Clinical trial results:
A randomised phase II trial of Olaparib maintenance versus placebo monotherapy in patients with non-small cell lung cancer

Summary

EudraCT number	2012-003383-51
Trial protocol	GB
Global end of trial date	05 April 2019

Results information

Result version number	v1 (current)
This version publication date	02 March 2020
First version publication date	02 March 2020
Summary attachment (see zip file)	Final statistical analysis report (PIN final analysis report version 1 FINAL dated 14022020.docx)

Trial information

Trial identification

Sponsor protocol code	2012/VCC/0037

Additional study identifiers

ISRCTN number	ISRCTN42518913
ClinicalTrials.gov id (NCT number)	NCT01788332
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Velindre NHS Trust
Sponsor organisation address	Unit 2 Charnwood Court Heol Billingsley, , Parc Nantgarw, Cardiff , United Kingdom, CF15 7QZ
Public contact	Georgina Gardner, Centre for Trials Research, 0044 2920687581, pin@cardiff.ac.uk
Scientific contact	Angela Casbard, Centre for Trials Research, 0044 2920687470, CasbardAC@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	10 February 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 February 2019
Global end of trial reached?	Yes
Global end of trial date	05 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial is to establish whether treatment with Olaparib in NSCLC patients who have already responded to induction chemotherapy delays disease progression compared to placebo.

Protection of trial subjects:

NA

Background therapy:

NA

Evidence for comparator:

Placebo

Actual start date of recruitment	22 July 2013
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: 70
Worldwide total number of subjects	70
EEA total number of subjects	70

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)	38
From 65 to 84 years	32
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

70 patients were randomised from 23 UK centres between August 2014 and November 2017.

Pre-assignment

Screening details:

Screening criteria are listed in the protocol Section 6.2. 264 were assessed for eligibility for randomisation. 139 were not eligible and 55 were eligible but not randomised.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo

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

Dosage and administration details:

300mg bd administered and reviewed in 21-day cycles until disease progression, unacceptable toxicity or patient withdrawal of consent.

Arm title	Olaparib

Arm description:

Olaparib
300mg po bd q21 until disease progression

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

Dosage and administration details:

300mg bd administered and reviewed in 21-day cycles until disease progression, unacceptable toxicity or patient withdrawal of consent.

Number of subjects in period 1	Placebo	Olaparib
Started	38	32
Completed	38	32

Period 2	
Period 2 title	Treatment and follow up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo

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

Dosage and administration details:

300mg bd administered and reviewed in 21-day cycles until disease progression, unacceptable toxicity or patient withdrawal of consent.

Arm title	Olaparib

Arm description:

Olaparib
300mg po bd q21 until disease progression

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

Dosage and administration details:

300mg bd administered and reviewed in 21-day cycles until disease progression, unacceptable toxicity or patient withdrawal of consent.

Number of subjects in period 2	Placebo	Olaparib
Started	38	32
Completed	38	31
Not completed	0	1
Found to be ineligible	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: Placebo	
Reporting group title	Olaparib
Reporting group description: Olaparib 300mg po bd q21 until disease progression	

Reporting group values	Placebo	Olaparib	Total
Number of subjects	38	32	70
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	63.3	64.7	
inter-quartile range (Q1-Q3)	58.6 to 69.9	60.5 to 71.5	-
Gender categorical Units: Subjects			
Female	14	16	30
Male	24	16	40
Non-small cell lung cancer type Units: Subjects			
Adenocarcinoma	18	19	37
Squamous	18	13	31
Large cell nos	1	0	1
Mixed adenocarcinoma/Squamous	1	0	1
T stage Units: Subjects			
T1	2	3	5
T2	3	6	9
T3	6	10	16
T4	23	12	35
TX	3	0	3
Missing	1	1	2
N stage			

