | 1 / 279 (0.36%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Constipation                                    |                  |  |  |
| subjects affected / exposed                     | 1 / 279 (0.36%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Intestinal obstruction                          |                  |  |  |
| subjects affected / exposed                     | 3 / 279 (1.08%)  |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Gastrointestinal wall thickening                |                  |  |  |
| subjects affected / exposed                     | 1 / 279 (0.36%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| Dyspepsia                                       |                 |  |  |  |
| subjects affected / exposed                     | 1 / 279 (0.36%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Mechanical ileus                                |                 |  |  |  |
| subjects affected / exposed                     | 1 / 279 (0.36%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pancreatitis                                    |                 |  |  |  |
| subjects affected / exposed                     | 1 / 279 (0.36%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pneumoperitoneum                                |                 |  |  |  |
| subjects affected / exposed                     | 1 / 279 (0.36%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Small intestinal obstruction                    |                 |  |  |  |
| subjects affected / exposed                     | 2 / 279 (0.72%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Vomiting  |                 |  |  |  |
| subjects affected / exposed                     | 1 / 279 (0.36%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Abdominal incarcerated hernia                   |                 |  |  |  |
| subjects affected / exposed                     | 1 / 279 (0.36%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Large intestinal obstruction                    |                 |  |  |  |
| subjects affected / exposed                     | 1 / 279 (0.36%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Subileus  |                 |  |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed                            | 1 / 279 (0.36%) |  |  |
| occurrences causally related to treatment / all        | 0 / 2           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| <b>Hepatobiliary disorders</b>                         |                 |  |  |
| Biliary dyskinesia                                     |                 |  |  |
| subjects affected / exposed                            | 1 / 279 (0.36%) |  |  |
| occurrences causally related to treatment / all        | 0 / 1           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| Cholecystitis  |                 |  |  |
| subjects affected / exposed                            | 1 / 279 (0.36%) |  |  |
| occurrences causally related to treatment / all        | 0 / 1           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| <b>Renal and urinary disorders</b>                     |                 |  |  |
| Acute kidney injury                                    |                 |  |  |
| subjects affected / exposed                            | 1 / 279 (0.36%) |  |  |
| occurrences causally related to treatment / all        | 1 / 1           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| <b>Musculoskeletal and connective tissue disorders</b> |                 |  |  |
| Osteoarthritis   |                 |  |  |
| subjects affected / exposed                            | 1 / 279 (0.36%) |  |  |
| occurrences causally related to treatment / all        | 0 / 1           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| <b>Infections and infestations</b>                     |                 |  |  |
| Pneumonia aspiration                                   |                 |  |  |
| subjects affected / exposed                            | 1 / 279 (0.36%) |  |  |
| occurrences causally related to treatment / all        | 0 / 1           |  |  |
| deaths causally related to treatment / all             | 0 / 1           |  |  |
| Appendicitis   |                 |  |  |
| subjects affected / exposed                            | 1 / 279 (0.36%) |  |  |
| occurrences causally related to treatment / all        | 0 / 1           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| Bacteraemia  |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 279 (0.36%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Endocarditis                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 279 (0.36%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastroenteritis                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 279 (0.36%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Lower respiratory tract infection               |                 |  |  |
| subjects affected / exposed                     | 1 / 279 (0.36%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumonia                                       |                 |  |  |
| subjects affected / exposed                     | 3 / 279 (1.08%) |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Sepsis  |                 |  |  |
| subjects affected / exposed                     | 2 / 279 (0.72%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Urinary tract infection                         |                 |  |  |
| subjects affected / exposed                     | 1 / 279 (0.36%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| COVID-19  |                 |  |  |
| subjects affected / exposed                     | 2 / 279 (0.72%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Metabolism and nutrition disorders              |                 |  |  |
| Dehydration                                     |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 279 (0.36%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hyponatraemia                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 279 (0.36%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

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

| <b>Non-serious adverse events</b>                                   | Olaparib 300mg BID |  |  |
|---|--------------------|--|--|
| Total subjects affected by non-serious adverse events               |                    |  |  |
| subjects affected / exposed   | 268 / 279 (96.06%) |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |  |  |
| Bowen's disease   |                    |  |  |
| subjects affected / exposed   | 1 / 279 (0.36%)    |  |  |
| occurrences (all)   | 1                  |  |  |
| Seborrhoeic keratosis   |                    |  |  |
| subjects affected / exposed   | 1 / 279 (0.36%)    |  |  |
| occurrences (all)   | 1                  |  |  |
| Vascular disorders  |                    |  |  |
| Deep vein thrombosis  |                    |  |  |
| subjects affected / exposed   | 2 / 279 (0.72%)    |  |  |
| occurrences (all)   | 2                  |  |  |
| Embolism  |                    |  |  |
| subjects affected / exposed   | 2 / 279 (0.72%)    |  |  |
| occurrences (all)   | 2                  |  |  |
| Flushing  |                    |  |  |
| subjects affected / exposed   | 4 / 279 (1.43%)    |  |  |
| occurrences (all)   | 5                  |  |  |
| Hot flush   |                    |  |  |
| subjects affected / exposed   | 4 / 279 (1.43%)    |  |  |
| occurrences (all)   | 4                  |  |  |
| Haematoma   |                    |  |  |

|  |                   |  |  |
|--|-------------------|--|--|
| subjects affected / exposed                          | 1 / 279 (0.36%)   |  |  |
| occurrences (all)                                    | 1                 |  |  |
| Hypertension   |                   |  |  |
| subjects affected / exposed                          | 7 / 279 (2.51%)   |  |  |
| occurrences (all)                                    | 7                 |  |  |
| Hypotension  |                   |  |  |
| subjects affected / exposed                          | 2 / 279 (0.72%)   |  |  |
| occurrences (all)                                    | 4                 |  |  |
| Lymphoedema  |                   |  |  |
| subjects affected / exposed                          | 2 / 279 (0.72%)   |  |  |
| occurrences (all)                                    | 2                 |  |  |
| Peripheral coldness                                  |                   |  |  |
| subjects affected / exposed                          | 1 / 279 (0.36%)   |  |  |
| occurrences (all)                                    | 1                 |  |  |
| Thrombosis   |                   |  |  |
| subjects affected / exposed                          | 1 / 279 (0.36%)   |  |  |
| occurrences (all)                                    | 1                 |  |  |
| General disorders and administration site conditions |                   |  |  |
| Adhesion   |                   |  |  |
| subjects affected / exposed                          | 1 / 279 (0.36%)   |  |  |
| occurrences (all)                                    | 1                 |  |  |
| Chest discomfort                                     |                   |  |  |
| subjects affected / exposed                          | 3 / 279 (1.08%)   |  |  |
| occurrences (all)                                    | 3                 |  |  |
| Asthenia   |                   |  |  |
| subjects affected / exposed                          | 46 / 279 (16.49%) |  |  |
| occurrences (all)                                    | 57                |  |  |
| Face oedema  |                   |  |  |
| subjects affected / exposed                          | 2 / 279 (0.72%)   |  |  |
| occurrences (all)                                    | 2                 |  |  |
| Early satiety  |                   |  |  |
| subjects affected / exposed                          | 2 / 279 (0.72%)   |  |  |
| occurrences (all)                                    | 2                 |  |  |
| Chills   |                   |  |  |

|                             |                   |  |  |
|-----------------------------|-------------------|--|--|
| subjects affected / exposed | 2 / 279 (0.72%)   |  |  |
| occurrences (all)           | 2                 |  |  |
| Chest pain                  |                   |  |  |
| subjects affected / exposed | 4 / 279 (1.43%)   |  |  |
| occurrences (all)           | 4                 |  |  |
| Fatigue                     |                   |  |  |
| subjects affected / exposed | 82 / 279 (29.39%) |  |  |
| occurrences (all)           | 103               |  |  |
| Influenza like illness      |                   |  |  |
| subjects affected / exposed | 5 / 279 (1.79%)   |  |  |
| occurrences (all)           | 5                 |  |  |
| Infusion site extravasation |                   |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)   |  |  |
| occurrences (all)           | 1                 |  |  |
| Localised oedema            |                   |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)   |  |  |
| occurrences (all)           | 1                 |  |  |
| Malaise                     |                   |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)   |  |  |
| occurrences (all)           | 1                 |  |  |
| Oedema                      |                   |  |  |
| subjects affected / exposed | 2 / 279 (0.72%)   |  |  |
| occurrences (all)           | 2                 |  |  |
| Non-cardiac chest pain      |                   |  |  |
| subjects affected / exposed | 5 / 279 (1.79%)   |  |  |
| occurrences (all)           | 5                 |  |  |
| Mucosal inflammation        |                   |  |  |
| subjects affected / exposed | 9 / 279 (3.23%)   |  |  |
| occurrences (all)           | 10                |  |  |
| Mass                        |                   |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)   |  |  |
| occurrences (all)           | 1                 |  |  |
| Oedema peripheral           |                   |  |  |
| subjects affected / exposed | 13 / 279 (4.66%)  |  |  |
| occurrences (all)           | 15                |  |  |
| Peripheral swelling         |                   |  |  |

|  |                        |  |  |
|--|------------------------|--|--|
| subjects affected / exposed<br>occurrences (all)                             | 1 / 279 (0.36%)<br>1   |  |  |
| Pain<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 279 (0.36%)<br>1   |  |  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)                  | 16 / 279 (5.73%)<br>23 |  |  |
| Swelling<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 279 (0.36%)<br>1   |  |  |
| Inflammation<br>subjects affected / exposed<br>occurrences (all)             | 1 / 279 (0.36%)<br>1   |  |  |
| Reproductive system and breast disorders                                     |                        |  |  |
| Pelvic pain<br>subjects affected / exposed<br>occurrences (all)              | 5 / 279 (1.79%)<br>5   |  |  |
| Pelvic discomfort<br>subjects affected / exposed<br>occurrences (all)        | 1 / 279 (0.36%)<br>1   |  |  |
| Vaginal discharge<br>subjects affected / exposed<br>occurrences (all)        | 1 / 279 (0.36%)<br>1   |  |  |
| Vaginal haemorrhage<br>subjects affected / exposed<br>occurrences (all)      | 2 / 279 (0.72%)<br>2   |  |  |
| Vulvovaginal pain<br>subjects affected / exposed<br>occurrences (all)        | 1 / 279 (0.36%)<br>1   |  |  |
| Heavy menstrual bleeding<br>subjects affected / exposed<br>occurrences (all) | 1 / 279 (0.36%)<br>3   |  |  |
| Respiratory, thoracic and mediastinal disorders                              |                        |  |  |

|                             |                   |  |  |
|-----------------------------|-------------------|--|--|
| Cough                       |                   |  |  |
| subjects affected / exposed | 31 / 279 (11.11%) |  |  |
| occurrences (all)           | 36                |  |  |
| Chronic respiratory disease |                   |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)   |  |  |
| occurrences (all)           | 2                 |  |  |
| Asthma                      |                   |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)   |  |  |
| occurrences (all)           | 1                 |  |  |
| Haemoptysis                 |                   |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)   |  |  |
| occurrences (all)           | 1                 |  |  |
| Dyspnoea                    |                   |  |  |
| subjects affected / exposed | 14 / 279 (5.02%)  |  |  |
| occurrences (all)           | 15                |  |  |
| Dysphonia                   |                   |  |  |
| subjects affected / exposed | 2 / 279 (0.72%)   |  |  |
| occurrences (all)           | 2                 |  |  |
| Hiccups                     |                   |  |  |
| subjects affected / exposed | 2 / 279 (0.72%)   |  |  |
| occurrences (all)           | 2                 |  |  |
| Dry throat                  |                   |  |  |
| subjects affected / exposed | 2 / 279 (0.72%)   |  |  |
| occurrences (all)           | 2                 |  |  |
| Hypoxia                     |                   |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)   |  |  |
| occurrences (all)           | 1                 |  |  |
| Nasal disorder              |                   |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)   |  |  |
| occurrences (all)           | 1                 |  |  |
| Nasal congestion            |                   |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)   |  |  |
| occurrences (all)           | 2                 |  |  |
| Lung infiltration           |                   |  |  |
| subjects affected / exposed | 2 / 279 (0.72%)   |  |  |
| occurrences (all)           | 2                 |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| Laryngeal pain              |                 |  |  |
| subjects affected / exposed | 2 / 279 (0.72%) |  |  |
| occurrences (all)           | 2               |  |  |
| Pleural effusion            |                 |  |  |
| subjects affected / exposed | 2 / 279 (0.72%) |  |  |
| occurrences (all)           | 2               |  |  |
| Pharyngeal inflammation     |                 |  |  |
| subjects affected / exposed | 1 / 279 (0.36%) |  |  |
| occurrences (all)           | 1               |  |  |
| Oropharyngeal pain          |                 |  |  |
| subjects affected / exposed | 6 / 279 (2.15%) |  |  |
| occurrences (all)           | 8               |  |  |
| Organising pneumonia        |                 |  |  |
| subjects affected / exposed | 1 / 279 (0.36%) |  |  |
| occurrences (all)           | 1               |  |  |
| Productive cough            |                 |  |  |
| subjects affected / exposed | 1 / 279 (0.36%) |  |  |
| occurrences (all)           | 1               |  |  |
| Upper-airway cough syndrome |                 |  |  |
| subjects affected / exposed | 1 / 279 (0.36%) |  |  |
| occurrences (all)           | 1               |  |  |
| Rhinorrhoea                 |                 |  |  |
| subjects affected / exposed | 5 / 279 (1.79%) |  |  |
| occurrences (all)           | 6               |  |  |
| Pulmonary embolism          |                 |  |  |
| subjects affected / exposed | 4 / 279 (1.43%) |  |  |
| occurrences (all)           | 4               |  |  |
| Dyspnoea exertional         |                 |  |  |
| subjects affected / exposed | 1 / 279 (0.36%) |  |  |
| occurrences (all)           | 1               |  |  |
| Psychiatric disorders       |                 |  |  |
| Affect lability             |                 |  |  |
| subjects affected / exposed | 1 / 279 (0.36%) |  |  |
| occurrences (all)           | 1               |  |  |
| Agitation                   |                 |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed             | 1 / 279 (0.36%)  |  |  |
| occurrences (all)                       | 1                |  |  |
| Anxiety                                 |                  |  |  |
| subjects affected / exposed             | 6 / 279 (2.15%)  |  |  |
| occurrences (all)                       | 6                |  |  |
| Bradyphrenia                            |                  |  |  |
| subjects affected / exposed             | 1 / 279 (0.36%)  |  |  |
| occurrences (all)                       | 1                |  |  |
| Depression                              |                  |  |  |
| subjects affected / exposed             | 7 / 279 (2.51%)  |  |  |
| occurrences (all)                       | 7                |  |  |
| Genito-pelvic pain/penetration disorder |                  |  |  |
| subjects affected / exposed             | 1 / 279 (0.36%)  |  |  |
| occurrences (all)                       | 1                |  |  |
| Panic attack                            |                  |  |  |
| subjects affected / exposed             | 1 / 279 (0.36%)  |  |  |
| occurrences (all)                       | 1                |  |  |
| Irritability                            |                  |  |  |
| subjects affected / exposed             | 1 / 279 (0.36%)  |  |  |
| occurrences (all)                       | 1                |  |  |
| Insomnia                                |                  |  |  |
| subjects affected / exposed             | 14 / 279 (5.02%) |  |  |
| occurrences (all)                       | 14               |  |  |
| Hallucination, visual                   |                  |  |  |
| subjects affected / exposed             | 1 / 279 (0.36%)  |  |  |
| occurrences (all)                       | 1                |  |  |
| Tension                                 |                  |  |  |
| subjects affected / exposed             | 1 / 279 (0.36%)  |  |  |
| occurrences (all)                       | 1                |  |  |
| Sleep disorder                          |                  |  |  |
| subjects affected / exposed             | 1 / 279 (0.36%)  |  |  |
| occurrences (all)                       | 1                |  |  |
| Restlessness                            |                  |  |  |
| subjects affected / exposed             | 3 / 279 (1.08%)  |  |  |
| occurrences (all)                       | 3                |  |  |

|  |                         |  |  |
|--|-------------------------|--|--|
| Mood swings<br>subjects affected / exposed<br>occurrences (all)  | 1 / 279 (0.36%)<br>1    |  |  |
| Product issues<br>Device breakage<br>subjects affected / exposed<br>occurrences (all)                      | 1 / 279 (0.36%)<br>1    |  |  |
| Investigations<br>Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all) | 2 / 279 (0.72%)<br>2    |  |  |
| Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)                   | 7 / 279 (2.51%)<br>9    |  |  |
| Amylase increased<br>subjects affected / exposed<br>occurrences (all)                                      | 1 / 279 (0.36%)<br>1    |  |  |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)                     | 6 / 279 (2.15%)<br>8    |  |  |
| Blood potassium decreased<br>subjects affected / exposed<br>occurrences (all)                              | 1 / 279 (0.36%)<br>2    |  |  |
| Blood creatinine increased<br>subjects affected / exposed<br>occurrences (all)                             | 29 / 279 (10.39%)<br>46 |  |  |
| Blood creatine increased<br>subjects affected / exposed<br>occurrences (all)                               | 3 / 279 (1.08%)<br>4    |  |  |
| Blood potassium increased<br>subjects affected / exposed<br>occurrences (all)                              | 1 / 279 (0.36%)<br>1    |  |  |
| Blood bilirubin increased<br>subjects affected / exposed<br>occurrences (all)                              | 4 / 279 (1.43%)<br>6    |  |  |
| Blood urea increased   |                         |  |  |

|                                      |                  |  |  |
|--------------------------------------|------------------|--|--|
| subjects affected / exposed          | 4 / 279 (1.43%)  |  |  |
| occurrences (all)                    | 4                |  |  |
| Creatinine renal clearance decreased |                  |  |  |
| subjects affected / exposed          | 2 / 279 (0.72%)  |  |  |
| occurrences (all)                    | 2                |  |  |
| Blood sodium decreased               |                  |  |  |
| subjects affected / exposed          | 1 / 279 (0.36%)  |  |  |
| occurrences (all)                    | 1                |  |  |
| Blood pressure decreased             |                  |  |  |
| subjects affected / exposed          | 1 / 279 (0.36%)  |  |  |
| occurrences (all)                    | 1                |  |  |
| Gamma-glutamyltransferase increased  |                  |  |  |
| subjects affected / exposed          | 1 / 279 (0.36%)  |  |  |
| occurrences (all)                    | 1                |  |  |
| Glomerular filtration rate decreased |                  |  |  |
| subjects affected / exposed          | 1 / 279 (0.36%)  |  |  |
| occurrences (all)                    | 1                |  |  |
| Haemoglobin decreased                |                  |  |  |
| subjects affected / exposed          | 2 / 279 (0.72%)  |  |  |
| occurrences (all)                    | 2                |  |  |
| Lipase increased                     |                  |  |  |
| subjects affected / exposed          | 1 / 279 (0.36%)  |  |  |
| occurrences (all)                    | 1                |  |  |
| Lymphocyte count decreased           |                  |  |  |
| subjects affected / exposed          | 4 / 279 (1.43%)  |  |  |
| occurrences (all)                    | 6                |  |  |
| Mean cell volume increased           |                  |  |  |
| subjects affected / exposed          | 2 / 279 (0.72%)  |  |  |
| occurrences (all)                    | 2                |  |  |
| Neutrophil count decreased           |                  |  |  |
| subjects affected / exposed          | 14 / 279 (5.02%) |  |  |
| occurrences (all)                    | 32               |  |  |
| Monocyte count increased             |                  |  |  |
| subjects affected / exposed          | 1 / 279 (0.36%)  |  |  |
| occurrences (all)                    | 2                |  |  |

|  |                        |  |  |
|--|------------------------|--|--|
| Occult blood<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 279 (0.36%)<br>1   |  |  |
| Troponin I increased<br>subjects affected / exposed<br>occurrences (all)             | 1 / 279 (0.36%)<br>1   |  |  |
| Platelet count decreased<br>subjects affected / exposed<br>occurrences (all)         | 16 / 279 (5.73%)<br>33 |  |  |
| Urine analysis abnormal<br>subjects affected / exposed<br>occurrences (all)          | 1 / 279 (0.36%)<br>1   |  |  |
| Vitamin B12 decreased<br>subjects affected / exposed<br>occurrences (all)            | 1 / 279 (0.36%)<br>1   |  |  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                 | 6 / 279 (2.15%)<br>6   |  |  |
| Weight increased<br>subjects affected / exposed<br>occurrences (all)                 | 3 / 279 (1.08%)<br>3   |  |  |
| White blood cell count decreased<br>subjects affected / exposed<br>occurrences (all) | 13 / 279 (4.66%)<br>29 |  |  |
| SARS-CoV-2 test positive<br>subjects affected / exposed<br>occurrences (all)         | 1 / 279 (0.36%)<br>1   |  |  |
| Injury, poisoning and procedural complications                                       |                        |  |  |
| Arthropod bite<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 279 (0.36%)<br>1   |  |  |
| Arthropod sting<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 279 (0.36%)<br>1   |  |  |
| Contusion  |                        |  |  |

|  |                      |  |  |
|--|----------------------|--|--|
| subjects affected / exposed<br>occurrences (all)                           | 3 / 279 (1.08%)<br>3 |  |  |
| Bone fissure<br>subjects affected / exposed<br>occurrences (all)           | 1 / 279 (0.36%)<br>1 |  |  |
| Fall<br>subjects affected / exposed<br>occurrences (all)                   | 3 / 279 (1.08%)<br>3 |  |  |
| Head injury<br>subjects affected / exposed<br>occurrences (all)            | 1 / 279 (0.36%)<br>1 |  |  |
| Hand fracture<br>subjects affected / exposed<br>occurrences (all)          | 2 / 279 (0.72%)<br>3 |  |  |
| Humerus fracture<br>subjects affected / exposed<br>occurrences (all)       | 1 / 279 (0.36%)<br>1 |  |  |
| Procedural pain<br>subjects affected / exposed<br>occurrences (all)        | 1 / 279 (0.36%)<br>1 |  |  |
| Joint injury<br>subjects affected / exposed<br>occurrences (all)           | 1 / 279 (0.36%)<br>1 |  |  |
| Rib fracture<br>subjects affected / exposed<br>occurrences (all)           | 3 / 279 (1.08%)<br>3 |  |  |
| Soft tissue injury<br>subjects affected / exposed<br>occurrences (all)     | 1 / 279 (0.36%)<br>1 |  |  |
| Tooth fracture<br>subjects affected / exposed<br>occurrences (all)         | 1 / 279 (0.36%)<br>1 |  |  |
| Stoma site haemorrhage<br>subjects affected / exposed<br>occurrences (all) | 1 / 279 (0.36%)<br>1 |  |  |
| Wound complication   |                      |  |  |

|  |                        |  |  |
|--|------------------------|--|--|
| subjects affected / exposed<br>occurrences (all)                             | 1 / 279 (0.36%)<br>1   |  |  |
| Cardiac disorders  |                        |  |  |
| Angina pectoris<br>subjects affected / exposed<br>occurrences (all)          | 1 / 279 (0.36%)<br>1   |  |  |
| Arrhythmia<br>subjects affected / exposed<br>occurrences (all)               | 1 / 279 (0.36%)<br>1   |  |  |
| Palpitations<br>subjects affected / exposed<br>occurrences (all)             | 3 / 279 (1.08%)<br>3   |  |  |
| Tachycardia<br>subjects affected / exposed<br>occurrences (all)              | 2 / 279 (0.72%)<br>2   |  |  |
| Nervous system disorders   |                        |  |  |
| Amnesia<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 279 (0.36%)<br>2   |  |  |
| Ageusia<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 279 (0.36%)<br>1   |  |  |
| Balance disorder<br>subjects affected / exposed<br>occurrences (all)         | 1 / 279 (0.36%)<br>3   |  |  |
| Carpal tunnel syndrome<br>subjects affected / exposed<br>occurrences (all)   | 1 / 279 (0.36%)<br>1   |  |  |
| Disturbance in attention<br>subjects affected / exposed<br>occurrences (all) | 2 / 279 (0.72%)<br>2   |  |  |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                | 17 / 279 (6.09%)<br>22 |  |  |
| Dysgeusia  |                        |  |  |

|                                      |                   |  |  |
|--------------------------------------|-------------------|--|--|
| subjects affected / exposed          | 40 / 279 (14.34%) |  |  |
| occurrences (all)                    | 44                |  |  |
| <b>Epilepsy</b>                      |                   |  |  |
| subjects affected / exposed          | 1 / 279 (0.36%)   |  |  |
| occurrences (all)                    | 2                 |  |  |
| <b>Nerve compression</b>             |                   |  |  |
| subjects affected / exposed          | 1 / 279 (0.36%)   |  |  |
| occurrences (all)                    | 1                 |  |  |
| <b>Migraine</b>                      |                   |  |  |
| subjects affected / exposed          | 1 / 279 (0.36%)   |  |  |
| occurrences (all)                    | 1                 |  |  |
| <b>Hypoaesthesia</b>                 |                   |  |  |
| subjects affected / exposed          | 1 / 279 (0.36%)   |  |  |
| occurrences (all)                    | 1                 |  |  |
| <b>Headache</b>                      |                   |  |  |
| subjects affected / exposed          | 24 / 279 (8.60%)  |  |  |
| occurrences (all)                    | 27                |  |  |
| <b>Neuropathy peripheral</b>         |                   |  |  |
| subjects affected / exposed          | 3 / 279 (1.08%)   |  |  |
| occurrences (all)                    | 3                 |  |  |
| <b>Peripheral sensory neuropathy</b> |                   |  |  |
| subjects affected / exposed          | 3 / 279 (1.08%)   |  |  |
| occurrences (all)                    | 3                 |  |  |
| <b>Paraesthesia</b>                  |                   |  |  |
| subjects affected / exposed          | 2 / 279 (0.72%)   |  |  |
| occurrences (all)                    | 2                 |  |  |
| <b>Neurotoxicity</b>                 |                   |  |  |
| subjects affected / exposed          | 4 / 279 (1.43%)   |  |  |
| occurrences (all)                    | 4                 |  |  |
| <b>Polyneuropathy</b>                |                   |  |  |
| subjects affected / exposed          | 2 / 279 (0.72%)   |  |  |
| occurrences (all)                    | 2                 |  |  |
| <b>Taste disorder</b>                |                   |  |  |
| subjects affected / exposed          | 3 / 279 (1.08%)   |  |  |
| occurrences (all)                    | 4                 |  |  |
| <b>Syncope</b>                       |                   |  |  |

|   |                    |  |  |
|---|--------------------|--|--|
| subjects affected / exposed                 | 2 / 279 (0.72%)    |  |  |
| occurrences (all)                           | 2                  |  |  |
| Somnolence                                  |                    |  |  |
| subjects affected / exposed                 | 1 / 279 (0.36%)    |  |  |
| occurrences (all)                           | 1                  |  |  |
| Transient ischaemic attack                  |                    |  |  |
| subjects affected / exposed                 | 1 / 279 (0.36%)    |  |  |
| occurrences (all)                           | 1                  |  |  |
| Tremor                                      |                    |  |  |
| subjects affected / exposed                 | 2 / 279 (0.72%)    |  |  |
| occurrences (all)                           | 2                  |  |  |
| Trigeminal nerve disorder                   |                    |  |  |
| subjects affected / exposed                 | 1 / 279 (0.36%)    |  |  |
| occurrences (all)                           | 1                  |  |  |
| Presyncope                                  |                    |  |  |
| subjects affected / exposed                 | 1 / 279 (0.36%)    |  |  |
| occurrences (all)                           | 1                  |  |  |
| Dyskinesia                                  |                    |  |  |
| subjects affected / exposed                 | 1 / 279 (0.36%)    |  |  |
| occurrences (all)                           | 1                  |  |  |
| Hypotonia                                   |                    |  |  |
| subjects affected / exposed                 | 1 / 279 (0.36%)    |  |  |
| occurrences (all)                           | 1                  |  |  |
| <b>Blood and lymphatic system disorders</b> |                    |  |  |
| <b>Anaemia</b>                              |                    |  |  |
| subjects affected / exposed                 | 102 / 279 (36.56%) |  |  |
| occurrences (all)                           | 197                |  |  |
| Anaemia macrocytic                          |                    |  |  |
| subjects affected / exposed                 | 1 / 279 (0.36%)    |  |  |
| occurrences (all)                           | 1                  |  |  |
| Lymphopenia                                 |                    |  |  |
| subjects affected / exposed                 | 6 / 279 (2.15%)    |  |  |
| occurrences (all)                           | 9                  |  |  |
| Lymphadenopathy                             |                    |  |  |
| subjects affected / exposed                 | 2 / 279 (0.72%)    |  |  |
| occurrences (all)                           | 2                  |  |  |

|                             |                   |  |  |
|-----------------------------|-------------------|--|--|
| Leukopenia                  |                   |  |  |
| subjects affected / exposed | 15 / 279 (5.38%)  |  |  |
| occurrences (all)           | 25                |  |  |
| Erythropenia                |                   |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)   |  |  |
| occurrences (all)           | 1                 |  |  |
| Macrocytosis                |                   |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)   |  |  |
| occurrences (all)           | 1                 |  |  |
| Thrombocytopenia            |                   |  |  |
| subjects affected / exposed | 20 / 279 (7.17%)  |  |  |
| occurrences (all)           | 31                |  |  |
| Neutropenia                 |                   |  |  |
| subjects affected / exposed | 31 / 279 (11.11%) |  |  |
| occurrences (all)           | 62                |  |  |
| Ear and labyrinth disorders |                   |  |  |
| Tinnitus                    |                   |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)   |  |  |
| occurrences (all)           | 1                 |  |  |
| Deafness                    |                   |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)   |  |  |
| occurrences (all)           | 1                 |  |  |
| Ear haemorrhage             |                   |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)   |  |  |
| occurrences (all)           | 1                 |  |  |
| Meniere's disease           |                   |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)   |  |  |
| occurrences (all)           | 1                 |  |  |
| Vertigo                     |                   |  |  |
| subjects affected / exposed | 4 / 279 (1.43%)   |  |  |
| occurrences (all)           | 5                 |  |  |
| Eye disorders               |                   |  |  |
| Amaurosis fugax             |                   |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)   |  |  |
| occurrences (all)           | 1                 |  |  |
| Cataract                    |                   |  |  |

|                             |                   |  |  |
|-----------------------------|-------------------|--|--|
| subjects affected / exposed | 2 / 279 (0.72%)   |  |  |
| occurrences (all)           | 2                 |  |  |
| Dry eye                     |                   |  |  |
| subjects affected / exposed | 2 / 279 (0.72%)   |  |  |
| occurrences (all)           | 2                 |  |  |
| Eye disorder                |                   |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)   |  |  |
| occurrences (all)           | 1                 |  |  |
| Vision blurred              |                   |  |  |
| subjects affected / exposed | 2 / 279 (0.72%)   |  |  |
| occurrences (all)           | 2                 |  |  |
| Visual impairment           |                   |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)   |  |  |
| occurrences (all)           | 1                 |  |  |
| Gastrointestinal disorders  |                   |  |  |
| Abdominal discomfort        |                   |  |  |
| subjects affected / exposed | 4 / 279 (1.43%)   |  |  |
| occurrences (all)           | 4                 |  |  |
| Abdominal distension        |                   |  |  |
| subjects affected / exposed | 13 / 279 (4.66%)  |  |  |
| occurrences (all)           | 13                |  |  |
| Abdominal hernia            |                   |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)   |  |  |
| occurrences (all)           | 1                 |  |  |
| Abdominal pain              |                   |  |  |
| subjects affected / exposed | 43 / 279 (15.41%) |  |  |
| occurrences (all)           | 52                |  |  |
| Abdominal pain lower        |                   |  |  |
| subjects affected / exposed | 6 / 279 (2.15%)   |  |  |
| occurrences (all)           | 7                 |  |  |
| Abdominal pain upper        |                   |  |  |
| subjects affected / exposed | 16 / 279 (5.73%)  |  |  |
| occurrences (all)           | 18                |  |  |
| Abnormal faeces             |                   |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)   |  |  |
| occurrences (all)           | 1                 |  |  |

|                             |                   |  |  |
|-----------------------------|-------------------|--|--|
| Angular cheilitis           |                   |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)   |  |  |
| occurrences (all)           | 1                 |  |  |
| Aerophagia                  |                   |  |  |
| subjects affected / exposed | 2 / 279 (0.72%)   |  |  |
| occurrences (all)           | 3                 |  |  |
| Aphthous ulcer              |                   |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)   |  |  |
| occurrences (all)           | 1                 |  |  |
| Chronic gastritis           |                   |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)   |  |  |
| occurrences (all)           | 1                 |  |  |
| Ascites                     |                   |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)   |  |  |
| occurrences (all)           | 1                 |  |  |
| Constipation                |                   |  |  |
| subjects affected / exposed | 23 / 279 (8.24%)  |  |  |
| occurrences (all)           | 28                |  |  |
| Defaecation urgency         |                   |  |  |
| subjects affected / exposed | 2 / 279 (0.72%)   |  |  |
| occurrences (all)           | 2                 |  |  |
| Diarrhoea                   |                   |  |  |
| subjects affected / exposed | 40 / 279 (14.34%) |  |  |
| occurrences (all)           | 55                |  |  |
| Dry mouth                   |                   |  |  |
| subjects affected / exposed | 6 / 279 (2.15%)   |  |  |
| occurrences (all)           | 6                 |  |  |
| Dyspepsia                   |                   |  |  |
| subjects affected / exposed | 16 / 279 (5.73%)  |  |  |
| occurrences (all)           | 18                |  |  |
| Dysphagia                   |                   |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)   |  |  |
| occurrences (all)           | 1                 |  |  |
| Enteritis                   |                   |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)   |  |  |
| occurrences (all)           | 1                 |  |  |

|                                  |                 |  |  |
|----------------------------------|-----------------|--|--|
| Eructation                       |                 |  |  |
| subjects affected / exposed      | 1 / 279 (0.36%) |  |  |
| occurrences (all)                | 1               |  |  |
| Epigastric discomfort            |                 |  |  |
| subjects affected / exposed      | 2 / 279 (0.72%) |  |  |
| occurrences (all)                | 2               |  |  |
| Faeces soft                      |                 |  |  |
| subjects affected / exposed      | 1 / 279 (0.36%) |  |  |
| occurrences (all)                | 1               |  |  |
| Gastrooesophageal reflux disease |                 |  |  |
| subjects affected / exposed      | 5 / 279 (1.79%) |  |  |
| occurrences (all)                | 5               |  |  |
| Gastritis                        |                 |  |  |
| subjects affected / exposed      | 2 / 279 (0.72%) |  |  |
| occurrences (all)                | 2               |  |  |
| Gastric ulcer                    |                 |  |  |
| subjects affected / exposed      | 1 / 279 (0.36%) |  |  |
| occurrences (all)                | 1               |  |  |
| Flatulence                       |                 |  |  |
| subjects affected / exposed      | 8 / 279 (2.87%) |  |  |
| occurrences (all)                | 8               |  |  |
| Gingival pain                    |                 |  |  |
| subjects affected / exposed      | 1 / 279 (0.36%) |  |  |
| occurrences (all)                | 1               |  |  |
| Lip dry                          |                 |  |  |
| subjects affected / exposed      | 1 / 279 (0.36%) |  |  |
| occurrences (all)                | 1               |  |  |
| Intestinal obstruction           |                 |  |  |
| subjects affected / exposed      | 3 / 279 (1.08%) |  |  |
| occurrences (all)                | 4               |  |  |
| Haemorrhoids                     |                 |  |  |
| subjects affected / exposed      | 3 / 279 (1.08%) |  |  |
| occurrences (all)                | 3               |  |  |
| Haemorrhoidal haemorrhage        |                 |  |  |
| subjects affected / exposed      | 1 / 279 (0.36%) |  |  |
| occurrences (all)                | 1               |  |  |

|                             |                    |  |  |
|-----------------------------|--------------------|--|--|
| Mouth ulceration            |                    |  |  |
| subjects affected / exposed | 2 / 279 (0.72%)    |  |  |
| occurrences (all)           | 2                  |  |  |
| Nausea                      |                    |  |  |
| subjects affected / exposed | 136 / 279 (48.75%) |  |  |
| occurrences (all)           | 187                |  |  |
| Odynophagia                 |                    |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)    |  |  |
| occurrences (all)           | 1                  |  |  |
| Oesophagitis                |                    |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)    |  |  |
| occurrences (all)           | 1                  |  |  |
| Oral mucosal exfoliation    |                    |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)    |  |  |
| occurrences (all)           | 1                  |  |  |
| Palatal disorder            |                    |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)    |  |  |
| occurrences (all)           | 1                  |  |  |
| Toothache                   |                    |  |  |
| subjects affected / exposed | 2 / 279 (0.72%)    |  |  |
| occurrences (all)           | 2                  |  |  |
| Tooth disorder              |                    |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)    |  |  |
| occurrences (all)           | 1                  |  |  |
| Stomatitis                  |                    |  |  |
| subjects affected / exposed | 13 / 279 (4.66%)   |  |  |
| occurrences (all)           | 13                 |  |  |
| Regurgitation               |                    |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)    |  |  |
| occurrences (all)           | 1                  |  |  |
| Vomiting                    |                    |  |  |
| subjects affected / exposed | 45 / 279 (16.13%)  |  |  |
| occurrences (all)           | 68                 |  |  |
| Tooth development disorder  |                    |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)    |  |  |
| occurrences (all)           | 1                  |  |  |

|  |                        |  |  |
|--|------------------------|--|--|
| Irritable bowel syndrome<br>subjects affected / exposed<br>occurrences (all) | 1 / 279 (0.36%)<br>1   |  |  |
| Faecal vomiting<br>subjects affected / exposed<br>occurrences (all)          | 1 / 279 (0.36%)<br>1   |  |  |
| Hepatobiliary disorders  |                        |  |  |
| Hyperbilirubinaemia<br>subjects affected / exposed<br>occurrences (all)      | 2 / 279 (0.72%)<br>3   |  |  |
| Hepatotoxicity<br>subjects affected / exposed<br>occurrences (all)           | 1 / 279 (0.36%)<br>1   |  |  |
| Liver disorder<br>subjects affected / exposed<br>occurrences (all)           | 1 / 279 (0.36%)<br>1   |  |  |
| Bile duct stenosis<br>subjects affected / exposed<br>occurrences (all)       | 1 / 279 (0.36%)<br>1   |  |  |
| Hepatic cytolysis<br>subjects affected / exposed<br>occurrences (all)        | 1 / 279 (0.36%)<br>1   |  |  |
| Skin and subcutaneous tissue disorders                                       |                        |  |  |
| Alopecia<br>subjects affected / exposed<br>occurrences (all)                 | 16 / 279 (5.73%)<br>16 |  |  |
| Cold sweat<br>subjects affected / exposed<br>occurrences (all)               | 1 / 279 (0.36%)<br>1   |  |  |
| Hyperhidrosis<br>subjects affected / exposed<br>occurrences (all)            | 2 / 279 (0.72%)<br>2   |  |  |
| Hyperkeratosis<br>subjects affected / exposed<br>occurrences (all)           | 1 / 279 (0.36%)<br>1   |  |  |
| Dry skin   |                        |  |  |

|                             |                  |  |  |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 6 / 279 (2.15%)  |  |  |
| occurrences (all)           | 7                |  |  |
| <b>Ecchymosis</b>           |                  |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)  |  |  |
| occurrences (all)           | 1                |  |  |
| <b>Eczema</b>               |                  |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)  |  |  |
| occurrences (all)           | 1                |  |  |
| <b>Erythema</b>             |                  |  |  |
| subjects affected / exposed | 4 / 279 (1.43%)  |  |  |
| occurrences (all)           | 4                |  |  |
| <b>Nail disorder</b>        |                  |  |  |
| subjects affected / exposed | 3 / 279 (1.08%)  |  |  |
| occurrences (all)           | 3                |  |  |
| <b>Lichen sclerosus</b>     |                  |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)  |  |  |
| occurrences (all)           | 1                |  |  |
| <b>Night sweats</b>         |                  |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)  |  |  |
| occurrences (all)           | 1                |  |  |
| <b>Onychoclasia</b>         |                  |  |  |
| subjects affected / exposed | 2 / 279 (0.72%)  |  |  |
| occurrences (all)           | 2                |  |  |
| <b>Pruritus</b>             |                  |  |  |
| subjects affected / exposed | 6 / 279 (2.15%)  |  |  |
| occurrences (all)           | 7                |  |  |
| <b>Rash erythematous</b>    |                  |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)  |  |  |
| occurrences (all)           | 1                |  |  |
| <b>Rash</b>                 |                  |  |  |
| subjects affected / exposed | 10 / 279 (3.58%) |  |  |
| occurrences (all)           | 13               |  |  |
| <b>Rash macular</b>         |                  |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)  |  |  |
| occurrences (all)           | 2                |  |  |
| <b>Rosacea</b>              |                  |  |  |

|  |                       |  |  |
|--|-----------------------|--|--|
| subjects affected / exposed<br>occurrences (all)                           | 2 / 279 (0.72%)<br>2  |  |  |
| Rash maculo-papular<br>subjects affected / exposed<br>occurrences (all)    | 4 / 279 (1.43%)<br>4  |  |  |
| Sensitive skin<br>subjects affected / exposed<br>occurrences (all)         | 1 / 279 (0.36%)<br>1  |  |  |
| Skin lesion<br>subjects affected / exposed<br>occurrences (all)            | 3 / 279 (1.08%)<br>4  |  |  |
| Urticaria<br>subjects affected / exposed<br>occurrences (all)              | 1 / 279 (0.36%)<br>1  |  |  |
| Hair texture abnormal<br>subjects affected / exposed<br>occurrences (all)  | 1 / 279 (0.36%)<br>1  |  |  |
| Nail ridging<br>subjects affected / exposed<br>occurrences (all)           | 1 / 279 (0.36%)<br>1  |  |  |
| Nail discolouration<br>subjects affected / exposed<br>occurrences (all)    | 1 / 279 (0.36%)<br>1  |  |  |
| Renal and urinary disorders  |                       |  |  |
| Acute kidney injury<br>subjects affected / exposed<br>occurrences (all)    | 1 / 279 (0.36%)<br>1  |  |  |
| Dysuria<br>subjects affected / exposed<br>occurrences (all)                | 9 / 279 (3.23%)<br>10 |  |  |
| Chronic kidney disease<br>subjects affected / exposed<br>occurrences (all) | 3 / 279 (1.08%)<br>3  |  |  |
| Haematuria<br>subjects affected / exposed<br>occurrences (all)             | 1 / 279 (0.36%)<br>1  |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| Hydronephrosis              |                 |  |  |
| subjects affected / exposed | 1 / 279 (0.36%) |  |  |
| occurrences (all)           | 1               |  |  |
| Nocturia                    |                 |  |  |
| subjects affected / exposed | 2 / 279 (0.72%) |  |  |
| occurrences (all)           | 2               |  |  |
| Micturition urgency         |                 |  |  |
| subjects affected / exposed | 2 / 279 (0.72%) |  |  |
| occurrences (all)           | 2               |  |  |
| Pollakiuria                 |                 |  |  |
| subjects affected / exposed | 3 / 279 (1.08%) |  |  |
| occurrences (all)           | 3               |  |  |
| Proteinuria                 |                 |  |  |
| subjects affected / exposed | 1 / 279 (0.36%) |  |  |
| occurrences (all)           | 1               |  |  |
| Polyuria                    |                 |  |  |
| subjects affected / exposed | 1 / 279 (0.36%) |  |  |
| occurrences (all)           | 1               |  |  |
| Renal disorder              |                 |  |  |
| subjects affected / exposed | 1 / 279 (0.36%) |  |  |
| occurrences (all)           | 1               |  |  |
| Renal failure               |                 |  |  |
| subjects affected / exposed | 1 / 279 (0.36%) |  |  |
| occurrences (all)           | 1               |  |  |
| Renal impairment            |                 |  |  |
| subjects affected / exposed | 3 / 279 (1.08%) |  |  |
| occurrences (all)           | 4               |  |  |
| Nephrolithiasis             |                 |  |  |
| subjects affected / exposed | 1 / 279 (0.36%) |  |  |
| occurrences (all)           | 1               |  |  |
| Urinary tract obstruction   |                 |  |  |
| subjects affected / exposed | 1 / 279 (0.36%) |  |  |
| occurrences (all)           | 1               |  |  |
| Urinary tract disorder      |                 |  |  |
| subjects affected / exposed | 1 / 279 (0.36%) |  |  |
| occurrences (all)           | 1               |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| Endocrine disorders                             |                  |  |  |
| Hypothyroidism                                  |                  |  |  |
| subjects affected / exposed                     | 2 / 279 (0.72%)  |  |  |
| occurrences (all)                               | 2                |  |  |
| Musculoskeletal and connective tissue disorders |                  |  |  |
| Arthralgia                                      |                  |  |  |
| subjects affected / exposed                     | 26 / 279 (9.32%) |  |  |
| occurrences (all)                               | 30               |  |  |
| Arthritis                                       |                  |  |  |
| subjects affected / exposed                     | 2 / 279 (0.72%)  |  |  |
| occurrences (all)                               | 2                |  |  |
| Back pain                                       |                  |  |  |
| subjects affected / exposed                     | 27 / 279 (9.68%) |  |  |
| occurrences (all)                               | 30               |  |  |
| Bone pain                                       |                  |  |  |
| subjects affected / exposed                     | 2 / 279 (0.72%)  |  |  |
| occurrences (all)                               | 8                |  |  |
| Coccydynia                                      |                  |  |  |
| subjects affected / exposed                     | 1 / 279 (0.36%)  |  |  |
| occurrences (all)                               | 1                |  |  |
| Flank pain                                      |                  |  |  |
| subjects affected / exposed                     | 1 / 279 (0.36%)  |  |  |
| occurrences (all)                               | 2                |  |  |
| Groin pain                                      |                  |  |  |
| subjects affected / exposed                     | 1 / 279 (0.36%)  |  |  |
| occurrences (all)                               | 1                |  |  |
| Muscle tightness                                |                  |  |  |
| subjects affected / exposed                     | 1 / 279 (0.36%)  |  |  |
| occurrences (all)                               | 1                |  |  |
| Joint effusion                                  |                  |  |  |
| subjects affected / exposed                     | 1 / 279 (0.36%)  |  |  |
| occurrences (all)                               | 1                |  |  |
| Joint swelling                                  |                  |  |  |
| subjects affected / exposed                     | 1 / 279 (0.36%)  |  |  |
| occurrences (all)                               | 1                |  |  |
| Muscle contracture                              |                  |  |  |

|                             |                  |  |  |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 1 / 279 (0.36%)  |  |  |
| occurrences (all)           | 1                |  |  |
| Muscle spasms               |                  |  |  |
| subjects affected / exposed | 16 / 279 (5.73%) |  |  |
| occurrences (all)           | 16               |  |  |
| Neck pain                   |                  |  |  |
| subjects affected / exposed | 3 / 279 (1.08%)  |  |  |
| occurrences (all)           | 3                |  |  |
| Myalgia                     |                  |  |  |
| subjects affected / exposed | 10 / 279 (3.58%) |  |  |
| occurrences (all)           | 11               |  |  |
| Musculoskeletal pain        |                  |  |  |
| subjects affected / exposed | 4 / 279 (1.43%)  |  |  |
| occurrences (all)           | 4                |  |  |
| Musculoskeletal chest pain  |                  |  |  |
| subjects affected / exposed | 3 / 279 (1.08%)  |  |  |
| occurrences (all)           | 3                |  |  |
| Osteoarthritis              |                  |  |  |
| subjects affected / exposed | 2 / 279 (0.72%)  |  |  |
| occurrences (all)           | 2                |  |  |
| Muscular weakness           |                  |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)  |  |  |
| occurrences (all)           | 1                |  |  |
| Osteopenia                  |                  |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)  |  |  |
| occurrences (all)           | 1                |  |  |
| Osteoporosis                |                  |  |  |
| subjects affected / exposed | 4 / 279 (1.43%)  |  |  |
| occurrences (all)           | 4                |  |  |
| Rheumatic disorder          |                  |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)  |  |  |
| occurrences (all)           | 1                |  |  |
| Pubic pain                  |                  |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)  |  |  |
| occurrences (all)           | 1                |  |  |
| Pain in extremity           |                  |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed                              | 7 / 279 (2.51%) |  |  |
| occurrences (all)  | 8               |  |  |
| Rotator cuff syndrome                                    |                 |  |  |
| subjects affected / exposed                              | 1 / 279 (0.36%) |  |  |
| occurrences (all)  | 1               |  |  |
| Spinal osteoarthritis                                    |                 |  |  |
| subjects affected / exposed                              | 1 / 279 (0.36%) |  |  |
| occurrences (all)  | 1               |  |  |
| Spinal pain  |                 |  |  |
| subjects affected / exposed                              | 1 / 279 (0.36%) |  |  |
| occurrences (all)  | 1               |  |  |
| Tendonitis   |                 |  |  |
| subjects affected / exposed                              | 1 / 279 (0.36%) |  |  |
| occurrences (all)  | 1               |  |  |
| Tenosynovitis stenosaurs                                 |                 |  |  |
| subjects affected / exposed                              | 1 / 279 (0.36%) |  |  |
| occurrences (all)  | 1               |  |  |
| Infections and infestations                              |                 |  |  |
| Abscess limb   |                 |  |  |
| subjects affected / exposed                              | 1 / 279 (0.36%) |  |  |
| occurrences (all)  | 1               |  |  |
| Atypical mycobacterial lower respiratory tract infection |                 |  |  |
| subjects affected / exposed                              | 1 / 279 (0.36%) |  |  |
| occurrences (all)  | 1               |  |  |
| Bacterial infection                                      |                 |  |  |
| subjects affected / exposed                              | 1 / 279 (0.36%) |  |  |
| occurrences (all)  | 1               |  |  |
| Bronchitis   |                 |  |  |
| subjects affected / exposed                              | 3 / 279 (1.08%) |  |  |
| occurrences (all)  | 4               |  |  |
| Candida infection  |                 |  |  |
| subjects affected / exposed                              | 2 / 279 (0.72%) |  |  |
| occurrences (all)  | 2               |  |  |
| Cellulitis   |                 |  |  |

|   |                        |  |  |
|---|------------------------|--|--|
| subjects affected / exposed<br>occurrences (all)  | 3 / 279 (1.08%)<br>3   |  |  |
| Diverticulitis<br>subjects affected / exposed<br>occurrences (all)                      | 2 / 279 (0.72%)<br>2   |  |  |
| Cystitis<br>subjects affected / exposed<br>occurrences (all)                            | 10 / 279 (3.58%)<br>15 |  |  |
| Conjunctivitis viral<br>subjects affected / exposed<br>occurrences (all)                | 1 / 279 (0.36%)<br>1   |  |  |
| Clostridium difficile infection<br>subjects affected / exposed<br>occurrences (all)     | 1 / 279 (0.36%)<br>1   |  |  |
| Ear infection<br>subjects affected / exposed<br>occurrences (all)                       | 2 / 279 (0.72%)<br>2   |  |  |
| Enteritis infectious<br>subjects affected / exposed<br>occurrences (all)                | 1 / 279 (0.36%)<br>1   |  |  |
| Erysipelas<br>subjects affected / exposed<br>occurrences (all)                          | 1 / 279 (0.36%)<br>1   |  |  |
| Escherichia urinary tract infection<br>subjects affected / exposed<br>occurrences (all) | 1 / 279 (0.36%)<br>1   |  |  |
| Eye infection<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 279 (0.36%)<br>1   |  |  |
| Fungal infection<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 279 (0.36%)<br>1   |  |  |
| Gastroenteritis norovirus<br>subjects affected / exposed<br>occurrences (all)           | 1 / 279 (0.36%)<br>1   |  |  |
| Gingivitis  |                        |  |  |

|                                   |                  |  |  |
|-----------------------------------|------------------|--|--|
| subjects affected / exposed       | 1 / 279 (0.36%)  |  |  |
| occurrences (all)                 | 1                |  |  |
| Herpes simplex                    |                  |  |  |
| subjects affected / exposed       | 1 / 279 (0.36%)  |  |  |
| occurrences (all)                 | 1                |  |  |
| Influenza                         |                  |  |  |
| subjects affected / exposed       | 6 / 279 (2.15%)  |  |  |
| occurrences (all)                 | 7                |  |  |
| Infection                         |                  |  |  |
| subjects affected / exposed       | 1 / 279 (0.36%)  |  |  |
| occurrences (all)                 | 1                |  |  |
| Laryngitis                        |                  |  |  |
| subjects affected / exposed       | 1 / 279 (0.36%)  |  |  |
| occurrences (all)                 | 1                |  |  |
| Lower respiratory tract infection |                  |  |  |
| subjects affected / exposed       | 3 / 279 (1.08%)  |  |  |
| occurrences (all)                 | 3                |  |  |
| Nasopharyngitis                   |                  |  |  |
| subjects affected / exposed       | 15 / 279 (5.38%) |  |  |
| occurrences (all)                 | 17               |  |  |
| Nail infection                    |                  |  |  |
| subjects affected / exposed       | 1 / 279 (0.36%)  |  |  |
| occurrences (all)                 | 1                |  |  |
| Oral candidiasis                  |                  |  |  |
| subjects affected / exposed       | 3 / 279 (1.08%)  |  |  |
| occurrences (all)                 | 3                |  |  |
| Pharyngitis                       |                  |  |  |
| subjects affected / exposed       | 1 / 279 (0.36%)  |  |  |
| occurrences (all)                 | 1                |  |  |
| Pharyngitis streptococcal         |                  |  |  |
| subjects affected / exposed       | 1 / 279 (0.36%)  |  |  |
| occurrences (all)                 | 1                |  |  |
| Oral herpes                       |                  |  |  |
| subjects affected / exposed       | 1 / 279 (0.36%)  |  |  |
| occurrences (all)                 | 3                |  |  |
| Otitis media                      |                  |  |  |

|   |                      |  |  |
|---|----------------------|--|--|
| subjects affected / exposed<br>occurrences (all)                                      | 1 / 279 (0.36%)<br>1 |  |  |
| Paronychia<br>subjects affected / exposed<br>occurrences (all)                        | 1 / 279 (0.36%)<br>1 |  |  |
| Pneumonia viral<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 279 (0.36%)<br>1 |  |  |
| Pneumonia<br>subjects affected / exposed<br>occurrences (all)                         | 6 / 279 (2.15%)<br>6 |  |  |
| Respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)       | 2 / 279 (0.72%)<br>2 |  |  |
| Rhinitis<br>subjects affected / exposed<br>occurrences (all)                          | 2 / 279 (0.72%)<br>2 |  |  |
| Respiratory tract infection viral<br>subjects affected / exposed<br>occurrences (all) | 1 / 279 (0.36%)<br>1 |  |  |
| Sinusitis<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 279 (0.36%)<br>1 |  |  |
| Tooth abscess<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 279 (0.36%)<br>1 |  |  |
| Skin infection<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 279 (0.36%)<br>1 |  |  |
| Tooth infection<br>subjects affected / exposed<br>occurrences (all)                   | 2 / 279 (0.72%)<br>2 |  |  |
| Urethritis<br>subjects affected / exposed<br>occurrences (all)                        | 1 / 279 (0.36%)<br>1 |  |  |
| Upper respiratory tract infection   |                      |  |  |

|                                    |                   |  |  |
|------------------------------------|-------------------|--|--|
| subjects affected / exposed        | 12 / 279 (4.30%)  |  |  |
| occurrences (all)                  | 12                |  |  |
| Urinary tract infection            |                   |  |  |
| subjects affected / exposed        | 27 / 279 (9.68%)  |  |  |
| occurrences (all)                  | 36                |  |  |
| Wound infection                    |                   |  |  |
| subjects affected / exposed        | 1 / 279 (0.36%)   |  |  |
| occurrences (all)                  | 1                 |  |  |
| Viral infection                    |                   |  |  |
| subjects affected / exposed        | 1 / 279 (0.36%)   |  |  |
| occurrences (all)                  | 1                 |  |  |
| COVID-19                           |                   |  |  |
| subjects affected / exposed        | 2 / 279 (0.72%)   |  |  |
| occurrences (all)                  | 2                 |  |  |
| Device related infection           |                   |  |  |
| subjects affected / exposed        | 1 / 279 (0.36%)   |  |  |
| occurrences (all)                  | 1                 |  |  |
| Gastrointestinal infection         |                   |  |  |
| subjects affected / exposed        | 1 / 279 (0.36%)   |  |  |
| occurrences (all)                  | 1                 |  |  |
| Pulpitis dental                    |                   |  |  |
| subjects affected / exposed        | 1 / 279 (0.36%)   |  |  |
| occurrences (all)                  | 1                 |  |  |
| Salmonellosis                      |                   |  |  |
| subjects affected / exposed        | 1 / 279 (0.36%)   |  |  |
| occurrences (all)                  | 1                 |  |  |
| Metabolism and nutrition disorders |                   |  |  |
| Hypercalcaemia                     |                   |  |  |
| subjects affected / exposed        | 2 / 279 (0.72%)   |  |  |
| occurrences (all)                  | 2                 |  |  |
| Dehydration                        |                   |  |  |
| subjects affected / exposed        | 1 / 279 (0.36%)   |  |  |
| occurrences (all)                  | 1                 |  |  |
| Decreased appetite                 |                   |  |  |
| subjects affected / exposed        | 32 / 279 (11.47%) |  |  |
| occurrences (all)                  | 34                |  |  |

|                             |                  |  |  |
|-----------------------------|------------------|--|--|
| Hypercholesterolaemia       |                  |  |  |
| subjects affected / exposed | 2 / 279 (0.72%)  |  |  |
| occurrences (all)           | 2                |  |  |
| Hypocalcaemia               |                  |  |  |
| subjects affected / exposed | 2 / 279 (0.72%)  |  |  |
| occurrences (all)           | 2                |  |  |
| Hypertriglyceridaemia       |                  |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)  |  |  |
| occurrences (all)           | 1                |  |  |
| Hyperkalaemia               |                  |  |  |
| subjects affected / exposed | 3 / 279 (1.08%)  |  |  |
| occurrences (all)           | 4                |  |  |
| Hyperglycaemia              |                  |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)  |  |  |
| occurrences (all)           | 1                |  |  |
| Hypochloraemia              |                  |  |  |
| subjects affected / exposed | 1 / 279 (0.36%)  |  |  |
| occurrences (all)           | 1                |  |  |
| Vitamin D deficiency        |                  |  |  |
| subjects affected / exposed | 2 / 279 (0.72%)  |  |  |
| occurrences (all)           | 2                |  |  |
| Hyponatraemia               |                  |  |  |
| subjects affected / exposed | 4 / 279 (1.43%)  |  |  |
| occurrences (all)           | 6                |  |  |
| Hypomagnesaemia             |                  |  |  |
| subjects affected / exposed | 6 / 279 (2.15%)  |  |  |
| occurrences (all)           | 8                |  |  |
| Hypokalaemia                |                  |  |  |
| subjects affected / exposed | 13 / 279 (4.66%) |  |  |
| occurrences (all)           | 20               |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment  |
|-----------------|--|
| 30 August 2017  | To improve clarity on study conduct, maintain consistency of information across protocol sections in line with revised AstraZeneca standard guidance. Details of retrospective Germline breast cancer susceptibility gene (gBRCA) testing added for sample collection. Details updated for biomarker analysis.   |
| 26 October 2018 | To improve clarity on study conduct, maintain consistency of information across protocol sections in line with revised AstraZeneca standard guidance. New study countries added (Norway and Finland), Japan deleted, number of planned patients updated. Modification of objectives. Addition of an acceptable chemotherapeutic. Summaries of previous studies updated. Addition of alternative creatinine clearance measure. Addition of excluded therapy. Updated to specify events and time required before final analysis. Definition of "lost to follow-up" revised. Updated details for biomarker testing. Revised management of anaemia section. Potential drug-drug interactions updated. Definition of "Time to treatment discontinuation (TDT)" revised. Updated information on primary analysis/study end date. Appendices updated. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported