



Clinical trial results:

OCTOPUS: Ovarian Cancer Trials of Weekly Paclitaxel - Umbrella Study A Randomised, Phase II Umbrella Trial of a Weekly Paclitxel +/- Novel Agents in Platinum-Resistant Ovarian Cancer

Summary

EudraCT number	2014-005221-12
Trial protocol	GB
Global end of trial date	01 February 2024

Results information

Result version number	v1 (current)
This version publication date	01 May 2025
First version publication date	01 May 2025
Summary attachment (see zip file)	OCTOPUS Manuscript Link (2014-005221-12 OCTOPUS publication summary.pdf)

Trial information

Trial identification

Sponsor protocol code	OCTOPUS-2014
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Additional study identifiers

ISRCTN number	ISRCTN16426935
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Greater Glasgow Health Board
Sponsor organisation address	Research and Innovation, Admin Building, Gartnavel General Hospital, 1055 Great Western Road, GLASGOW, United Kingdom, G12 OXH
Public contact	Melissa Robert, Greater Glasgow Health Board, melissa.robert@nhs.net
Scientific contact	Melissa Robert, Greater Glasgow Health Board, melissa.robert@nhs.net
Sponsor organisation name	University of Glasgow
Sponsor organisation address	University Avenue, GLASGOW, United Kingdom, G12 8QQ
Public contact	Marcela Gavigan, University of Glasgow, marcela.gavigan@glasgow.ac.uk
Scientific contact	Marcela Gavigan, University of Glasgow, marcela.gavigan@glasgow.ac.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
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Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 August 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 August 2019
Global end of trial reached?	Yes
Global end of trial date	01 February 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate whether the addition of a novel agent to weekly paclitaxel improves efficacy (how well treatment works), compared with paclitaxel plus placebo, in patients with relapsed platinum-resistant ovarian cancer.

The progression free survival (the length of time during and after cancer treatment that a patient lives with the disease but it does not get worse) will be compared.

Protection of trial subjects:

As part of this study patients required to attend for additional clinic visits and investigations which would be above those considered to be standard care. The visit schedule and the number and type of investigations were fully explained to patients verbally and in writing via the patient information sheet to ensure patients were fully aware what was entailed in participating in the trial prior to them consenting to the study.

The side effects of Paclitaxell (standard of care) along with Vistusertib (AZD2014) were explained in the patient information sheet. All patients were closely monitored throughout the course of the study for adverse events and advised to report any side effects to their study nurse/doctor as they arose.

Background therapy:

Not Applicable.

Evidence for comparator:

Several mechanisms have been proposed for platinum and taxane resistance in high grade serous ovarian cancer, one of which is abnormalities in the PI3 kinase/Akt /mTOR signalling pathway. Activation of the phosphatidylinositide-3-kinase pathway as measured by p-p70S6K has been associated with resistance to chemotherapy in studies using ovarian cancer cells isolated from ascites. Preclinical studies have suggested a potential for modulation of this pathway to overcome resistance to chemotherapy in ovarian cancer.

Vistusertib (AZD2014), a novel mTORC1/2 inhibitor, and paclitaxel were shown to have additive growth inhibitory effects in a panel of ovarian cancer cell lines.¹² Drugs targeting this pathway in combination with conventional chemotherapy may lead to improved clinical efficacy in ovarian cancer. Weekly paclitaxel is a useful strategy in platinum-resistant disease. Clinical trials in ovarian cancer have utilised weekly paclitaxel to explore the effects of novel targeted agents in platinum-resistant ovarian cancer. Examples include, OSI906, an IGFR inhibitor, and saracatinib (AZD0530). To date, there are no open clinical trials of mTOR kinase inhibitor in combination with weekly paclitaxel in ovarian cancer. Therefore a trial of weekly paclitaxel plus the dual mTORC1/2 inhibitor, Vistusertib (AZD2014), is indicated with the aim of further improving clinical efficacy for patients with platinum-resistant ovarian cancer. This led to the development of the phase I combination of Vistusertib (AZD2014) and weekly paclitaxel in patients with solid tumours (TAX-TORC) in order to establish the optimal dose for the combination. The phase I study has shown encouraging activity and tolerability at an MTD of 50 mg bd Vistusertib (AZD2014) 3 days on, 4 days off and weekly paclitaxel (80 mg/m²).

Actual start date of recruitment	13 January 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 140
Worldwide total number of subjects	140
EEA total number of subjects	0

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)	74
From 65 to 84 years	65
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This study opened to recruitment on the 8th December 2015 and closed to recruitment on the 23rd March 2018. A total of 140 patients were recruited (70 each arm).

Pre-assignment

Screening details:

The screening period for the study was up to 42 days prior to randomisation. Prior to screening investigations commencing patient must have provided written informed consent to participate in the study.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm X

Arm description:

Paclitaxel 80mg/m² IV D1, 8, 15 of a 28 day cycle (3 weeks on, 1 week off) + Vistusertib (AZD2014) 50mg twice daily on days 1-3, 8-10, 15-17 of a 28 day cycle.

Patients will have 6 cycles (24 weeks) of combination treatment. Thereafter, patients who do not have progressive disease (and have completed at least 4 cycles of combination treatment) can continue on Vistusertib (AZD2014) or placebo alone as continuous maintenance therapy. Please note, patients can continue beyond 6 cycles of paclitaxel and Vistusertib (AZD2014) or placebo before receiving maintenance therapy, at the discretion of the Investigator, provided the patient has not progressed and after discussion with the Chief Investigator.

Arm type	Experimental
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel 80mg/m² administered by IV infusion in Sodium Chloride 0.9% over 1 hour on days 1, 8 and 15 of a 28 day cycle For 6 cycles. Patients can continue beyond 6 cycles at the discretion of the Investigator.

Investigational medicinal product name	Vistusertib (AZD2014)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Vistusertib (AZD2014) 50mg orally twice daily on Days 1-3, 8-10 and 15-17 of a 28 day cycle.

For 6 cycles. Patients can continue beyond 6 cycles at the discretion of the Investigator. Thereafter, patients who do not have progressive disease (and have completed at least 4 cycles of combination treatment with Vistusertib (AZD2014) and paclitaxel) can then continue on continuous Vistusertib (AZD2014) alone as maintenance.

Arm title	Arm Y
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Arm description:

Paclitaxel 80mg/m² IV D1, 8, 15 of a 28 day cycle (3 weeks on, 1 week off) + Placebo 50mg twice daily on days 1-3, 8-10, 15-17 of a 28 day cycle.

Patients will have 6 cycles (24 weeks) of combination treatment. Thereafter, patients who do not have progressive disease (and have completed at least 4 cycles of combination treatment) can continue on Vistusertib (AZD2014) or placebo alone as continuous maintenance therapy. Please note, patients can continue beyond 6 cycles of paclitaxel and Vistusertib (AZD2014) or placebo before receiving maintenance therapy, at the discretion of the Investigator, provided the patient has not progressed and after discussion with the Chief Investigator.

Arm type	Placebo
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel 80mg/m² administered by IV infusion in Sodium Chloride 0.9% over 1 hour on days 1, 8 and 15 of a 28 day cycle For 6 cycles. Patients can continue beyond 6 cycles at the discretion of the Investigator.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo orally twice daily on Days 1-3, 8-10 and 15-17 of a 28 day cycle

For 6 cycles. Patients can continue beyond 6 cycles at the discretion of the Investigator. Thereafter, patients who do not have progressive disease (and have completed at least 4 cycles of combination treatment with placebo and paclitaxel) can then continue on continuous placebo alone as maintenance.

Number of subjects in period 1	Arm X	Arm Y
Started	70	70
Completed	70	70

Baseline characteristics

Reporting groups

Reporting group title	Arm X
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Reporting group description:

Paclitaxel 80mg/m² IV D1, 8, 15 of a 28 day cycle (3 weeks on, 1 week off) + Vistusertib (AZD2014) 50mg twice daily on days 1-3, 8-10, 15-17 of a 28 day cycle.

Patients will have 6 cycles (24 weeks) of combination treatment. Thereafter, patients who do not have progressive disease (and have completed at least 4 cycles of combination treatment) can continue on Vistusertib (AZD2014) or placebo alone as continuous maintenance therapy. Please note, patients can continue beyond 6 cycles of paclitaxel and Vistusertib (AZD2014) or placebo before receiving maintenance therapy, at the discretion of the Investigator, provided the patient has not progressed and after discussion with the Chief Investigator.

Reporting group title	Arm Y
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Reporting group description:

Paclitaxel 80mg/m² IV D1, 8, 15 of a 28 day cycle (3 weeks on, 1 week off) + Placebo 50mg twice daily on days 1-3, 8-10, 15-17 of a 28 day cycle.

Patients will have 6 cycles (24 weeks) of combination treatment. Thereafter, patients who do not have progressive disease (and have completed at least 4 cycles of combination treatment) can continue on Vistusertib (AZD2014) or placebo alone as continuous maintenance therapy. Please note, patients can continue beyond 6 cycles of paclitaxel and Vistusertib (AZD2014) or placebo before receiving maintenance therapy, at the discretion of the Investigator, provided the patient has not progressed and after discussion with the Chief Investigator.

Reporting group values	Arm X	Arm Y	Total
Number of subjects	70	70	140
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	31	43	74
From 65-84 years	39	26	65
85 years and over	0	1	1
Gender categorical			
Units: Subjects			
Female	70	70	140
Male	0	0	0

Subject analysis sets

Subject analysis set title	Arm X
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

All patients randomised to Arm X

Subject analysis set title	Arm Y
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

All patients randomised to Arm Y

Reporting group values	Arm X	Arm Y	
Number of subjects	70	70	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	31	43	
From 65-84 years	39	26	
85 years and over	0	1	
Gender categorical			
Units: Subjects			
Female	70	70	
Male	0	0	

End points

End points reporting groups

Reporting group title	Arm X
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Reporting group description:

Paclitaxel 80mg/m² IV D1, 8, 15 of a 28 day cycle (3 weeks on, 1 week off) + Vistusertib (AZD2014) 50mg twice daily on days 1-3, 8-10, 15-17 of a 28 day cycle.

Patients will have 6 cycles (24 weeks) of combination treatment. Thereafter, patients who do not have progressive disease (and have completed at least 4 cycles of combination treatment) can continue on Vistusertib (AZD2014) or placebo alone as continuous maintenance therapy. Please note, patients can continue beyond 6 cycles of paclitaxel and Vistusertib (AZD2014) or placebo before receiving maintenance therapy, at the discretion of the Investigator, provided the patient has not progressed and after discussion with the Chief Investigator.

Reporting group title	Arm Y
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Reporting group description:

Paclitaxel 80mg/m² IV D1, 8, 15 of a 28 day cycle (3 weeks on, 1 week off) + Placebo 50mg twice daily on days 1-3, 8-10, 15-17 of a 28 day cycle.

Patients will have 6 cycles (24 weeks) of combination treatment. Thereafter, patients who do not have progressive disease (and have completed at least 4 cycles of combination treatment) can continue on Vistusertib (AZD2014) or placebo alone as continuous maintenance therapy. Please note, patients can continue beyond 6 cycles of paclitaxel and Vistusertib (AZD2014) or placebo before receiving maintenance therapy, at the discretion of the Investigator, provided the patient has not progressed and after discussion with the Chief Investigator.

Subject analysis set title	Arm X
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

All patients randomised to Arm X

Subject analysis set title	Arm Y
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

All patients randomised to Arm Y

Primary: Arm X

End point title	Arm X
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End point description:

Progression free survival (PFS) was defined as the time from randomisation to first appearance of progressive disease as defined by a combined RECIST v1.1 and GCIG CA125 criteria or death from any cause. Patients still alive and without progression at the time of analysis were censored at the last date known to be alive.

End point type	Primary
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End point timeframe:

Patients were followed up every 8 weeks for the first year and every 12 weeks thereafter or until evidence of disease progression whichever was sooner.

End point values	Arm X	Arm Y		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70	70		
Units: Weeks				
median (confidence interval 80%)	19.6 (17.0 to 24.0)	18.0 (16.1 to 20.4)		

Statistical analyses

Statistical analysis title	Cox regression
Statistical analysis description: The primary analysis of the progression-free survival endpoint was conducted using Cox regression via a model incorporating the blinded study arm and the factors used in the minimisation algorithm.	
Comparison groups	Arm X v Arm Y
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.1
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.67
upper limit	1.07

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Arm X
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Reporting group description: -

Reporting group title	Arm Y
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Reporting group description: -

Serious adverse events	Arm X	Arm Y	
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 68 (42.65%)	20 / 68 (29.41%)	
number of deaths (all causes)	3	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify	Additional description: Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Thromboembolic event	Additional description: Thromboembolic event		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Infusion related reaction	Additional description: Infusion related reaction		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain	Additional description: Pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions - Other, specify	Additional description: General disorders and administration site conditions - Other, specify		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever	Additional description: Fever		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 68 (2.94%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue	Additional description: Fatigue		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 68 (2.94%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergic reaction	Additional description: Allergic reaction		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Vaginal fistula	Additional description: Vaginal fistula		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion	Additional description: Pleural effusion		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 68 (4.41%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnea			
Dyspnea	Additional description: Dyspnea		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
Pneumonitis	Additional description: Pneumonitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 68 (2.94%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders - Other, specify			
Respiratory, thoracic and mediastinal disorders - Other, specify	Additional description: Respiratory, thoracic and mediastinal disorders - Other, specify		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Neutrophil count decreased	Additional description: Neutrophil count decreased		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Bruising	Additional description: Bruising		
alternative assessment type: Non-			

systematic			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction	Additional description: Myocardial infarction		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dizziness	Additional description: Dizziness		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia	Additional description: Febrile neutropenia		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain	Additional description: Abdominal pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 68 (4.41%)	2 / 68 (2.94%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension	Additional description: Abdominal distension		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic fistula	Additional description: Colonic fistula		

alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhea	Additional description: Diarrhea		
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 68 (7.35%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	5 / 6	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation	Additional description: Constipation		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 68 (5.88%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic obstruction	Additional description: Colonic obstruction		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 68 (2.94%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites	Additional description: Ascites		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 68 (2.94%)	3 / 68 (4.41%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting	Additional description: Vomiting		
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 68 (10.29%)	2 / 68 (2.94%)	
occurrences causally related to treatment / all	3 / 8	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction	Additional description: Small intestinal obstruction		
alternative assessment type: Non-systematic			

subjects affected / exposed	2 / 68 (2.94%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea	Additional description: Nausea		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 68 (5.88%)	2 / 68 (2.94%)	
occurrences causally related to treatment / all	3 / 5	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal obstruction	Additional description: Ileal obstruction		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal fistula	Additional description: Gastrointestinal fistula		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders - Other, specify	Additional description: Gastrointestinal disorders - Other, specify		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis	Additional description: Cholecystitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders - Other, specify	Additional description: Hepatobiliary disorders - Other, specify		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary frequency	Additional description: Urinary frequency		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain	Additional description: Back pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest wall pain	Additional description: Chest wall pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal infection	Additional description: Abdominal infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection	Additional description: Lung infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 68 (2.94%)	3 / 68 (4.41%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infections and infestations - Other, specify	Additional description: Infections and infestations - Other, specify		
alternative assessment type: Non-systematic			

subjects affected / exposed	3 / 68 (4.41%)	2 / 68 (2.94%)	
occurrences causally related to treatment / all	1 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial infection	Additional description: Bronchial infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis	Additional description: Sepsis		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection	Additional description: Skin infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory infection	Additional description: Upper respiratory infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection	Additional description: Urinary tract infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	8 / 68 (11.76%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	1 / 11	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Anorexia	Additional description: Anorexia		
alternative assessment type: Non-systematic			

subjects affected / exposed	2 / 68 (2.94%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcemia	Additional description: Hypocalcemia		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalemia	Additional description: Hypokalemia		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesemia	Additional description: Hypomagnesemia		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	2 / 68 (2.94%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm X	Arm Y	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	66 / 68 (97.06%)	68 / 68 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumor pain	Additional description: Tumor pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify	Additional description: Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Vascular disorders			
Flushing	Additional description: Flushing		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	5 / 68 (7.35%)	
occurrences (all)	1	12	
Hematoma	Additional description: Hematoma		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	2	
Thromboembolic event	Additional description: Thromboembolic event		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 68 (2.94%)	1 / 68 (1.47%)	
occurrences (all)	2	2	
Hypertension	Additional description: Hypertension		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	4 / 68 (5.88%)	
occurrences (all)	2	9	
Lymphedema	Additional description: Lymphedema		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	3 / 68 (4.41%)	
occurrences (all)	5	7	
Superficial thrombophlebitis	Additional description: Superficial thrombophlebitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	2	
Hot flashes	Additional description: Hot flashes		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 68 (2.94%)	5 / 68 (7.35%)	
occurrences (all)	3	7	
General disorders and administration site conditions			
Chills	Additional description: Chills		
alternative assessment type: Non-systematic			

subjects affected / exposed	2 / 68 (2.94%)	0 / 68 (0.00%)	
occurrences (all)	6	0	
Edema face	Additional description: Edema face		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Fatigue	Additional description: Fatigue		
alternative assessment type: Non-systematic			
subjects affected / exposed	57 / 68 (83.82%)	55 / 68 (80.88%)	
occurrences (all)	249	247	
Fever	Additional description: Fever		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 68 (4.41%)	7 / 68 (10.29%)	
occurrences (all)	4	8	
Flu like symptoms	Additional description: Flu like symptoms		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	5 / 68 (7.35%)	
occurrences (all)	1	6	
Infusion related reaction	Additional description: Infusion related reaction		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Infusion site extravasation	Additional description: Infusion site extravasation		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 68 (2.94%)	0 / 68 (0.00%)	
occurrences (all)	2	0	
Injection site reaction	Additional description: Injection site reaction		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Non-cardiac chest pain	Additional description: Non-cardiac chest pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	

Pain alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Pain		
	16 / 68 (23.53%)	19 / 68 (27.94%)	
	25	39	
Edema limbs alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Edema limbs		
	10 / 68 (14.71%)	7 / 68 (10.29%)	
	23	22	
Immune system disorders Allergic reaction alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Allergic reaction		
	2 / 68 (2.94%)	4 / 68 (5.88%)	
	5	10	
Social circumstances Social circumstances - Other, specify alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Social circumstances - Other, specify		
	1 / 68 (1.47%)	0 / 68 (0.00%)	
	5	0	
Reproductive system and breast disorders Vaginal fistula alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Vaginal discharge alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Pelvic pain alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Menorrhagia alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Vaginal fistula		
	1 / 68 (1.47%)	0 / 68 (0.00%)	
	1	0	
	Additional description: Vaginal discharge		
	2 / 68 (2.94%)	2 / 68 (2.94%)	
	10	3	
	Additional description: Pelvic pain		
	1 / 68 (1.47%)	1 / 68 (1.47%)	
	2	1	
	Additional description: Menorrhagia		
	1 / 68 (1.47%)	0 / 68 (0.00%)	
	1	0	

Vaginal hemorrhage alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Vaginal hemorrhage		
	2 / 68 (2.94%) 3	3 / 68 (4.41%) 6	
Respiratory, thoracic and mediastinal disorders			
	Additional description: Allergic rhinitis		
	1 / 68 (1.47%) 2	0 / 68 (0.00%) 0	
	Additional description: Cough		
	17 / 68 (25.00%) 36	15 / 68 (22.06%) 32	
	Additional description: Dyspnea		
	22 / 68 (32.35%) 53	13 / 68 (19.12%) 28	
	Additional description: Epistaxis		
	7 / 68 (10.29%) 12	4 / 68 (5.88%) 13	
	Additional description: Hoarseness		
	0 / 68 (0.00%) 0	2 / 68 (2.94%) 2	
	Additional description: Laryngeal hemorrhage		
	0 / 68 (0.00%) 0	1 / 68 (1.47%) 1	
	Additional description: Laryngopharyngeal dysesthesia		
	0 / 68 (0.00%) 0	1 / 68 (1.47%) 1	
	Additional description: Nasal congestion		

systematic			
subjects affected / exposed	1 / 68 (1.47%)	2 / 68 (2.94%)	
occurrences (all)	1	3	
Pleural effusion	Additional description: Pleural effusion		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 68 (2.94%)	2 / 68 (2.94%)	
occurrences (all)	3	2	
Pneumonitis	Additional description: Pneumonitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Sneezing	Additional description: Sneezing		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	1 / 68 (1.47%)	
occurrences (all)	1	2	
Sore throat	Additional description: Sore throat		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 68 (4.41%)	2 / 68 (2.94%)	
occurrences (all)	3	3	
Voice alteration	Additional description: Voice alteration		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	4	
Psychiatric disorders			
Restlessness	Additional description: Restlessness		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	1 / 68 (1.47%)	
occurrences (all)	1	3	
Psychiatric disorders - Other, specify	Additional description: Psychiatric disorders - Other, specify		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences (all)	7	0	
Insomnia	Additional description: Insomnia		
alternative assessment type: Non-systematic			

subjects affected / exposed	11 / 68 (16.18%)	7 / 68 (10.29%)	
occurrences (all)	23	18	
Depression	Additional description: Depression		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 68 (4.41%)	5 / 68 (7.35%)	
occurrences (all)	3	12	
Anxiety	Additional description: Anxiety		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	4 / 68 (5.88%)	
occurrences (all)	8	11	
Investigations			
Alanine aminotransferase increased	Additional description: Alanine aminotransferase increased		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 68 (2.94%)	1 / 68 (1.47%)	
occurrences (all)	3	1	
Alkaline phosphatase increased	Additional description: Alkaline phosphatase increased		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	1 / 68 (1.47%)	
occurrences (all)	1	1	
Aspartate aminotransferase increased	Additional description: Aspartate aminotransferase increased		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 68 (2.94%)	0 / 68 (0.00%)	
occurrences (all)	3	0	
Cholesterol high	Additional description: Cholesterol high		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	2 / 68 (2.94%)	
occurrences (all)	1	7	
Creatinine increased	Additional description: Creatinine increased		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	2 / 68 (2.94%)	
occurrences (all)	0	2	
GGT increased	Additional description: GGT increased		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 68 (1.47%)	1 / 68 (1.47%)	
occurrences (all)	1	1	
Neutrophil count decreased	Additional description: Neutrophil count decreased		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 68 (2.94%)	2 / 68 (2.94%)	
occurrences (all)	2	2	
Weight loss	Additional description: Weight loss		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 68 (2.94%)	1 / 68 (1.47%)	
occurrences (all)	2	2	
Injury, poisoning and procedural complications			
Bruising	Additional description: Bruising		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	3 / 68 (4.41%)	
occurrences (all)	2	7	
Burn	Additional description: Burn		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	1 / 68 (1.47%)	
occurrences (all)	1	1	
Injury, poisoning and procedural complications - Other, specify	Additional description: Injury, poisoning and procedural complications - Other, specify		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 68 (2.94%)	0 / 68 (0.00%)	
occurrences (all)	3	0	
Vascular access complication	Additional description: Vascular access complication		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	5	
Cardiac disorders			
Cardiac disorders - Other, specify	Additional description: Cardiac disorders - Other, specify		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	4	
Sinus tachycardia	Additional description: Sinus tachycardia		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences (all)	2	0	
Cardiac disorders	Additional description: Cardiac disorders		
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 68 (7.35%)	2 / 68 (2.94%)	
occurrences (all)	10	3	
Nervous system disorders			
Peripheral motor neuropathy	Additional description: Peripheral motor neuropathy		
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 68 (10.29%)	9 / 68 (13.24%)	
occurrences (all)	9	23	
Paresthesia	Additional description: Paresthesia		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 68 (2.94%)	2 / 68 (2.94%)	
occurrences (all)	2	6	
Neuralgia	Additional description: Neuralgia		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	2	
Movements involuntary	Additional description: Movements involuntary		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	2 / 68 (2.94%)	
occurrences (all)	0	2	
Lethargy	Additional description: Lethargy		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	3 / 68 (4.41%)	
occurrences (all)	1	4	
Headache	Additional description: Headache		
alternative assessment type: Non-systematic			
subjects affected / exposed	9 / 68 (13.24%)	11 / 68 (16.18%)	
occurrences (all)	24	21	
Dysphasia	Additional description: Dysphasia		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Dysgeusia	Additional description: Dysgeusia		
alternative assessment type: Non-systematic			
subjects affected / exposed	10 / 68 (14.71%)	6 / 68 (8.82%)	
occurrences (all)	31	15	
Dysarthria	Additional description: Dysarthria		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Dizziness	Additional description: Dizziness		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 68 (4.41%)	5 / 68 (7.35%)	
occurrences (all)	11	13	
Concentration impairment	Additional description: Concentration impairment		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Ataxia	Additional description: Ataxia		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Amnesia	Additional description: Amnesia		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Akathisia	Additional description: Akathisia		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences (all)	4	0	
Tremor	Additional description: Tremor		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	1 / 68 (1.47%)	
occurrences (all)	4	4	

<p>Spasticity</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	Additional description: Spasticity		
	2 / 68 (2.94%)	1 / 68 (1.47%)	
	3	1	
<p>Sinus pain</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	Additional description: Sinus pain		
	0 / 68 (0.00%)	1 / 68 (1.47%)	
	0	2	
<p>Peripheral sensory neuropathy</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	Additional description: Peripheral sensory neuropathy		
	33 / 68 (48.53%)	39 / 68 (57.35%)	
	128	129	
<p>Blood and lymphatic system disorders</p> <p>Anemia</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	Additional description: Anemia		
	10 / 68 (14.71%)	6 / 68 (8.82%)	
	14	16	
<p>Ear and labyrinth disorders</p> <p>Ear and labyrinth disorders - Other, specify</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	Additional description: Ear and labyrinth disorders - Other, specify		
	0 / 68 (0.00%)	1 / 68 (1.47%)	
	0	2	
<p>Ear pain</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	Additional description: Ear pain		
	1 / 68 (1.47%)	0 / 68 (0.00%)	
	1	0	
<p>Hearing impaired</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	Additional description: Hearing impaired		
	0 / 68 (0.00%)	1 / 68 (1.47%)	
	0	1	
<p>Tinnitus</p> <p>alternative assessment type: Non-systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	Additional description: Tinnitus		
	0 / 68 (0.00%)	4 / 68 (5.88%)	
	0	5	
<p>Vertigo</p>	Additional description: Vertigo		

alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1	0 / 68 (0.00%) 0	
Eye disorders			
Blurred vision	Additional description: Blurred vision		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	5 / 68 (7.35%) 12	4 / 68 (5.88%) 13	
Dry eye	Additional description: Dry eye		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	3 / 68 (4.41%) 12	2 / 68 (2.94%) 2	
Eye disorders - Other, specify	Additional description: Eye disorders - Other, specify		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	4 / 68 (5.88%) 4	1 / 68 (1.47%) 1	
Eye pain	Additional description: Eye pain		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1	0 / 68 (0.00%) 0	
Eyelid function disorder	Additional description: Eyelid function disorder		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1	1 / 68 (1.47%) 3	
Flashing lights	Additional description: Flashing lights		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1	0 / 68 (0.00%) 0	
Floaters	Additional description: Floaters		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 2	0 / 68 (0.00%) 0	
Watering eyes	Additional description: Watering eyes		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 68 (1.47%)	2 / 68 (2.94%)	
occurrences (all)	3	10	
Gastrointestinal disorders			
Abdominal distension	Additional description: Abdominal distension		
alternative assessment type: Non-systematic			
subjects affected / exposed	12 / 68 (17.65%)	4 / 68 (5.88%)	
occurrences (all)	21	9	
Abdominal pain	Additional description: Abdominal pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	36 / 68 (52.94%)	37 / 68 (54.41%)	
occurrences (all)	80	89	
Ascites	Additional description: Ascites		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 68 (5.88%)	5 / 68 (7.35%)	
occurrences (all)	8	10	
Bloating	Additional description: Bloating		
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 68 (8.82%)	7 / 68 (10.29%)	
occurrences (all)	11	14	
Colonic obstruction	Additional description: Colonic obstruction		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Constipation	Additional description: Constipation		
alternative assessment type: Non-systematic			
subjects affected / exposed	28 / 68 (41.18%)	29 / 68 (42.65%)	
occurrences (all)	61	93	
Diarrhea	Additional description: Diarrhea		
alternative assessment type: Non-systematic			
subjects affected / exposed	38 / 68 (55.88%)	27 / 68 (39.71%)	
occurrences (all)	107	71	
Dry mouth	Additional description: Dry mouth		
alternative assessment type: Non-systematic			

subjects affected / exposed	4 / 68 (5.88%)	2 / 68 (2.94%)	
occurrences (all)	12	7	
Dyspepsia	Additional description: Dyspepsia		
alternative assessment type: Non-systematic			
subjects affected / exposed	9 / 68 (13.24%)	6 / 68 (8.82%)	
occurrences (all)	15	14	
Fecal incontinence	Additional description: Fecal incontinence		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	3	
Flatulence	Additional description: Flatulence		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 68 (5.88%)	2 / 68 (2.94%)	
occurrences (all)	7	2	
Gastroesophageal reflux disease	Additional description: Gastroesophageal reflux disease		
alternative assessment type: Non-systematic			
subjects affected / exposed	11 / 68 (16.18%)	5 / 68 (7.35%)	
occurrences (all)	16	17	
Gastrointestinal disorders - Other, specify	Additional description: Gastrointestinal disorders - Other, specify		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	4 / 68 (5.88%)	
occurrences (all)	1	7	
Hemorrhoids	Additional description: Hemorrhoids		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Ileal obstruction	Additional description: Ileal obstruction		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Mucositis oral	Additional description: Mucositis oral		
alternative assessment type: Non-systematic			
subjects affected / exposed	24 / 68 (35.29%)	20 / 68 (29.41%)	
occurrences (all)	43	40	

Nausea alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Nausea		
	43 / 68 (63.24%)	42 / 68 (61.76%)	
	112	110	
Oral pain alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Oral pain		
	1 / 68 (1.47%)	0 / 68 (0.00%)	
	1	0	
Stomach pain alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Stomach pain		
	2 / 68 (2.94%)	1 / 68 (1.47%)	
	2	1	
Stomatitis alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Stomatitis		
	7 / 68 (10.29%)	3 / 68 (4.41%)	
	9	7	
Toothache alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Toothache		
	1 / 68 (1.47%)	1 / 68 (1.47%)	
	1	1	
Vomiting alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Vomiting		
	23 / 68 (33.82%)	22 / 68 (32.35%)	
	39	52	
Anal pain alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Anal pain		
	1 / 68 (1.47%)	0 / 68 (0.00%)	
	1	0	
Hepatobiliary disorders Cholecystitis alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Cholecystitis		
	1 / 68 (1.47%)	0 / 68 (0.00%)	
	1	0	
Skin and subcutaneous tissue disorders			

Nail loss alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Nail loss		
	1 / 68 (1.47%) 2	2 / 68 (2.94%) 9	
Nail ridging alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Nail ridging		
	0 / 68 (0.00%) 0	2 / 68 (2.94%) 7	
Pain of skin alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Pain of skin		
	1 / 68 (1.47%) 1	0 / 68 (0.00%) 0	
Palmar-plantar erythrodysesthesia syndrome alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Palmar-plantar erythrodysesthesia syndrome		
	0 / 68 (0.00%) 0	2 / 68 (2.94%) 8	
Photosensitivity alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Photosensitivity		
	1 / 68 (1.47%) 2	1 / 68 (1.47%) 6	
Pruritus alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Pruritus		
	6 / 68 (8.82%) 9	3 / 68 (4.41%) 5	
Rash acneiform alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Rash acneiform		
	4 / 68 (5.88%) 14	2 / 68 (2.94%) 2	
Rash maculo-papular alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Rash maculo-papular		
	16 / 68 (23.53%) 57	7 / 68 (10.29%) 16	
Skin and subcutaneous tissue disorders - Other, specify alternative assessment type: Non-systematic	Additional description: Skin and subcutaneous tissue disorders - Other, specify		

subjects affected / exposed	7 / 68 (10.29%)	9 / 68 (13.24%)	
occurrences (all)	20	15	
Skin hyperpigmentation	Additional description: Skin hyperpigmentation		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	3 / 68 (4.41%)	
occurrences (all)	0	6	
Skin ulceration	Additional description: Skin ulceration		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 68 (2.94%)	1 / 68 (1.47%)	
occurrences (all)	2	1	
Alopecia	Additional description: Alopecia		
alternative assessment type: Non-systematic			
subjects affected / exposed	42 / 68 (61.76%)	38 / 68 (55.88%)	
occurrences (all)	178	188	
Bullous dermatitis	Additional description: Bullous dermatitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Dry skin	Additional description: Dry skin		
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 68 (7.35%)	7 / 68 (10.29%)	
occurrences (all)	17	37	
Nail discoloration	Additional description: Nail discoloration		
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 68 (7.35%)	6 / 68 (8.82%)	
occurrences (all)	11	14	
Urticaria	Additional description: Urticaria		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Urinary urgency	Additional description: Urinary urgency		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	2	
Urinary tract pain	Additional description: Urinary tract pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Urinary incontinence	Additional description: Urinary incontinence		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 68 (2.94%)	5 / 68 (7.35%)	
occurrences (all)	5	9	
Urinary frequency	Additional description: Urinary frequency		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 68 (2.94%)	2 / 68 (2.94%)	
occurrences (all)	3	4	
Renal colic	Additional description: Renal colic		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Hematuria	Additional description: Hematuria		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	1 / 68 (1.47%)	
occurrences (all)	1	1	
Cystitis noninfective	Additional description: Cystitis noninfective		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	3	
Acute kidney injury	Additional description: Acute kidney injury		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Endocrine disorders			
Endocrine disorders - Other, specify	Additional description: Endocrine disorders - Other, specify		
alternative assessment type: Non-systematic			

subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1	0 / 68 (0.00%) 0	
Musculoskeletal and connective tissue disorders			
Arthralgia	Additional description: Arthralgia		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 68 (4.41%)	7 / 68 (10.29%)	
occurrences (all)	14	18	
Arthritis	Additional description: Arthritis		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	2 / 68 (2.94%)	
occurrences (all)	1	5	
Pain in extremity	Additional description: Pain in extremity		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 68 (2.94%)	4 / 68 (5.88%)	
occurrences (all)	5	5	
Neck pain	Additional description: Neck pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Myalgia	Additional description: Myalgia		
alternative assessment type: Non-systematic			
subjects affected / exposed	14 / 68 (20.59%)	15 / 68 (22.06%)	
occurrences (all)	31	51	
Musculoskeletal and connective tissue disorder - Other, specify	Additional description: Musculoskeletal and connective tissue disorder - Other, specify		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	1 / 68 (1.47%)	
occurrences (all)	2	1	
Generalized muscle weakness	Additional description: Generalized muscle weakness		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	1 / 68 (1.47%)	
occurrences (all)	1	1	
Flank pain	Additional description: Flank pain		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 68 (0.00%)	2 / 68 (2.94%)	
occurrences (all)	0	3	
Back pain	Additional description: Back pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 68 (10.29%)	11 / 68 (16.18%)	
occurrences (all)	13	19	
Infections and infestations			
Rash pustular	Additional description: Rash pustular		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Device related infection	Additional description: Device related infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Esophageal infection	Additional description: Esophageal infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Eye infection	Additional description: Eye infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Gum infection	Additional description: Gum infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Infections and infestations - Other, specify	Additional description: Infections and infestations - Other, specify		
alternative assessment type: Non-systematic			
subjects affected / exposed	8 / 68 (11.76%)	6 / 68 (8.82%)	
occurrences (all)	8	9	
Lip infection	Additional description: Lip infection		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	2	
Lung infection	Additional description: Lung infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	3 / 68 (4.41%)	
occurrences (all)	0	3	
Mucosal infection	Additional description: Mucosal infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Nail infection	Additional description: Nail infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	2 / 68 (2.94%)	
occurrences (all)	1	2	
Papulopustular rash	Additional description: Papulopustular rash		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Paronychia	Additional description: Paronychia		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	5	
Sinusitis	Additional description: Sinusitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 68 (2.94%)	1 / 68 (1.47%)	
occurrences (all)	2	2	
Skin infection	Additional description: Skin infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 68 (5.88%)	2 / 68 (2.94%)	
occurrences (all)	4	5	
Tooth infection	Additional description: Tooth infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	2 / 68 (2.94%)	
occurrences (all)	0	2	

Upper respiratory infection alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Upper respiratory infection		
	3 / 68 (4.41%)	3 / 68 (4.41%)	
	13	10	
Urinary tract infection alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Urinary tract infection		
	9 / 68 (13.24%)	10 / 68 (14.71%)	
	12	14	
Vaginal infection alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Vaginal infection		
	1 / 68 (1.47%)	1 / 68 (1.47%)	
	1	2	
Metabolism and nutrition disorders			
	Additional description: Anorexia		
	25 / 68 (36.76%)	19 / 68 (27.94%)	
	42	37	
	Additional description: Hyperglycemia		
	3 / 68 (4.41%)	1 / 68 (1.47%)	
	4	1	
	Additional description: Hypertriglyceridemia		
	1 / 68 (1.47%)	0 / 68 (0.00%)	
	1	0	
	Additional description: Hypoalbuminemia		
	2 / 68 (2.94%)	0 / 68 (0.00%)	
	2	0	
	Additional description: Hypoglycemia		
	1 / 68 (1.47%)	1 / 68 (1.47%)	
	1	2	
	Additional description: Hypomagnesemia		

subjects affected / exposed	7 / 68 (10.29%)	3 / 68 (4.41%)	
occurrences (all)	13	4	
Hyponatremia	Additional description: Hyponatremia		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 June 2016	<p>Protocol Version 4</p> <ul style="list-style-type: none">- exclusion criteria 6, to include the exception for tumour biopsies- exclusion criteria 8, removal of the exception for patients on 1mg daily warfarin for the prevention of hickman line clotting- Removal of requirements for patients to fast prior to taking study drug- Dose modification tables (2 and 4) for paclitaxel updated re AST/ALT to allow for patients with liver metastases- Translational section updated to collect a baseline research blood sample <p>Appendix 1:</p> <ul style="list-style-type: none">- Exclusion Criteria 2 updated re excluded medications- Exclusion Criteria 10 reworded- Section 3.4 title updated to inclusion patients continuing novel agent/placebo.- ECG has also been given a one week window either side.- Section 4.3 Concomitant Therapy updated.- Removal of requirements for patients to fast prior to taking study drug- Inconsistencies between Schedule of assessments and visits corrected <p>Safety sections - various updates throughout</p> <p>Appendix 3 updated to include guidance on CA125 response in patients with measurable disease</p> <p>Appendix 5 updated based on new clinical guidance from AstraZeneca</p> <p>Appendix 6 added (Potent/Moderate PGP and BRCP Transported Enzyme Inhibitors/Inducers</p> <p>Appendix 7 (previously Appendix 6) updated based on new clinical guidance from AstraZeneca</p> <p>Appendix 7 from original version of the protocol (Drugs that may prolong QT interval) removed</p> <p>Appendix 9 Correct version of EQ-5D added</p>
11 October 2016	<p>Protocol Version 4.1</p> <p>Correction to a typo in the inclusion criteria which was part of the changes made at Amendment No 1.</p> <p>Appendix 1 Inclusion Criteria No 2</p> <p>PT/INR \leq 1.5 ULN and PTT (aPTT) \leq 1.5 x ULN</p>

08 August 2017	<p>Protocol Version 5</p> <p>Changes to membership of the Trial Management Group</p> <p>Exclusion Criteria No 9 updated re use of haemopoietic growth factors to add that long-term erythropoietic treatment is excepted</p> <p>Exclusion Criteria No 15 added - patients cannot start treatment as an inpatient</p> <p>Clarification throughout regarding minimum number of cycles of combination treatment before patient can start on continuous maintenance and maintenance being documented separately so that this is clear</p> <p>Clarification throughout that CT scan is to be within 28 days of randomisation</p> <p>Clarification re paclitaxel delays/omissions and chemotherapy holidays</p> <p>Clarification on the use of GCSF</p> <p>PV updated to state that SAEs will be reported from consent</p> <p>Section 11.3 Record Retention and Archiving reworded</p> <p>Removal of reference to ICH GCP</p> <p>Consent section updated so that sites can follow their own practice</p> <p>Appendix 1 4.3 Concomitant meds updated to list acceptable treatments for UTIs and also Section 4.4 addition to Prohibited Therapy of St John's Wort and Cannabis Oil</p> <p>Appendix I updated to Section 4.5 interactions with other medicines to use with caution medications that prolong the QTc interval</p> <p>Appendix 1 Section 4.6 - Dose Delays - updated to mirror the main protocol for ease of reference</p> <p>Appendix 1 - Sections 4.7 Dose Modifications updated extensively in line with new IB.</p> <p>Appendices 5-7 updated to add/remove drugs as per updated IB</p>
18 July 2018	<p>Protocol Version 5.1</p> <p>Change to Sponsor Contact name and contact details</p>
24 March 2022	<p>2 Protocol Version 6</p> <p>Extension of study end date until 31/Dec/2026 and update to End of Trial Definition</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/36928279>