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

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

subjects affected / exposed	5 / 47 (10.64%)	2 / 31 (6.45%)	7 / 78 (8.97%)
occurrences (all)	5	2	7
ALT			
subjects affected / exposed	4 / 47 (8.51%)	2 / 31 (6.45%)	6 / 78 (7.69%)
occurrences (all)	4	2	6
AST			
subjects affected / exposed	3 / 47 (6.38%)	3 / 31 (9.68%)	6 / 78 (7.69%)
occurrences (all)	4	4	8
Alkaline phosphatase			
subjects affected / exposed	3 / 47 (6.38%)	3 / 31 (9.68%)	6 / 78 (7.69%)
occurrences (all)	4	4	8
Bilirubin			
subjects affected / exposed	0 / 47 (0.00%)	1 / 31 (3.23%)	1 / 78 (1.28%)
occurrences (all)	0	1	1
Creatinine			
subjects affected / exposed	1 / 47 (2.13%)	2 / 31 (6.45%)	3 / 78 (3.85%)
occurrences (all)	1	2	3
GGT			
subjects affected / exposed	2 / 47 (4.26%)	2 / 31 (6.45%)	4 / 78 (5.13%)
occurrences (all)	2	2	4
Injury, poisoning and procedural complications			
Bruising			
subjects affected / exposed	3 / 47 (6.38%)	2 / 31 (6.45%)	5 / 78 (6.41%)
occurrences (all)	3	2	5
Fracture			
subjects affected / exposed	2 / 47 (4.26%)	0 / 31 (0.00%)	2 / 78 (2.56%)
occurrences (all)	3	0	3
Intraoperative injury - other (specify)			
subjects affected / exposed	0 / 47 (0.00%)	1 / 31 (3.23%)	1 / 78 (1.28%)
occurrences (all)	0	1	1
Cardiac disorders			
Palpitations			
subjects affected / exposed	2 / 47 (4.26%)	0 / 31 (0.00%)	2 / 78 (2.56%)
occurrences (all)	2	0	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	0 / 47 (0.00%)	1 / 31 (3.23%)	1 / 78 (1.28%)
occurrences (all)	0	1	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 monitroing 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	0 / 47 (0.00%)	1 / 31 (3.23%)	1 / 78 (1.28%)
occurrences (all)	0	1	1
Pain - dental/teeth/peridontal			
subjects affected / exposed	1 / 47 (2.13%)	0 / 31 (0.00%)	1 / 78 (1.28%)
occurrences (all)	2	0	2
Pain - stomach			
subjects affected / exposed	0 / 47 (0.00%)	1 / 31 (3.23%)	1 / 78 (1.28%)
occurrences (all)	0	2	2
Hepatobiliary disorders			
Haemorrhage gastrointestinal - rectum			
subjects affected / exposed	0 / 47 (0.00%)	1 / 31 (3.23%)	1 / 78 (1.28%)
occurrences (all)	0	1	1
Liver dysfunction			
subjects affected / exposed	0 / 47 (0.00%)	1 / 31 (3.23%)	1 / 78 (1.28%)
occurrences (all)	0	1	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 47 (6.38%)	3 / 31 (9.68%)	6 / 78 (7.69%)
occurrences (all)	4	3	7
Dermatology - other (specify)			
subjects affected / exposed	5 / 47 (10.64%)	4 / 31 (12.90%)	9 / 78 (11.54%)
occurrences (all)	7	4	11
Dry skin			
subjects affected / exposed	0 / 47 (0.00%)	2 / 31 (6.45%)	2 / 78 (2.56%)
occurrences (all)	0	2	2
Erythema multiforme			
subjects affected / exposed	1 / 47 (2.13%)	0 / 31 (0.00%)	1 / 78 (1.28%)
occurrences (all)	1	0	1
Nail changes			
subjects affected / exposed	1 / 47 (2.13%)	0 / 31 (0.00%)	1 / 78 (1.28%)
occurrences (all)	1	0	1
Photosensitivity			
subjects affected / exposed	0 / 47 (0.00%)	1 / 31 (3.23%)	1 / 78 (1.28%)
occurrences (all)	0	1	1
Pruritus			

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

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

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.

Notes:

Online references

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