Units: Subjects			
N0	2	6	8
N1	3	1	4
N2	16	9	25
N3	15	13	28
NX	1	2	3
Missing	1	1	2
M stage Units: Subjects			
M0	10	10	20
M1a	15	10	25
M1b	13	11	24
Missing	0	1	1
Stage of NSCLC Units: Subjects			
IIIB	13	10	23
IV	25	22	47
Sites affected Units: Subjects			
Adrenal gland	0	1	1
Bone metastases	4	2	6
Brain metastases	1	0	1
Chest wall; lung metastases	0	1	1
Chest wall; Mediastinum	1	0	1
Chest wall; Trachea	0	1	1
Chest wall; Trachea; Lung metastases	1	0	1
Heart pericardium; Bone metastases; Brain metastas	0	1	1
Heart pericardium; Lung metastases	1	0	1
Ipsilateral hilar, Mediastinal and supraclavicular	0	1	1
Left hilar region	1	0	1
Left lower lobe of bronchus	1	0	1
Liver metastases; Adrenal gland	1	1	2
Liver metastases; Bone metastases	1	2	3
Liver metastases; Lung metastases	1	0	1
Lung metastases	7	2	9
Lung metastases; Adrenal gland; Mediastinum	0	1	1
Lung metastases; Mediastinum	0	1	1
Lung metastases; Primary Mass	0	1	1
Lung metastases; Retroperitoneal	1	0	1
Lung metastases; side neck nodes	1	0	1
Lung metastases; sub aortic lymph node; para aorti	1	0	1
Lung; lymph node	1	0	1
Lymph nodes	1	0	1
None	2	5	7
Oesophagus; Pleura; Liver metastases	0	1	1
Oesophagus; Trachea	1	0	1
Pericardial effusion	1	0	1

Pleura	0	1	1
Pleura; Bone metastases	1	0	1
Pleura; Heart pericardium; Pulmonary Artery; Right	1	0	1
Pleura; Liver metastases; Lung metastases; Bone me	0	1	1
Pleura; Lung metastases	1	2	3
Pleura; Lymph node	0	1	1
Pleura; Regional nodes; Distant nodes.	0	1	1
Right upper lobe	3	1	4
Rib	0	1	1
RIGHT HILAR LESION	0	1	1
Right Neck Lymph Nodes	1	0	1
Right upper lobe; mediastinal lymphadenopathy	0	1	1
Spleen	1	0	1
Trachea; Adrenal gland	1	0	1
Trachea; Lung metastases; right hilar	0	1	1
Type of induction chemotherapy Units: Subjects			
Carboplatin	1	0	1
Carboplatin; Vinorelbine	3	1	4
Cisplatin	0	1	1
Cisplatin; Carboplatin	1	0	1
Cisplatin; Pemetrexed	5	4	9
Cisplatin; Vinorelbine	1	1	2
Gemcitabine	2	3	5
Gemcitabine; Carboplatin	11	6	17
Gemcitabine; Docetaxel	1	0	1
Gemcitabine; Pemetrexed	0	1	1
Not known	1	3	4
Paclitaxel	0	1	1
Pemetrexed	5	3	8
Pemetrexed; Carboplatin	7	8	15
Response to induction chemotherapy Units: Subjects			
Complete response	1	2	3
Partial response	34	28	62
Other evidence of tumour shrinkage/Mixed stable	3	2	5
Smoking history Units: Subjects			
Never smoked	3	3	6
Ever smoked	35	29	64
ECOG status Units: Subjects			
Zero	13	9	22
One	25	23	48
Site of target tumour Units: Subjects			
Anterior mediastinal mass; Left anterior lung mass	0	1	1

Aortopulmonary soft tissue mass; Splenic lesion	1	0	1
Apical segment, posteriorly right lower lobe; righ	0	1	1
Central left lung mass; paracardiac chest wall mas	1	0	1
Left Adrenal; Left Hilum	0	1	1
Left basal; Liver mets	1	0	1
Left hilar mass	2	1	3
Left hilar; left upper lobe mass	1	0	1
Left lower lobe	0	1	1
Left lung	1	2	3
Left lung; liver	1	1	2
LEFT PERIHILAR LUNG LESION; SUBCARINAL LYMPH NODE	1	0	1
LEFT PERIHILAR MASS; RIGHT UPPER LOBE LESION	1	0	1
Left posterior lower zone; Left anterior upper zon	1	0	1
Left supraclavicular region; right lung base	0	1	1
Left upper lobe	4	2	6
Left upper lobe; Apical left lower lobe metastases	1	0	1
Left upper lobe; Apical right lower lobe	0	1	1
Left upper lobe; left hilar	1	1	2
Left upper lobe; liver	0	1	1
Left upper lobe; right hilar	1	0	1
Low right paratrachael / precarninal node; Subcari	1	0	1
Mediastinal mass	1	0	1
Not known	2	2	4
Pleural deposit adjacent to aortic arch; Pleural d	1	0	1
POSTERIOR RIGHT PERIHILAR LUNG LESION; ANTERIOR RI	0	1	1
Right apical lower lobe; Left upper lobe mass	0	1	1
RIGHT HILAR ANTERIOR; RIGHT HILAR POSTERIOR	0	1	1
RIGHT HILAR LESION; RIGHT UPPER POLE RENAL LESION	0	1	1
Right Hilar Mass; Pretracheal	1	0	1
Right hilar mass; right adrenal mass	1	0	1
Right lower lobe	1	3	4
RIGHT LOWER LOBE CAVITY; CONGLOMERATE OF MEDIASTIN	1	0	1
Right paratracheal lymph node	0	1	1
Right peri hilar mass	1	0	1
Right upper lobe	6	3	9
RIGHT UPPER LOBE LUNG LESION; RIGHT OBLIQUE FISSUR	0	1	1
Right upper lobe; left adrenal gland	0	1	1
Right upper lobe; Right lower paratracheal lymph n	1	0	1

Rt Paratrachael LN; Right upper lobe	0	1	1
SEGMENT 5; INFERIOR TIP	0	1	1
Soft tissue anterior; subcarinal node	1	0	1
Sub pleural left lung lesion	0	1	1
Subcarinal node	1	0	1
Sub-carinal node; Right hilar node	1	0	1
Number of cycles of induction chemotherapy			
Units: Number			
median	4	4	
inter-quartile range (Q1-Q3)	4 to 4	4 to 4	-
Systolic blood pressure			
Units: mmHg			
median	132	133	
inter-quartile range (Q1-Q3)	124 to 146	123.5 to 150	-
Diastolic blood pressure			
Units: mmHg			
median	76.5	73.5	
inter-quartile range (Q1-Q3)	73.0 to 87.0	69.5 to 86.5	-
Oxygen saturation			
Units: percentage			
median	97	97.5	
inter-quartile range (Q1-Q3)	96 to 98	97 to 98	-
Pulse			
Units: Bpm			
median	86.0	80.0	
inter-quartile range (Q1-Q3)	77.0 to 95.0	74.0 to 88.5	-
Weight			
Units: kg			
median	74.9	75.7	
inter-quartile range (Q1-Q3)	62.3 to 93.8	63.3 to 83.6	-
ECG Resting QTc			
Units: msec			
median	431.0	425.5	
inter-quartile range (Q1-Q3)	417.0 to 445.0	413.0 to 439.0	-
Longest diameter of tumours: Primary			
Units: mm			
median	39.5	29.5	
inter-quartile range (Q1-Q3)	24.0 to 55.5	15.0 to 40.0	-
Longest diameter of tumours: Lymph node			
Units: mm			
median	16.0	16.5	
inter-quartile range (Q1-Q3)	10.0 to 19.0	13.5 to 19.0	-
Longest diameter of tumours: Liver			
Units: mm			
median	26.0	14.0	
inter-quartile range (Q1-Q3)	26.0 to 26.0	14.0 to 14.0	-
Longest diameter of tumours: Adrenal glands			
Units: mm			

median	15.5	47.5	
inter-quartile range (Q1-Q3)	11.0 to 20.0	36.0 to 59.0	-
Longest diameter of tumours: Other			
Units: mm			
median	35.0	34.5	
inter-quartile range (Q1-Q3)	24.5 to 46.0	30.0 to 39.0	-
Target tumours: Sum of longest diameters			
Units: mm			
median	44.5	53.5	
inter-quartile range (Q1-Q3)	33.0 to 62.5	30.0 to 69.0	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo	
Reporting group title	Olaparib
Reporting group description:	
Olaparib 300mg po bd q21 until disease progression	

Reporting group title	Placebo
Reporting group description:	
Placebo	
Reporting group title	Olaparib
Reporting group description:	
Olaparib 300mg po bd q21 until disease progression	

Primary: Progression-free survival

End point title	Progression-free survival
End point description:	

End point type	Primary
End point timeframe:	
From date of randomisation to date of disease progression or death, whichever comes first	

End point values	Placebo	Olaparib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	32		
Units: weeks				
median (inter-quartile range (Q1-Q3))	12.0 (5.6 to 18.7)	16.6 (7.1 to 21.7)		

Statistical analyses

Statistical analysis title	PFS unadjusted
Statistical analysis description:	
Unadjusted analysis	
Comparison groups	Placebo v Olaparib

Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.23 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.6
upper limit	1.15

Notes:

[1] - Sample size calculation based on 80% power and a one-sided α (type I error) of 0.2. Result not statistically significant.

Statistical analysis title	PFS adjusted

Statistical analysis description:

Adjusted for smoking history and histology

Comparison groups	Placebo v Olaparib
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.11 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.52
upper limit	1.02

Notes:

[2] - Sample size calculation based on 80% power and a one-sided α (type I error) of 0.2. Result statistically significant.

Secondary: Overall survival

End point title	Overall survival

End point description:

End point type	Secondary

End point timeframe:

Measured from date of randomisation to date of death, with those still alive censored at date last seen.

End point values	Placebo	Olaparib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	32		
Units: weeks				
median (inter-quartile range (Q1-Q3))	31.3 (22.4 to 58.6)	59.4 (38.7 to 67.9)		

Statistical analyses

Statistical analysis title	Overall survival
Comparison groups	Placebo v Olaparib
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.22 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	1.26

Notes:

[3] - Two-sided p-value

Secondary: Objective response rate

End point title	Objective response rate

End point description:

End point type	Secondary

End point timeframe:

From date of randomisation to RECIST assessment at 6 weeks post randomisation (end of Cycle 2).

End point values	Placebo	Olaparib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	32		
Units: Subjects				
number (not applicable)				
Complete response	0	0		
Partial response	1	0		
Stable disease	22	20		
Progressive disease	12	7		
Not evaluable	0	1		
RECIST assessment not done	0	1		

Did not reach end of cycle 2 RECIST timepoint	3	3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline screening assessments to disease progression or death (whichever comes first) or if still alive and not progressed date data collection ended.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Olaparib

Reporting group description: -

Serious adverse events	Placebo	Olaparib	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 38 (26.32%)	9 / 31 (29.03%)	
number of deaths (all causes)	25	18	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pathological fracture imminent			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 38 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Pericardial effusion			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 38 (2.63%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
alternative dictionary used: MedDRA 19			

subjects affected / exposed	1 / 38 (2.63%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 38 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 38 (2.63%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 38 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dysphagia			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 38 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Device occlusion			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 38 (2.63%)	0 / 31 (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			
Dyspnea			
alternative dictionary used: MedDRA 19			

subjects affected / exposed	2 / 38 (5.26%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reaspiratory tract haemorrhage			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 38 (2.63%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicide attempt			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 38 (2.63%)	0 / 31 (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			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 38 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Lung infection			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	2 / 38 (5.26%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 38 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Olaparib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 38 (100.00%)	31 / 31 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	9 / 38 (23.68%)	3 / 31 (9.68%)	
occurrences (all)	18	15	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	2 / 38 (5.26%)	2 / 31 (6.45%)	
occurrences (all)	3	2	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 38 (15.79%)	6 / 31 (19.35%)	
occurrences (all)	6	8	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 38 (26.32%)	15 / 31 (48.39%)	
occurrences (all)	26	45	
Lymphopenia			
subjects affected / exposed	2 / 38 (5.26%)	2 / 31 (6.45%)	
occurrences (all)	2	7	
Neutropenia			
subjects affected / exposed	0 / 38 (0.00%)	4 / 31 (12.90%)	
occurrences (all)	0	6	
Thrombocytopenia			
subjects affected / exposed	1 / 38 (2.63%)	4 / 31 (12.90%)	
occurrences (all)	3	12	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	25 / 38 (65.79%)	29 / 31 (93.55%)	
occurrences (all)	66	50	
Oedema peripheral			
subjects affected / exposed	4 / 38 (10.53%)	3 / 31 (9.68%)	
occurrences (all)	6	8	
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	4 / 38 (10.53%)	4 / 31 (12.90%)	
occurrences (all)	7	9	
Diarrhoea			
subjects affected / exposed	7 / 38 (18.42%)	4 / 31 (12.90%)	
occurrences (all)	12	12	
Dry mouth			
subjects affected / exposed	4 / 38 (10.53%)	1 / 31 (3.23%)	
occurrences (all)	5	1	
Dyspepsia			
subjects affected / exposed	7 / 38 (18.42%)	3 / 31 (9.68%)	
occurrences (all)	13	4	
Flatulence			
subjects affected / exposed	5 / 38 (13.16%)	1 / 31 (3.23%)	
occurrences (all)	3	1	
Nausea			
subjects affected / exposed	11 / 38 (28.95%)	17 / 31 (54.84%)	
occurrences (all)	21	44	
Vomiting			
subjects affected / exposed	4 / 38 (10.53%)	7 / 31 (22.58%)	
occurrences (all)	5	17	
Respiratory, thoracic and mediastinal disorders			
Coughing			
subjects affected / exposed	22 / 38 (57.89%)	11 / 31 (35.48%)	
occurrences (all)	47	33	
Dyspnoea			
subjects affected / exposed	15 / 38 (39.47%)	13 / 31 (41.94%)	
occurrences (all)	35	28	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	2 / 38 (5.26%)	3 / 31 (9.68%)	
occurrences (all)	1	3	
Rash			
subjects affected / exposed	3 / 38 (7.89%)	4 / 31 (12.90%)	
occurrences (all)	3	10	
Pruritus			

subjects affected / exposed	2 / 38 (5.26%)	3 / 31 (9.68%)	
occurrences (all)	2	10	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	6 / 38 (15.79%)	2 / 31 (6.45%)	
occurrences (all)	8	9	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 38 (5.26%)	3 / 31 (9.68%)	
occurrences (all)	3	4	
Back pain			
subjects affected / exposed	8 / 38 (21.05%)	5 / 31 (16.13%)	
occurrences (all)	10	6	
Dizziness			
subjects affected / exposed	3 / 38 (7.89%)	6 / 31 (19.35%)	
occurrences (all)	3	6	
Infections and infestations			
Upper respiratory infection			
subjects affected / exposed	5 / 38 (13.16%)	4 / 31 (12.90%)	
occurrences (all)	9	7	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	12 / 38 (31.58%)	11 / 31 (35.48%)	
occurrences (all)	21	22	
Hyponatremia			
subjects affected / exposed	2 / 38 (5.26%)	3 / 31 (9.68%)	
occurrences (all)	3	3	

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