Clinical trial results:
Evaluation of the safety of CEdiranib in the prevention of Bowel perforation in platinum-resistant Ovarian Cancer

Summary

EudraCT number	2016-004618-93
Trial protocol	GB
Global end of trial date	23 July 2024

Results information

Result version number	v1 (current)
This version publication date	20 March 2025
First version publication date	20 March 2025
Summary attachment (see zip file)	CEBOC (Once_daily_cediranib_and_weekl.pdf)

Trial information

Trial identification

Sponsor protocol code	R120502

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1200-5948

Notes:

Sponsors

Sponsor organisation name	University of Manchester
Sponsor organisation address	Oxford Road, Manchester, United Kingdom, M13 9PL
Public contact	CEBOC Trial Manager, Cancer Division Centre for Trials Research Cardiff, +44 02920687465, CEBOC@cardiff.ac.uk
Scientific contact	CEBOC Trial Manager, Cancer Division Centre for Trials Research Cardiff, +44 02920687465, CEBOC@cardiff.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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 June 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 May 2022
Global end of trial reached?	Yes
Global end of trial date	23 July 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The trial is trying to find out if it is safe to treat women who have advanced ovarian cancer and are at risk of developing malignant bowel obstruction (bowel blockage due to advanced cancer) with a weekly dose of standard chemotherapy (paclitaxel) plus a new oral tablet medication (cediranib).

Protection of trial subjects:

The trial would stop if:
- More than 1 patient experienced an event (bowel perforation/ fistula) in stage 1

OR:
- Three (03) or more participants experienced an event at any point in the trial

The trial may also be terminated for other safety reasons if recommended by the IDMC and agreed by the TSC.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable (single-arm)

Actual start date of recruitment	27 November 2017
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: 30
Worldwide total number of subjects	30
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)	17
From 65 to 84 years	12
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Recruited started March 2018 and ended February 2021

Pre-assignment

Screening details:

Prior to paclitaxel/nab-paclitaxel and cediranib: Histologically confirmed, progressive, platinum-resistant or refractory, high-grade ovarian, fallopian tube or primary peritoneal cancer for which weekly paclitaxel or nab-paclitaxel would be a potential treatment option. Prior to cediranib and olaparib Radiological evidence of PD

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Arm title	Paclitaxel +/- cediranib

Arm description:

This is a single arm, phase II trial of cediranib 20mg/day with weekly paclitaxel 70mg/m2/week in patients with recurrent platinum-resistant ovarian cancer and clinical and/or radiological features indicating an increased risk of developing subacute bowel obstruction. At the point of developing progressive disease (PD), participants cease paclitaxel and have the option of continuing cediranib 20mg/day with olaparib 300mg bd twice daily continuously until further PD occurs.

Arm type	Single arm
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Paclitaxel will be administered at a dose of 70mg/m2 on days 1, 8 and 15 of a 21-day cycle for a maximum of 6 cycles.

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

Dosage and administration details:

20 mg daily. Maintenance cediranib will start up to 9 weeks after cycle 1 day 1 of weekly paclitaxel. Cediranib can be initiated when bowel symptoms have abated to grade 1 or less or the risk to the patient’s bowel has been minimised. Participants will be given one bottle containing 35 tablets. Further cediranib may be dispensed mid-cycle if necessary, to manage dose reductions. Within each bottle all tablets will be the same strength (either 20 mg or 15 mg).

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

Dosage and administration details:

The olaparib trial treatment will be dispensed to patients for a dose of 300 mg twice daily equivalent to a total daily dose of 600 mg which is equivalent to the 400 mg capsules twice daily dose16. The 100 mg and 150 mg tablets will be used to manage dose reductions. On the first day of each 21-day cycle, participants will be given three bottles each containing 32 tablets. Further olaparib may be dispensed mid-cycle if necessary, to manage dose reductions. Within each bottle all tablets will be the same strength (either 100 mg or 150 mg).

Number of subjects in period 1	Paclitaxel +/- cediranib
Started	30
Completed	30

Period 2

Period 2 title	Cediranib treatment
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Paclitaxel +/- cediranib

Arm description:

This is a single arm, phase II trial of cediranib 20mg/day with weekly paclitaxel 70mg/m2/week in patients with recurrent platinum-resistant ovarian cancer and clinical and/or radiological features indicating an increased risk of developing subacute bowel obstruction. At the point of developing progressive disease (PD), participants cease paclitaxel and have the option of continuing cediranib 20mg/day with olaparib 300mg bd twice daily continuously until further PD occurs.

