



Clinical trial results:

A Cancer Research UK Phase II Proof of Principle Trial of the activity of the PARP-1 inhibitor, AG-014699, in known carriers of a BRCA 1 or BRCA 2 mutation with locally advanced or metastatic breast or advanced ovarian cancer

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2006-002348-27 |
| Trial protocol | GB |
| Global end of trial date | 22 January 2015 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 06 May 2016 |
| First version publication date | 06 May 2016 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | PH2/052 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00664781 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Cancer Research UK |
| Sponsor organisation address | 407 St John Street, London, United Kingdom, EC1V 4AD |
| Public contact | Centre for Drug Development, Cancer Research UK, +44 02072420200, regquery@cancer.org.uk |
| Scientific contact | Centre for Drug Development, Cancer Research UK, +44 02072420200, regquery@cancer.org.uk |

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 | 26 June 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 22 January 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 22 January 2015 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

1) To determine whether AG-014699 has antitumour activity in locally advanced or metastatic breast and advanced ovarian cancer shown to express the BRCA 1 or 2 mutations.

2) To evaluate the toxicity of treatment with AG-014699 in these populations.

Protection of trial subjects:

None

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 14 January 2008 |
| 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 | United Kingdom: 78 |
| Worldwide total number of subjects | 78 |
| EEA total number of subjects | 78 |

Notes:

Subjects enrolled per age group

| | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 69 |
| From 65 to 84 years | 9 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Study participants were enrolled from 08 January 2008 to 22 January 2015 in 8 clinical study centres in the UK.

Pre-assignment

Screening details:

Patients aged 18 years or over, proven or considered highly likely to be carriers of a mutation of BRAC1 or BRAC2 with histologically confirmed locally advanced or metastatic breast cancer or advanced ovarian cancer. Life expectancy of at least 12 weeks, WHO status of 0 or 1 and no more than five prior chemotherapy regimens in the last 5 years.

Period 1

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

Arms

| | |
|------------------------------|-----------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | AG-014699 Intravenous |

Arm description:

AG-014699 intravenous administration

| | |
|--|----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | AG-014699 |
| Investigational medicinal product code | AG-014699 |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Administered as a 30 minute intravenous (IV) infusion daily for the first 5 days of each treatment cycle (cycle length of 21 days). Intravenous doses of AG-014699 administered were 4, 12 and 18 mg/m².

| | |
|------------------|----------------|
| Arm title | AG-014699 Oral |
|------------------|----------------|

Arm description:

AG-014699 oral administration

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | AG-014699 |
| Investigational medicinal product code | AG-014699 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Administered in tablet form for daily dosing within each treatment cycle (cycle length of 21 days). Oral doses of AG-014699 were administered with escalating doses and duration of dosing as follows: 92 mg/day (Days 1-7); 92 mg/day (Days 1-14); 92 mg/day (Days 1-21); 120 mg/day (Days 1-21); 240 mg/day (Days 1-21); 240 mg/day (Days 1-21); 480 mg/day (Days 1-21); 240 mg twice daily (BID) (Days 1-21); 480 mg BID (Days 1-21) and 600 mg BID (Days 1-21).

| Number of subjects in period 1 | AG-014699 Intravenous | AG-014699 Oral |
|---------------------------------------|--------------------------|----------------|
| Started | 47 | 31 |
| Completed | 47 | 31 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------------------|
| Reporting group title | AG-014699 Intravenous |
|-----------------------|-----------------------|

Reporting group description:

AG-014699 intravenous administration

| | |
|-----------------------|----------------|
| Reporting group title | AG-014699 Oral |
|-----------------------|----------------|

Reporting group description:

AG-014699 oral administration

| Reporting group values | AG-014699 Intravenous | AG-014699 Oral | Total |
|---------------------------------------|--------------------------|----------------|-------|
| Number of subjects | 47 | 31 | 78 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 41 | 28 | 69 |
| From 65-84 years | 6 | 3 | 9 |
| Gender categorical Units: Subjects | | | |
| Female | 47 | 31 | 78 |
| Male | 0 | 0 | 0 |

End points

End points reporting groups

| | |
|--|-----------------------|
| Reporting group title | AG-014699 Intravenous |
| Reporting group description: AG-014699 intravenous administration | |
| Reporting group title | AG-014699 Oral |
| Reporting group description: AG-014699 oral administration | |
| Subject analysis set title | All Treated Patients |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: All enrolled and eligible patients who received at least one dose of AG-014699. | |

Primary: Safety

| | |
|--|-----------------------|
| End point title | Safety ^[1] |
| End point description: The causality and severity grading of each adverse event (AE), according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0. AEs with a causality of possibly, probably or almost certainly related to AG-014699 were considered to indicate relatedness. A dose limiting toxicity (DLT) was defined as occurring within the first cycle for patients on the oral administration or the first and second cycle for IV patients, and were almost certainly or probably related to AG-014699: a) Neutropenia Grade 4 for ≥ 5 days. b) Febrile neutropenia (fever of unknown origin without documented infection) with Grade 3 or 4 neutropenia. c) Infection with Grade 3 or 4 neutropenia. d) Thrombocytopenia Grade 4 for ≥ 5 days or associated with active bleeding or requiring platelet transfusion. e) Grade 3 or 4 toxicity to organs other than the bone marrow (including Grade 3 or 4 biochemical AEs) excluding nausea, vomiting and diarrhoea. f) death. | |
| End point type | Primary |
| End point timeframe: From patient consent to 28 days post last dose of AG-014699. | |
| 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: All safety data were presented in a descriptive fashion, with adverse events presented by CTCAE adverse event term by worst grade observed. | |

| End point values | AG-014699 Intravenous | AG-014699 Oral | All Treated Patients | |
|-----------------------------|-----------------------|-----------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 47 | 31 | 78 | |
| Units: Number of AEs | | | | |
| All AEs | 621 | 493 | 1114 | |
| Related AEs | 198 | 190 | 388 | |
| DLTs | 0 | 2 | 2 | |

Statistical analyses

No statistical analyses for this end point

Primary: Anti-Tumour Activity

| | |
|-----------------|-------------------------------------|
| End point title | Anti-Tumour Activity ^[2] |
|-----------------|-------------------------------------|

End point description:

Assessment of antitumour activity according to Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.0. Assessment of objective response was made by measuring tumour size clinically or radiologically with computerised tomography, magnetic resonance imaging, plain X-ray, or other imaging techniques.

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

End point timeframe:

From baseline until after at least 2 cycles.

Notes:

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

Justification: All response data were presented in a descriptive fashion with a best overall response assigned for each patient.

| End point values | AG-014699 Intravenous | AG-014699 Oral | All Treated Patients | |
|---|--------------------------|-------------------|-------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 47 | 31 | 78 | |
| Units: Number of subjects with a response | | | | |
| Complete response | 0 | 1 | 1 | |
| Partial response | 1 | 3 | 4 | |
| Stable disease | 21 | 17 | 38 | |
| Progressive disease | 22 | 6 | 28 | |
| Early progression | 0 | 1 | 1 | |
| Not evaluable | 3 | 3 | 6 | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From patient consent to 28 days post last dose of AG-014699

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

Dictionary used

| | |
|-----------------|-----------|
| Dictionary name | NCI-CTCAE |
|-----------------|-----------|

| | |
|--------------------|-----|
| Dictionary version | 3.0 |
|--------------------|-----|

Reporting groups

| | |
|-----------------------|-----------------------|
| Reporting group title | AG-014699 Intravenous |
|-----------------------|-----------------------|

Reporting group description: -

| | |
|-----------------------|----------------|
| Reporting group title | AG-014699 Oral |
|-----------------------|----------------|

Reporting group description: -

| | |
|-----------------------|----------------------|
| Reporting group title | All Treated Patients |
|-----------------------|----------------------|

Reporting group description:

All patients administered IV or oral AG-014699

| Serious adverse events | AG-014699 Intravenous | AG-014699 Oral | All Treated Patients |
|---|-----------------------|------------------|----------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 17 / 47 (36.17%) | 15 / 31 (48.39%) | 32 / 78 (41.03%) |
| number of deaths (all causes) | 3 | 2 | 5 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Vascular disorders | | | |
| Thrombosis/embolism (vascular access) | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 31 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombosis/thrombus/embolism | | | |
| subjects affected / exposed | 2 / 47 (4.26%) | 0 / 31 (0.00%) | 2 / 78 (2.56%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Intraoperative injury - other (specify) | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 31 (3.23%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration | | | |

| | | | |
|---|----------------|----------------|----------------|
| site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 2 / 31 (6.45%) | 2 / 78 (2.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fever | | | |
| subjects affected / exposed | 2 / 47 (4.26%) | 0 / 31 (0.00%) | 2 / 78 (2.56%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constitutional symptoms - other (specify) | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 31 (3.23%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Death - disease progression not otherwise specified | | | |
| subjects affected / exposed | 2 / 47 (4.26%) | 2 / 31 (6.45%) | 4 / 78 (5.13%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 4 |
| Pain - other (specify) | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 1 / 31 (3.23%) | 2 / 78 (2.56%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Haemorrhage genitourinary - vagina | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 31 (3.23%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain - breast | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 31 (3.23%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fistula genitourinary - vagina | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 31 (3.23%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 47 (4.26%) | 2 / 31 (6.45%) | 4 / 78 (5.13%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Cardiac ischaemia/infarction | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 31 (3.23%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Pain- headache | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 1 / 31 (3.23%) | 2 / 78 (2.56%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Haemoglobin | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 31 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Ascites | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 31 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 31 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 31 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Distension | | | |
| subjects affected / exposed | 2 / 47 (4.26%) | 0 / 31 (0.00%) | 2 / 78 (2.56%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal - other (specify) | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 31 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 3 / 47 (6.38%) | 0 / 31 (0.00%) | 3 / 78 (3.85%) |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 0 | 1 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Obstruction gastrointestinal - colon | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 31 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Obstruction gastrointestinal - small bowel not otherwise specified | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 31 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 4 / 47 (8.51%) | 2 / 31 (6.45%) | 6 / 78 (7.69%) |
| occurrences causally related to treatment / all | 1 / 6 | 0 / 2 | 1 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage gastrointestinal - rectum | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 31 (3.23%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain - abdomen not otherwise specified | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 4 / 47 (8.51%) | 2 / 31 (6.45%) | 6 / 78 (7.69%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 2 | 0 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hepatic - other (specify) | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 31 (3.23%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Liver dysfunction | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 31 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Obstruction genitourinary - ureter | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 4 / 31 (12.90%) | 5 / 78 (6.41%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 5 | 0 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal extremity - lower | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 31 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain - back | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 31 (3.23%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain - extremity limb | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 2 / 31 (6.45%) | 2 / 78 (2.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Infection documented clinically - urinary tract not otherwise specified | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 31 (3.23%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection with unknown ANC - catheter related | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 31 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection - other (specify) | | | |
| subjects affected / exposed | 2 / 47 (4.26%) | 1 / 31 (3.23%) | 3 / 78 (3.85%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 31 (3.23%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | AG-014699 Intravenous | AG-014699 Oral | All Treated Patients |
|---|--------------------------|-------------------|----------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 47 / 47 (100.00%) | 31 / 31 (100.00%) | 78 / 78 (100.00%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 31 (0.00%) | 1 / 78 (1.28%) |
| occurrences (all) | 2 | 0 | 2 |
| Flushing | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 31 (3.23%) | 1 / 78 (1.28%) |
| occurrences (all) | 0 | 1 | 1 |
| Hot flashes | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 3 / 31 (9.68%) | 4 / 78 (5.13%) |
| occurrences (all) | 1 | 3 | 4 |
| Thrombosis/thrombus/embolism | | | |

| | | | |
|--|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 47 (0.00%) | 2 / 31 (6.45%) | 2 / 78 (2.56%) |
| occurrences (all) | 0 | 3 | 3 |
| Vascular - other (specify) | | | |
| subjects affected / exposed | 3 / 47 (6.38%) | 0 / 31 (0.00%) | 3 / 78 (3.85%) |
| occurrences (all) | 3 | 0 | 3 |
| General disorders and administration site conditions | | | |
| Constitutional symptoms - other (specify) | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 31 (0.00%) | 1 / 78 (1.28%) |
| occurrences (all) | 1 | 0 | 1 |
| Fatigue | | | |
| subjects affected / exposed | 26 / 47 (55.32%) | 17 / 31 (54.84%) | 43 / 78 (55.13%) |
| occurrences (all) | 43 | 30 | 73 |
| Fever | | | |
| subjects affected / exposed | 5 / 47 (10.64%) | 4 / 31 (12.90%) | 9 / 78 (11.54%) |
| occurrences (all) | 5 | 4 | 9 |
| Rigors/chills | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 1 / 31 (3.23%) | 2 / 78 (2.56%) |
| occurrences (all) | 1 | 1 | 2 |
| Sweating | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 2 / 31 (6.45%) | 3 / 78 (3.85%) |
| occurrences (all) | 1 | 2 | 3 |
| Injection site reaction | | | |
| subjects affected / exposed | 9 / 47 (19.15%) | 0 / 31 (0.00%) | 9 / 78 (11.54%) |
| occurrences (all) | 16 | 0 | 16 |
| Lymphatics - other (specify) | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 31 (0.00%) | 1 / 78 (1.28%) |
| occurrences (all) | 1 | 0 | 1 |
| Oedema - head and neck | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 31 (3.23%) | 1 / 78 (1.28%) |
| occurrences (all) | 0 | 1 | 1 |
| Oedema - limb | | | |
| subjects affected / exposed | 10 / 47 (21.28%) | 4 / 31 (12.90%) | 14 / 78 (17.95%) |
| occurrences (all) | 11 | 5 | 16 |
| Pain - face | | | |

| | | | |
|--|------------------------|----------------------|------------------------|
| subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | 0 / 31 (0.00%) 0 | 1 / 78 (1.28%) 1 |
| Pain - other (specify) subjects affected / exposed occurrences (all) | 15 / 47 (31.91%) 20 | 4 / 31 (12.90%) 5 | 19 / 78 (24.36%) 25 |
| Flu-like syndrome subjects affected / exposed occurrences (all) | 5 / 47 (10.64%) 6 | 5 / 31 (16.13%) 5 | 10 / 78 (12.82%) 11 |
| Immune system disorders Allergy - other (specify) subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | 0 / 31 (0.00%) 0 | 1 / 78 (1.28%) 1 |
| Reproductive system and breast disorders Haemorrhage genitourinary - vagina subjects affected / exposed occurrences (all) | 3 / 47 (6.38%) 8 | 1 / 31 (3.23%) 1 | 4 / 78 (5.13%) 9 |
| Pain - breast subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | 1 / 31 (3.23%) 1 | 2 / 78 (2.56%) 2 |
| Pain - pelvis subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | 0 / 31 (0.00%) 0 | 1 / 78 (1.28%) 1 |
| Pain - vagina subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 1 / 31 (3.23%) 1 | 1 / 78 (1.28%) 1 |
| Vaginal discharge subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | 0 / 31 (0.00%) 0 | 1 / 78 (1.28%) 1 |
| Respiratory, thoracic and mediastinal disorders Pain - chest/thorax not otherwise specified subjects affected / exposed occurrences (all) | 7 / 47 (14.89%) 9 | 3 / 31 (9.68%) 3 | 10 / 78 (12.82%) 12 |
| Pain - throat/pharynx/larynx subjects affected / exposed occurrences (all) | 4 / 47 (8.51%) 4 | 6 / 31 (19.35%) 7 | 10 / 78 (12.82%) 11 |

| | | | |
|---|----------------------|-----------------------|------------------------|
| Bronchospasm subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 1 / 31 (3.23%) 1 | 1 / 78 (1.28%) 1 |
| Cough subjects affected / exposed occurrences (all) | 8 / 47 (17.02%) 9 | 6 / 31 (19.35%) 10 | 14 / 78 (17.95%) 19 |
| Dyspnoea subjects affected / exposed occurrences (all) | 5 / 47 (10.64%) 9 | 6 / 31 (19.35%) 8 | 11 / 78 (14.10%) 17 |
| Pleural effusion subjects affected / exposed occurrences (all) | 2 / 47 (4.26%) 2 | 0 / 31 (0.00%) 0 | 2 / 78 (2.56%) 2 |
| Pulmonary - other (specify) subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 2 / 31 (6.45%) 4 | 2 / 78 (2.56%) 4 |
| Psychiatric disorders | | | |
| Insomnia subjects affected / exposed occurrences (all) | 4 / 47 (8.51%) 4 | 5 / 31 (16.13%) 5 | 9 / 78 (11.54%) 9 |
| Confusion subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 1 / 31 (3.23%) 1 | 1 / 78 (1.28%) 1 |
| Mood - anxiety subjects affected / exposed occurrences (all) | 4 / 47 (8.51%) 4 | 3 / 31 (9.68%) 3 | 7 / 78 (8.97%) 7 |
| Mood - depression subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | 3 / 31 (9.68%) 5 | 4 / 78 (5.13%) 6 |
| Investigations | | | |
| INR subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | 0 / 31 (0.00%) 0 | 1 / 78 (1.28%) 1 |
| Weight gain subjects affected / exposed occurrences (all) | 2 / 47 (4.26%) 2 | 0 / 31 (0.00%) 0 | 2 / 78 (2.56%) 2 |
| Weight loss | | | |

| | | | |
|--|----------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 5 / 47 (10.64%) 5 | 2 / 31 (6.45%) 2 | 7 / 78 (8.97%) 7 |
| ALT | | | |
| subjects affected / exposed occurrences (all) | 4 / 47 (8.51%) 4 | 2 / 31 (6.45%) 2 | 6 / 78 (7.69%) 6 |
| AST | | | |
| subjects affected / exposed occurrences (all) | 3 / 47 (6.38%) 4 | 3 / 31 (9.68%) 4 | 6 / 78 (7.69%) 8 |
| Alkaline phosphatase | | | |
| subjects affected / exposed occurrences (all) | 3 / 47 (6.38%) 4 | 3 / 31 (9.68%) 4 | 6 / 78 (7.69%) 8 |
| Bilirubin | | | |
| subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 1 / 31 (3.23%) 1 | 1 / 78 (1.28%) 1 |
| Creatinine | | | |
| subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | 2 / 31 (6.45%) 2 | 3 / 78 (3.85%) 3 |
| GGT | | | |
| subjects affected / exposed occurrences (all) | 2 / 47 (4.26%) 2 | 2 / 31 (6.45%) 2 | 4 / 78 (5.13%) 4 |
| Injury, poisoning and procedural complications | | | |
| Bruising | | | |
| subjects affected / exposed occurrences (all) | 3 / 47 (6.38%) 3 | 2 / 31 (6.45%) 2 | 5 / 78 (6.41%) 5 |
| Fracture | | | |
| subjects affected / exposed occurrences (all) | 2 / 47 (4.26%) 3 | 0 / 31 (0.00%) 0 | 2 / 78 (2.56%) 3 |
| Intraoperative injury - other (specify) | | | |
| subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 1 / 31 (3.23%) 1 | 1 / 78 (1.28%) 1 |
| Cardiac disorders | | | |
| Palpitations | | | |
| subjects affected / exposed occurrences (all) | 2 / 47 (4.26%) 2 | 0 / 31 (0.00%) 0 | 2 / 78 (2.56%) 2 |
| Supraventricular sinus bradycardia | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 47 (2.13%) | 2 / 31 (6.45%) | 3 / 78 (3.85%) |
| occurrences (all) | 1 | 5 | 6 |
| Supraventricular sinus tachycardia | | | |
| subjects affected / exposed | 2 / 47 (4.26%) | 1 / 31 (3.23%) | 3 / 78 (3.85%) |
| occurrences (all) | 2 | 1 | 3 |
| vasovagal episode | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 31 (0.00%) | 1 / 78 (1.28%) |
| occurrences (all) | 1 | 0 | 1 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 10 / 47 (21.28%) | 6 / 31 (19.35%) | 16 / 78 (20.51%) |
| occurrences (all) | 16 | 10 | 26 |
| Neurology - CN III pupil upper eyelid extra ocular movements | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 31 (0.00%) | 1 / 78 (1.28%) |
| occurrences (all) | 1 | 0 | 1 |
| Neurology - CN IV downward inward movement of eye | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 31 (0.00%) | 1 / 78 (1.28%) |
| occurrences (all) | 1 | 0 | 1 |
| Neuropathy - sensory | | | |
| subjects affected / exposed | 7 / 47 (14.89%) | 0 / 31 (0.00%) | 7 / 78 (8.97%) |
| occurrences (all) | 10 | 0 | 10 |
| Somnolence | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 31 (3.23%) | 1 / 78 (1.28%) |
| occurrences (all) | 0 | 1 | 1 |
| Syncope | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 31 (3.23%) | 1 / 78 (1.28%) |
| occurrences (all) | 0 | 1 | 1 |
| Tremor | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 31 (3.23%) | 1 / 78 (1.28%) |
| occurrences (all) | 0 | 1 | 1 |
| Pain - headache | | | |
| subjects affected / exposed | 10 / 47 (21.28%) | 14 / 31 (45.16%) | 24 / 78 (30.77%) |
| occurrences (all) | 15 | 36 | 51 |
| Pain - sinus | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 1 / 31 (3.23%) 1 | 1 / 78 (1.28%) 1 |
| Blood and lymphatic system disorders | | | |
| Haemoglobin | | | |
| subjects affected / exposed | 5 / 47 (10.64%) | 6 / 31 (19.35%) | 11 / 78 (14.10%) |
| occurrences (all) | 5 | 11 | 16 |
| Leucocytes | | | |
| subjects affected / exposed | 3 / 47 (6.38%) | 0 / 31 (0.00%) | 3 / 78 (3.85%) |
| occurrences (all) | 3 | 0 | 3 |
| Lymphopenia | | | |
| subjects affected / exposed | 2 / 47 (4.26%) | 2 / 31 (6.45%) | 4 / 78 (5.13%) |
| occurrences (all) | 2 | 4 | 6 |
| Neutrophils | | | |
| subjects affected / exposed | 3 / 47 (6.38%) | 2 / 31 (6.45%) | 5 / 78 (6.41%) |
| occurrences (all) | 3 | 4 | 7 |
| Platelets | | | |
| subjects affected / exposed | 3 / 47 (6.38%) | 0 / 31 (0.00%) | 3 / 78 (3.85%) |
| occurrences (all) | 3 | 0 | 3 |
| Haemorrhage - other (specify) | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 31 (0.00%) | 1 / 78 (1.28%) |
| occurrences (all) | 1 | 0 | 1 |
| Ear and labyrinth disorders | | | |
| Auditory/ear - other (specify) | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 31 (0.00%) | 1 / 78 (1.28%) |
| occurrences (all) | 1 | 0 | 1 |
| Hearing (without monitoring program) | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 31 (0.00%) | 1 / 78 (1.28%) |
| occurrences (all) | 1 | 0 | 1 |
| Tinnitus | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 31 (0.00%) | 1 / 78 (1.28%) |
| occurrences (all) | 1 | 0 | 1 |
| Eye disorders | | | |
| Dry eye | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 1 / 31 (3.23%) | 2 / 78 (2.56%) |
| occurrences (all) | 1 | 1 | 2 |
| Flashing lights | | | |

| | | | |
|------------------------------------|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 31 (3.23%) | 1 / 78 (1.28%) |
| occurrences (all) | 0 | 1 | 1 |
| Ocular - other (specify) | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 2 / 31 (6.45%) | 2 / 78 (2.56%) |
| occurrences (all) | 0 | 2 | 2 |
| Vitreous haemorrhage | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 31 (0.00%) | 1 / 78 (1.28%) |
| occurrences (all) | 1 | 0 | 1 |
| Watery eye | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 31 (3.23%) | 1 / 78 (1.28%) |
| occurrences (all) | 0 | 1 | 1 |
| Gastrointestinal disorders | | | |
| Ascites | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 31 (0.00%) | 1 / 78 (1.28%) |
| occurrences (all) | 1 | 0 | 1 |
| Constipation | | | |
| subjects affected / exposed | 13 / 47 (27.66%) | 12 / 31 (38.71%) | 25 / 78 (32.05%) |
| occurrences (all) | 18 | 14 | 32 |
| Diarrhoea | | | |
| subjects affected / exposed | 17 / 47 (36.17%) | 5 / 31 (16.13%) | 22 / 78 (28.21%) |
| occurrences (all) | 28 | 6 | 34 |
| Distension | | | |
| subjects affected / exposed | 10 / 47 (21.28%) | 8 / 31 (25.81%) | 18 / 78 (23.08%) |
| occurrences (all) | 12 | 9 | 21 |
| Dry mouth | | | |
| subjects affected / exposed | 4 / 47 (8.51%) | 2 / 31 (6.45%) | 6 / 78 (7.69%) |
| occurrences (all) | 4 | 2 | 6 |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 1 / 31 (3.23%) | 2 / 78 (2.56%) |
| occurrences (all) | 1 | 1 | 2 |
| Flatulence | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 31 (0.00%) | 1 / 78 (1.28%) |
| occurrences (all) | 1 | 0 | 1 |
| Gastrointestinal - other (specify) | | | |
| subjects affected / exposed | 2 / 47 (4.26%) | 2 / 31 (6.45%) | 4 / 78 (5.13%) |
| occurrences (all) | 3 | 2 | 5 |

| | | | |
|---|------------------|------------------|------------------|
| Heartburn | | | |
| subjects affected / exposed | 7 / 47 (14.89%) | 6 / 31 (19.35%) | 13 / 78 (16.67%) |
| occurrences (all) | 7 | 15 | 22 |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 31 (3.23%) | 1 / 78 (1.28%) |
| occurrences (all) | 0 | 1 | 1 |
| Mucositis oral cavity (clinical exam) | | | |
| subjects affected / exposed | 2 / 47 (4.26%) | 5 / 31 (16.13%) | 7 / 78 (8.97%) |
| occurrences (all) | 3 | 9 | 12 |
| Mucositis oral cavity (functional/symptomatic) | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 31 (3.23%) | 1 / 78 (1.28%) |
| occurrences (all) | 0 | 1 | 1 |
| Nausea | | | |
| subjects affected / exposed | 25 / 47 (53.19%) | 18 / 31 (58.06%) | 43 / 78 (55.13%) |
| occurrences (all) | 37 | 41 | 78 |
| Obstruction gastrointestinal - colon | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 31 (0.00%) | 1 / 78 (1.28%) |
| occurrences (all) | 1 | 0 | 1 |
| Peridontal | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 31 (3.23%) | 1 / 78 (1.28%) |
| occurrences (all) | 0 | 1 | 1 |
| Taste alteration | | | |
| subjects affected / exposed | 2 / 47 (4.26%) | 6 / 31 (19.35%) | 8 / 78 (10.26%) |
| occurrences (all) | 2 | 9 | 11 |
| Teeth | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 1 / 31 (3.23%) | 2 / 78 (2.56%) |
| occurrences (all) | 1 | 2 | 3 |
| Vomiting | | | |
| subjects affected / exposed | 17 / 47 (36.17%) | 7 / 31 (22.58%) | 24 / 78 (30.77%) |
| occurrences (all) | 33 | 14 | 47 |
| Pain - abdomen not otherwise specified | | | |
| subjects affected / exposed | 16 / 47 (34.04%) | 16 / 31 (51.61%) | 32 / 78 (41.03%) |
| occurrences (all) | 23 | 23 | 46 |
| Pain - anus | | | |

| | | | |
|---|----------------------|----------------------|-----------------------|
| subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 1 / 31 (3.23%) 1 | 1 / 78 (1.28%) 1 |
| Pain - dental/teeth/periodontal subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 2 | 0 / 31 (0.00%) 0 | 1 / 78 (1.28%) 2 |
| Pain - stomach subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 1 / 31 (3.23%) 2 | 1 / 78 (1.28%) 2 |
| Hepatobiliary disorders Haemorrhage gastrointestinal - rectum subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 1 / 31 (3.23%) 1 | 1 / 78 (1.28%) 1 |
| Liver dysfunction subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 1 / 31 (3.23%) 1 | 1 / 78 (1.28%) 1 |
| Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) | 3 / 47 (6.38%) 4 | 3 / 31 (9.68%) 3 | 6 / 78 (7.69%) 7 |
| Dermatology - other (specify) subjects affected / exposed occurrences (all) | 5 / 47 (10.64%) 7 | 4 / 31 (12.90%) 4 | 9 / 78 (11.54%) 11 |
| Dry skin subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 2 / 31 (6.45%) 2 | 2 / 78 (2.56%) 2 |
| Erythema multiforme subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | 0 / 31 (0.00%) 0 | 1 / 78 (1.28%) 1 |
| Nail changes subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | 0 / 31 (0.00%) 0 | 1 / 78 (1.28%) 1 |
| Photosensitivity subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 1 / 31 (3.23%) 1 | 1 / 78 (1.28%) 1 |
| Pruritus | | | |

| | | | |
|---|----------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 3 / 47 (6.38%) 12 | 4 / 31 (12.90%) 4 | 7 / 78 (8.97%) 16 |
| Rash subjects affected / exposed occurrences (all) | 4 / 47 (8.51%) 4 | 2 / 31 (6.45%) 2 | 6 / 78 (7.69%) 6 |
| Ulceration subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 1 / 31 (3.23%) 1 | 1 / 78 (1.28%) 1 |
| Renal and urinary disorders Haemorrhage genotourinary - urethra subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 1 / 31 (3.23%) 1 | 1 / 78 (1.28%) 1 |
| Haemorrhage genitourgenital - urinary not otherwise specified subjects affected / exposed occurrences (all) | 2 / 47 (4.26%) 2 | 3 / 31 (9.68%) 3 | 5 / 78 (6.41%) 5 |
| Pain - bladder subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 1 / 31 (3.23%) 1 | 1 / 78 (1.28%) 1 |
| Cystitis subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 1 / 31 (3.23%) 1 | 1 / 78 (1.28%) 1 |
| Renal - other (specify) subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | 2 / 31 (6.45%) 2 | 3 / 78 (3.85%) 3 |
| Urinary frequency subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | 1 / 31 (3.23%) 1 | 2 / 78 (2.56%) 2 |
| Endocrine disorders Pain - oral cavity subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 2 / 31 (6.45%) 2 | 2 / 78 (2.56%) 2 |
| Musculoskeletal and connective tissue disorders Musculoskeletal - other (specify) subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 2 | 3 / 31 (9.68%) 3 | 4 / 78 (5.13%) 5 |

| | | | |
|--|-----------------------|----------------------|------------------------|
| Pain - back subjects affected / exposed occurrences (all) | 9 / 47 (19.15%) 11 | 3 / 31 (9.68%) 4 | 12 / 78 (15.38%) 15 |
| Pain - bone subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | 1 / 31 (3.23%) 1 | 2 / 78 (2.56%) 2 |
| Pain - chest wall subjects affected / exposed occurrences (all) | 2 / 47 (4.26%) 2 | 2 / 31 (6.45%) 3 | 4 / 78 (5.13%) 5 |
| Pain - extremity limb subjects affected / exposed occurrences (all) | 9 / 47 (19.15%) 10 | 6 / 31 (19.35%) 6 | 15 / 78 (19.23%) 16 |
| Pain - joint subjects affected / exposed occurrences (all) | 9 / 47 (19.15%) 18 | 1 / 31 (3.23%) 1 | 10 / 78 (12.82%) 19 |
| Pain - muscle subjects affected / exposed occurrences (all) | 7 / 47 (14.89%) 10 | 6 / 31 (19.35%) 8 | 13 / 78 (16.67%) 18 |
| Pain - neck subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | 0 / 31 (0.00%) 0 | 1 / 78 (1.28%) 1 |
| Infections and infestations | | | |
| Colitis infectious subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | 0 / 31 (0.00%) 0 | 1 / 78 (1.28%) 1 |
| Infection documented clinically - catheter related subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 1 / 31 (3.23%) 1 | 1 / 78 (1.28%) 1 |
| Infection documented clinically - lung (pneumonia) subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 1 / 31 (3.23%) 1 | 1 / 78 (1.28%) 1 |
| Infection documented clinically - skin (cellulitis) subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 1 / 31 (3.23%) 1 | 1 / 78 (1.28%) 1 |
| Infection documented clinically - | | | |

| | | | |
|--|----------------|----------------|----------------|
| urinary tract not otherwise specified | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 3 / 31 (9.68%) | 4 / 78 (5.13%) |
| occurrences (all) | 1 | 3 | 4 |
| Infection documented clinically - vagina | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 31 (0.00%) | 1 / 78 (1.28%) |
| occurrences (all) | 1 | 0 | 1 |
| Infection with unknown ANC - dental tooth | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 31 (0.00%) | 1 / 78 (1.28%) |
| occurrences (all) | 2 | 0 | 2 |
| Infection with unknown ANC - oral cavity gums (gingivitis) | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 31 (3.23%) | 1 / 78 (1.28%) |
| occurrences (all) | 0 | 1 | 1 |
| Infection with unknown ANC - sinus | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 31 (0.00%) | 1 / 78 (1.28%) |
| occurrences (all) | 1 | 0 | 1 |
| Infection with unknown ANC - urinary tract not otherwise specified | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 2 / 31 (6.45%) | 3 / 78 (3.85%) |
| occurrences (all) | 1 | 2 | 3 |
| Infection with unknown ANC - vagina | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 31 (0.00%) | 1 / 78 (1.28%) |
| occurrences (all) | 1 | 0 | 1 |
| Infection with normal ANC - biliary tree | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 31 (3.23%) | 1 / 78 (1.28%) |
| occurrences (all) | 0 | 1 | 1 |
| Infection with normal ANC - dental tooth | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 31 (0.00%) | 1 / 78 (1.28%) |
| occurrences (all) | 1 | 0 | 1 |
| Infection with normal ANC - rectum | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 31 (3.23%) | 1 / 78 (1.28%) |
| occurrences (all) | 0 | 1 | 1 |
| Infection with normal ANC - skin (cellulitis) | | | |

| | | | |
|---|------------------|-----------------|------------------|
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 31 (0.00%) | 1 / 78 (1.28%) |
| occurrences (all) | 1 | 0 | 1 |
| Infection with normal ANC - urinary tract not otherwise specified | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 3 / 31 (9.68%) | 4 / 78 (5.13%) |
| occurrences (all) | 1 | 4 | 5 |
| Infection - other (specify) | | | |
| subjects affected / exposed | 10 / 47 (21.28%) | 8 / 31 (25.81%) | 18 / 78 (23.08%) |
| occurrences (all) | 11 | 11 | 22 |
| Metabolism and nutrition disorders | | | |
| Anorexia | | | |
| subjects affected / exposed | 10 / 47 (21.28%) | 7 / 31 (22.58%) | 17 / 78 (21.79%) |
| occurrences (all) | 10 | 7 | 17 |
| Dehydration | | | |
| subjects affected / exposed | 2 / 47 (4.26%) | 4 / 31 (12.90%) | 6 / 78 (7.69%) |
| occurrences (all) | 2 | 5 | 7 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 2 / 47 (4.26%) | 0 / 31 (0.00%) | 2 / 78 (2.56%) |
| occurrences (all) | 2 | 0 | 2 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 31 (0.00%) | 1 / 78 (1.28%) |
| occurrences (all) | 1 | 0 | 1 |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 1 / 31 (3.23%) | 2 / 78 (2.56%) |
| occurrences (all) | 1 | 1 | 2 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 31 (0.00%) | 1 / 78 (1.28%) |
| occurrences (all) | 2 | 0 | 2 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 2 / 31 (6.45%) | 2 / 78 (2.56%) |
| occurrences (all) | 0 | 2 | 2 |
| Metabolic/lab - other (specify) | | | |
| subjects affected / exposed | 3 / 47 (6.38%) | 0 / 31 (0.00%) | 3 / 78 (3.85%) |
| occurrences (all) | 3 | 0 | 3 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 12 February 2008 | Six new trial sites added, change to inclusion criteria to allow patients with BRCA1 mutations (previously just BRCA2 carriers) with testing to include both genes, clarification of the pharmacokinetic assay, PARP expression pharmacodynamic assay downgraded to tertiary assay (previously secondary), clarification of the method for dose escalation and the collection and monitoring of adverse events. |
| 11 December 2008 | Change to the schedule of events to confirm time windows for various measurements. Inclusion criteria updated to allow extra ovarian cancer subdivision patients to enter the trial; to only include chemotherapy in the last 5 years and to clarify the measurements and specify the formula to calculate GFR. Change to the exclusion criterion which stated that any patient that had previously received biological or investigational agents or PARP inhibitors would now be excluded. Revision to the number of study centres and Investigators. |
| 22 July 2010 | Primary objective changed from determining the response rate to AG-014699, to determining whether AG-014699 has anti-tumour activity. Confirmation that recruitment into sub-groups could stop once a confirmed clinical response had been observed. Update to the inclusion criterion relating to the maximum number of prior chemotherapies a patient could have had before entering the trial (increased from three to five). Clarification of which evaluations were required at specified points during the trial and end of trial definition amended. |
| 09 September 2011 | The trial was originally set up with the IV formulation of AG-014699 but was revised when an oral formulation of AG-014699 was developed and made available for use. Addition of the oral formulation of AG-014699 to be used in the trial with updates throughout the protocol to reflect the change from an IV to oral formulation. Inclusion criteria updated to allow patients to enter the study (oral dose escalation phase) who were previously considered ineligible due to having high grade serous ovarian cancer, duration of the study increased from 24 to 60 months and confirmation that Sponsor approval is required for patients to continue beyond 12 cycles of treatment. |
| 10 September 2012 | Dose escalation procedure updated to allow further dose escalation beyond 120 mg. The duration of the trial was also increased from 60 to 65 months, with clarification of the procedure for patients remaining on study for extended periods of time. |
| 11 March 2013 | Change to the dose escalation procedure to allow intra-patient dose escalations. Amendment to the study design and enrolment criteria for Stage 2 and clarification of the Stage 2 dosing regimen. Addition of a new exclusion criterion to exclude patients who had been administered strong CYP1A2 or CYP3A4 inhibitors/inducers within 1 week of the start of study treatment. Clarification of required laboratory tests, amendment of the tertiary objectives, duration of the study increased from 65 to 75 months and information regarding the original IV study design removed. |
| 14 October 2013 | End of trial definition revised. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

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| The trial was terminated early on 22 January 2015 and recruitment stopped in October 2013 due to constraints with drug supply for further patients and decisions by the Sponsor. Patients already recruited continued to receive drug as per protocol. |
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Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/27002934>