Arm type	Single arm
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Paclitaxel will be administered at a dose of 70mg/m2 on days 1, 8 and 15 of a 21-day cycle for a maximum of 6 cycles.

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

Dosage and administration details:

20 mg daily. Maintenance cediranib will start up to 9 weeks after cycle 1 day 1 of weekly paclitaxel. Cediranib can be initiated when bowel symptoms have abated to grade 1 or less or the risk to the patient’s bowel has been minimised. Participants will be given one bottle containing 35 tablets. Further cediranib may be dispensed mid-cycle if necessary, to manage dose reductions. Within each bottle all

tablets will be the same strength (either 20 mg or 15 mg).

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

Dosage and administration details:

The olaparib trial treatment will be dispensed to patients for a dose of 300 mg twice daily equivalent to a total daily dose of 600 mg which is equivalent to the 400 mg capsules twice daily dose16. The 100 mg and 150 mg tablets will be used to manage dose reductions. On the first day of each 21-day cycle, participants will be given three bottles each containing 32 tablets. Further olaparib may be dispensed mid-cycle if necessary, to manage dose reductions. Within each bottle all tablets will be the same strength (either 100 mg or 150 mg).

Number of subjects in period 2	Paclitaxel +/- cediranib
Started	30
Completed	30

Baseline characteristics

Reporting groups	
Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	30	30	
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)	17	17	
From 65-84 years	12	12	
85 years and over	1	1	
Gender categorical Units: Subjects			
Female	30	30	
Male	0	0	
Missing	0	0	
Histopathological diagnosis Units: Subjects			
Ovarian	21	21	
Primary peritoneal	3	3	
Fallopian tube	5	5	
Ovarian and primary peritoneal	1	1	
Histological ovarian subtype Units: Subjects			
High grade serous	28	28	
Carcinosarcoma	1	1	
High grade serous and carcinosarcoma	1	1	
FIGO stage at diagnosis Units: Subjects			
Stage 1A	1	1	
Stage 1 C2	1	1	
Stage 2A	1	1	
Stage 2B	1	1	
Stage 3B	3	3	
Stage 3C	17	17	
Stage 4A	2	2	
Stage 4B	4	4	
Symptoms of bowel obstruction risk Units: Subjects			

Yes	29	29	
No	1	1	
Prior first-line platinum based chemotherapy Units: Subjects			
Yes	30	30	
No	0	0	
Received prior radiotherapy Units: Subjects			
Yes	1	1	
No	29	29	
Prior surgery Units: Subjects			
Yes	28	28	
No	2	2	
Residual disease left Units: Subjects			
>10mm	10	10	
<10mm	18	18	
Missing	2	2	
Received anti-cancer treatment in first line setting Units: Subjects			
Yes	30	30	
No	0	0	
If yes, number of lines Units: Subjects			
One	5	5	
Two	6	6	
Three	8	8	
Four	7	7	
Five	2	2	
Six	2	2	
ECOG status Units: Subjects			
Zero	12	12	
One	15	15	
Two	3	3	
Three	0	0	
Prior first line platinum based chemotherapy number of cycles Units: Number of cycles			
median	6		
inter-quartile range (Q1-Q3)	6 to 6	-	
Total dose of prior radiotherapy Units: gray			
median	20.0		
inter-quartile range (Q1-Q3)	20.0 to 20.0	-	
Total fractions of radiotherapy Units: Fractions			
median	5		
inter-quartile range (Q1-Q3)	5 to 5	-	

End points

End points reporting groups

Reporting group title	Paclitaxel +/- cediranib

Reporting group description:

This is a single arm, phase II trial of cediranib 20mg/day with weekly paclitaxel 70mg/m2/week in patients with recurrent platinum-resistant ovarian cancer and clinical and/or radiological features indicating an increased risk of developing subacute bowel obstruction. At the point of developing progressive disease (PD), participants cease paclitaxel and have the option of continuing cediranib 20mg/day with olaparib 300mg bd twice daily continuously until further PD occurs.

Reporting group title	Paclitaxel +/- cediranib

Reporting group description:

This is a single arm, phase II trial of cediranib 20mg/day with weekly paclitaxel 70mg/m2/week in patients with recurrent platinum-resistant ovarian cancer and clinical and/or radiological features indicating an increased risk of developing subacute bowel obstruction. At the point of developing progressive disease (PD), participants cease paclitaxel and have the option of continuing cediranib 20mg/day with olaparib 300mg bd twice daily continuously until further PD occurs.

Primary: Grade III-V gastrointestinal perforation or fistula

End point title	Grade III-V gastrointestinal perforation or fistula[1]

End point description:

End point type	Primary

End point timeframe:

During treatment with cediranib

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: The primary endpoint was summarised as the proportion of patients with objective response with an exact 95% confidence interval in the ITT population. No statistical test was performed as this was primarily a safety trial.

End point values	Paclitaxel +/- cediranib			
Subject group type	Reporting group			
Number of subjects analysed	17[2]			
Units: Subjects				
Yes	0			
No	17			

Notes:

[2] - 17 patients started treatment with cediranib. Two started in cycle 1 and the rest following paclitax

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During treatment

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	Paclitaxel + cediranib

Reporting group description:

This is a single arm, phase II trial of cediranib 20mg/day with weekly paclitaxel 70mg/m2/week in patients with recurrent platinum-resistant ovarian cancer and clinical and/or radiological features indicating an increased risk of developing subacute bowel obstruction. At the point of developing progressive disease (PD), participants cease paclitaxel and have the option of continuing cediranib 20mg/day with olaparib 300mg bd twice daily continuously until further PD occurs.

Reporting group title	Olaparib+cediranib

Reporting group description: -

Reporting group title	Paclitaxel only

Reporting group description: -

Serious adverse events	Paclitaxel + cediranib	Olaparib+cediranib	Paclitaxel only
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 17 (35.29%)	1 / 5 (20.00%)	5 / 12 (41.67%)
number of deaths (all causes)	7	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Hypocalcaemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Transient ischaemic attack			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			

subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	0 / 17 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 17 (5.88%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	2 / 17 (11.76%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain lower			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucosal inflammation			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Groin pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal infection			
subjects affected / exposed	2 / 17 (11.76%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 17 (11.76%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0.05 %

Non-serious adverse events	Paclitaxel + cediranib	Olaparib+cediranib	Paclitaxel only
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 17 (100.00%)	4 / 5 (80.00%)	12 / 12 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 17 (47.06%)	1 / 5 (20.00%)	3 / 12 (25.00%)
occurrences (all)	27	1	4
Thromboembolic event			

subjects affected / exposed	3 / 17 (17.65%)	0 / 5 (0.00%)	2 / 12 (16.67%)
occurrences (all)	4	0	3
Hot flush			
subjects affected / exposed	0 / 17 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Transient ischaemic attack			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Surgical and medical procedures			
Reaction to paclitaxel			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	15 / 17 (88.24%)	2 / 5 (40.00%)	8 / 12 (66.67%)
occurrences (all)	65	12	16
Oedema peripheral			
subjects affected / exposed	0 / 17 (0.00%)	1 / 5 (20.00%)	3 / 12 (25.00%)
occurrences (all)	0	1	4
Pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Peripheral swelling			
subjects affected / exposed	0 / 17 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Pyrexia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	3
Immune system disorders			
Allergic reaction			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	2 / 12 (16.67%)
occurrences (all)	1	0	2
Anaphylaxis			
subjects affected / exposed	3 / 17 (17.65%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	3	0	1
Hypersensitivity			

subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Vulvovaginal dryness			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 17 (41.18%)	2 / 5 (40.00%)	0 / 12 (0.00%)
occurrences (all)	17	4	0
Dyspnoea			
subjects affected / exposed	5 / 17 (29.41%)	1 / 5 (20.00%)	1 / 12 (8.33%)
occurrences (all)	16	9	3
Hoarseness			
subjects affected / exposed	4 / 17 (23.53%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	4	0	0
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	2 / 17 (11.76%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Bronchitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Dysphonia			
subjects affected / exposed	2 / 17 (11.76%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	7	0	0
Epistaxis			
subjects affected / exposed	3 / 17 (17.65%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	5	0	1
Nasal congestion			
subjects affected / exposed	2 / 17 (11.76%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	7	0	0
Oropharyngeal pain			

subjects affected / exposed	2 / 17 (11.76%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Rhinitis allergic			
subjects affected / exposed	0 / 17 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Upper-airway cough syndrome			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	3	0	0
Psychiatric disorders			
Hallucination			
subjects affected / exposed	0 / 17 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	3
Insomnia			
subjects affected / exposed	4 / 17 (23.53%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	18	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	8 / 17 (47.06%)	3 / 5 (60.00%)	4 / 12 (33.33%)
occurrences (all)	24	10	4
Alkaline phosphatase increased			
subjects affected / exposed	6 / 17 (35.29%)	0 / 5 (0.00%)	4 / 12 (33.33%)
occurrences (all)	19	0	7
Blood bilirubin increased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 5 (20.00%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Creatinine urine increased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	4	0	0
ECG QTc prolonged			
subjects affected / exposed	0 / 17 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Neutrophil count decreased			
subjects affected / exposed	8 / 17 (47.06%)	1 / 5 (20.00%)	4 / 12 (33.33%)
occurrences (all)	13	5	5
Platelet count decreased			

subjects affected / exposed	0 / 17 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Blood folate decreased			
subjects affected / exposed	2 / 17 (11.76%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	9	0	0
Blood iron decreased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	5	0	0
Blood magnesium decreased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	6	0	1
Weight decreased			
subjects affected / exposed	2 / 17 (11.76%)	1 / 5 (20.00%)	1 / 12 (8.33%)
occurrences (all)	2	3	1
Weight increased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	4	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 17 (5.88%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	1	2	0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	2 / 17 (11.76%)	2 / 5 (40.00%)	0 / 12 (0.00%)
occurrences (all)	6	5	0
Palpitations			
subjects affected / exposed	0 / 17 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	9	0
Sinus bradycardia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 17 (17.65%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	9	4	0
Dysgeusia			

subjects affected / exposed	4 / 17 (23.53%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	11	1	0
Headache			
subjects affected / exposed	6 / 17 (35.29%)	2 / 5 (40.00%)	1 / 12 (8.33%)
occurrences (all)	8	5	1
Ischemia cerebrovascular			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Peripheral motor neuropathy			
subjects affected / exposed	3 / 17 (17.65%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	6	0	0
Peripheral sensory neuropathy			
subjects affected / exposed	13 / 17 (76.47%)	3 / 5 (60.00%)	2 / 12 (16.67%)
occurrences (all)	88	18	4
Reversible posterior leukoencephalopathy syndrome			
subjects affected / exposed	0 / 17 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Amnesia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Anxiety			
subjects affected / exposed	2 / 17 (11.76%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	12	3	0
Depressed mood			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Depression			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	5	0	0
Lethargy			
subjects affected / exposed	3 / 17 (17.65%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	6	0	0
Restless legs syndrome			
subjects affected / exposed	0 / 17 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	3

Seizure			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Tremor			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 17 (52.94%)	1 / 5 (20.00%)	9 / 12 (75.00%)
occurrences (all)	40	8	17
Febrile neutropenia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Vertigo			
subjects affected / exposed	0 / 17 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	9	0
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Lacrimation increased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	5	0	0
Vision blurred			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	11 / 17 (64.71%)	2 / 5 (40.00%)	8 / 12 (66.67%)
occurrences (all)	30	4	13
Diarrhoea			
subjects affected / exposed	16 / 17 (94.12%)	4 / 5 (80.00%)	5 / 12 (41.67%)
occurrences (all)	127	17	9

Dyspepsia			
subjects affected / exposed	3 / 17 (17.65%)	1 / 5 (20.00%)	4 / 12 (33.33%)
occurrences (all)	6	2	8
Infectious colitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Mucositis oral			
subjects affected / exposed	8 / 17 (47.06%)	1 / 5 (20.00%)	1 / 12 (8.33%)
occurrences (all)	18	1	1
Nausea			
subjects affected / exposed	14 / 17 (82.35%)	3 / 5 (60.00%)	9 / 12 (75.00%)
occurrences (all)	47	13	14
Vomiting			
subjects affected / exposed	9 / 17 (52.94%)	2 / 5 (40.00%)	6 / 12 (50.00%)
occurrences (all)	19	6	6
Other non-infectious GE or colitis			
subjects affected / exposed	2 / 17 (11.76%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Abdominal distension			
subjects affected / exposed	5 / 17 (29.41%)	2 / 5 (40.00%)	3 / 12 (25.00%)
occurrences (all)	15	6	5
Abdominal mass			
subjects affected / exposed	2 / 17 (11.76%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	2	0	1
Abdominal pain upper			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Angular cheilitis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Ascites			
subjects affected / exposed	2 / 17 (11.76%)	0 / 5 (0.00%)	3 / 12 (25.00%)
occurrences (all)	4	0	6
Dry mouth			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	6	0	0

Abdominal pain			
subjects affected / exposed	13 / 17 (76.47%)	3 / 5 (60.00%)	10 / 12 (83.33%)
occurrences (all)	82	14	20
Abdominal infection			
subjects affected / exposed	0 / 17 (0.00%)	0 / 5 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	4
Bile duct stenosis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Gastrointestinal sounds abnormal			
subjects affected / exposed	11 / 17 (64.71%)	1 / 5 (20.00%)	4 / 12 (33.33%)
occurrences (all)	42	1	8
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	7	0	3
Gingivitis			
subjects affected / exposed	2 / 17 (11.76%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	5	0	0
Intestinal obstruction			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Large intestinal obstruction			
subjects affected / exposed	0 / 17 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Oral candidiasis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Oral pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Proctalgia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Small intestinal obstruction			
subjects affected / exposed	0 / 17 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1

Hepatobiliary disorders			
Perihepatic discomfort			
subjects affected / exposed	0 / 17 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	9 / 17 (52.94%)	1 / 5 (20.00%)	5 / 12 (41.67%)
occurrences (all)	45	1	7
Contusion			
subjects affected / exposed	0 / 17 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Dry skin			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Hyperhidrosis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	4	0	1
Hyperkeratosis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	6	0	0
Laceration			
subjects affected / exposed	1 / 17 (5.88%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	3	2	0
Nail discolouration			
subjects affected / exposed	3 / 17 (17.65%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	8	1	0
Nail disorder			
subjects affected / exposed	4 / 17 (23.53%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	26	1	0
Onychomadesis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	2 / 17 (11.76%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	4	0	0
Rash			

subjects affected / exposed	5 / 17 (29.41%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	16	0	0
Rash maculo-papular			
subjects affected / exposed	2 / 17 (11.76%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	3	0	0
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	2 / 17 (11.76%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Bladder pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Renal colic			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	2 / 17 (11.76%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Hypothyroidism			
subjects affected / exposed	2 / 17 (11.76%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	5	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 17 (29.41%)	1 / 5 (20.00%)	1 / 12 (8.33%)
occurrences (all)	20	1	1
Back pain			
subjects affected / exposed	5 / 17 (29.41%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	22	0	1
Groin pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Muscle spasms			
subjects affected / exposed	1 / 17 (5.88%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	1	12	0
Myalgia			

subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	2 / 17 (11.76%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	7	0	0
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	9 / 17 (52.94%)	1 / 5 (20.00%)	1 / 12 (8.33%)
occurrences (all)	21	2	2
COVID-19			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Fungal infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Herpes zoster			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Lower respiratory tract infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Lung infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Oral herpes			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Pelvic infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0

Tinea infections			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Tooth abscess			
subjects affected / exposed	2 / 17 (11.76%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Viral infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Wound infection			
subjects affected / exposed	1 / 17 (5.88%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	1	2	0
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	7 / 17 (41.18%)	2 / 5 (40.00%)	4 / 12 (33.33%)
occurrences (all)	64	15	9
Dehydration			
subjects affected / exposed	2 / 17 (11.76%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	6	0	2
Decreased appetite			
subjects affected / exposed	0 / 17 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Folate deficiency			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Hypercalcaemia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Hyperkalaemia			
subjects affected / exposed	0 / 17 (0.00%)	2 / 5 (40.00%)	0 / 12 (0.00%)
occurrences (all)	0	6	0
Hypocalcaemia			

subjects affected / exposed	1 / 17 (5.88%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Hypokalaemia			
subjects affected / exposed	1 / 17 (5.88%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Hypomagnesaemia			
subjects affected / exposed	4 / 17 (23.53%)	1 / 5 (20.00%)	1 / 12 (8.33%)
occurrences (all)	15	3	1
Iron deficiency			
subjects affected / exposed	1 / 17 (5.88%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	5	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported