Clinical trial results:
An Open-Label, Single-Arm, Multicenter, Phase 2 Trial of Lenvatinib for the Treatment of Anaplastic Thyroid Cancer (ATC)

Summary

EudraCT number	2015-001929-17
Trial protocol	IT
Global end of trial date	26 September 2018

Results information

Result version number	v1 (current)
This version publication date	07 March 2020
First version publication date	07 March 2020

Trial information

Trial identification

Sponsor protocol code	E7080-M000-213

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02657369
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eisai Inc.
Sponsor organisation address	100 Tice Boulevard, Woodcliff Lake, New Jersey, United States, 07677
Public contact	Eisai Medical Information, Eisai Inc., +1 8882472378, esi_oncmedinfo@eisai.com
Scientific contact	Eisai Medical Information, Eisai Inc., +1 882472378, esi_oncmedinfo@eisai.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 September 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 September 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary purpose of the study is to evaluate objective response rate ([ORR]: complete response [CR] and partial response [PR]) by investigator review in subjects with ATC treated with lenvatinib.

Protection of trial subjects:

This study was conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following: - Principles of the World Medical Association Declaration of Helsinki (World Medical Association, 2008) - International Council on Harmonisation (ICH) E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use - Title 21 of the United States (US) Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and Institutional Review Board (IRB) regulations and applicable sections of US 21 CFR Part 312 - European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All suspected unexpected serious adverse reactions were reported, as required, to the Competent Authorities of all involved EU member states.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	07 July 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 23
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	United Kingdom: 2
Worldwide total number of subjects	34
EEA total number of subjects	10

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)	16
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 13 investigative sites in France, Italy, United Kingdom, Australia and the United States from 07 July 2016 to 26 September 2018.

Pre-assignment

Screening details:

A total of 48 subjects were screened, of which 14 were screen failures and 34 were enrolled to receive study treatment.

Period 1

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

Arms

Arm title	Lenvatinib 24 mg

Arm description:

Subjects received lenvatinib 24 milligram (mg) (two 10-mg capsules and one 4-mg capsule), orally, once daily in a 28-days treatment cycle up to disease progression, development of unacceptable toxicity, lost to follow up, withdrawal of consent, subject's choice, pregnancy, or study termination by sponsor (approximately 27 months).

Arm type	Experimental
Investigational medicinal product name	Lenvatinib
Investigational medicinal product code	
Other name	E7080, Lenvima
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Lenvatinib 24 mg (two 10-mg capsules and one 4-mg capsule), orally, once daily in a 28-days treatment cycle up to disease progression, development of unacceptable toxicity, lost to follow up, withdrawal of consent, subject's choice, pregnancy, or study termination by sponsor (approximately 27 months).

Number of subjects in period 1	Lenvatinib 24 mg
Started	34
Completed	0
Not completed	34
Death	27
Study terminated by sponsor	7

Baseline characteristics

Reporting groups	
Reporting group title	Lenvatinib 24 mg
Reporting group description:	
Subjects received lenvatinib 24 milligram (mg) (two 10-mg capsules and one 4-mg capsule), orally, once daily in a 28-days treatment cycle up to disease progression, development of unacceptable toxicity, lost to follow up, withdrawal of consent, subject's choice, pregnancy, or study termination by sponsor (approximately 27 months).	

Reporting group values	Lenvatinib 24 mg	Total	
Number of subjects	34	34	
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)	16	16	
From 65-84 years	18	18	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	65.4		
standard deviation	± 10.09	-	
Gender categorical Units: Subjects			
Female	21	21	
Male	13	13	
Ethnicity Units: Subjects			
Hispanic or Latino	2	2	
Not Hispanic or Latino	29	29	
Unknown or Not Reported	3	3	
Race Units: Subjects			
White	27	27	
Black Or African American	3	3	
Asian	1	1	
American Indian Or Alaskan Native	0	0	
Native Hawaiian Or Other Pacific Islander	0	0	
Other	1	1	
Missing/ Not reported	2	2	

End points

End points reporting groups

Reporting group title	Lenvatinib 24 mg

Reporting group description:

Subjects received lenvatinib 24 milligram (mg) (two 10-mg capsules and one 4-mg capsule), orally, once daily in a 28-days treatment cycle up to disease progression, development of unacceptable toxicity, lost to follow up, withdrawal of consent, subject's choice, pregnancy, or study termination by sponsor (approximately 27 months).

Primary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)[1]

End point description:

ORR was defined as the percentage of subjects with best overall response (BOR) of complete response (CR) or partial response (PR) as determined by investigator review using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 for target lesions. CR was defined as disappearance of all target lesions. Confirmation of CR or PR was performed at least 28 days following the initial achievement of the response. All pathological lymph nodes (whether target or non-target) must have a reduction in their short axis to less than 10 millimeter (mm). PR was defined as at least a 30 percent (%) decrease in the sum of the longest diameters of target lesions, taking as reference the Baseline sum diameters. The evaluable analysis set included all subjects with histological diagnosis of ATC that was confirmed by central pathology review and who received at least one dose of lenvatinib.

End point type	Primary

End point timeframe:

From the date of beginning of lenvatinib administration to the date of first documentation of disease progression or death, whichever occurred first (up to Month 27)

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: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Lenvatinib 24 mg			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: percentage of subjects				
number (confidence interval 95%)	3.0 (0.1 to 15.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS) Rate

End point title	Progression-free Survival (PFS) Rate

End point description:

Twelve-week PFS rate was the percentage of subjects in the analysis population who remain alive and progression-free at 12 weeks. PFS was defined as the time from the date of beginning of lenvatinib administration to the date of first documentation of confirmed disease progression or death, whichever occurred first. The Kaplan-Meier estimated rate method was used to estimate 12-week PFS, along with the corresponding 95% confidence interval (CI). Subjects who were off study due to lost to follow up,

withdrew consent, or study terminated by sponsor, had new anti-cancer treatment, had no baseline/post-baseline tumor assessments, or missed 2 or more visits prior to event were censored. The full analysis set included all subjects who received at least one dose of lenvatinib.

End point type	Secondary

End point timeframe:

From the date of beginning of lenvatinib administration up to the date of first documentation of confirmed disease progression or death, whichever occurred first (up to Week 12)

End point values	Lenvatinib 24 mg			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: percentage of subjects				
number (confidence interval 95%)	36.4 (20.6 to 52.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) Rate

End point title	Overall Survival (OS) Rate

End point description:

Six-month OS rate was defined as the percentage of subjects in the analysis population who are alive at 6 months. OS was defined as the time from the date of beginning of lenvatinib administration until date of death from any cause. The Kaplan-Meier estimated rate method was used to estimate six-month OS, along with the corresponding 95% CI. Subjects with last known alive date as study terminated by sponsor were censored. The full analysis set included all subjects who received at least one dose of lenvatinib.

End point type	Secondary

End point timeframe:

From the date of beginning of lenvatinib administration up to date of death from any cause (up to Month 6)

End point values	Lenvatinib 24 mg			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: percentage of subjects				
number (confidence interval 95%)	41.2 (24.8 to 56.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Median PFS

End point title	Median PFS

End point description:

PFS was defined as the time from the date of beginning of lenvatinib administration to the date of first documentation of confirmed disease progression or death, whichever occurs first. Median PFS was estimated using the Kaplan-Meier method. Subjects who were off study due to lost to follow up, withdrew consent, or study terminated by sponsor, had new anti-cancer treatment, had no baseline/post-baseline tumor assessments, or missed 2 or more visits prior to event were censored. The full analysis set included all subjects who received at least one dose of lenvatinib.

End point type	Secondary

End point timeframe:

From the date of beginning of lenvatinib administration to the date of first documentation of confirmed disease progression or death, whichever occurred first (up to Month 27)

End point values	Lenvatinib 24 mg			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: months				
median (confidence interval 95%)	2.6 (1.4 to 2.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Median OS

End point title	Median OS

End point description:

OS was defined as the time from the date of beginning of lenvatinib administration until date of death from any cause. Median OS was estimated using the Kaplan-Meier method. Subjects with last known alive date as study terminated by sponsor were censored. The full analysis set included all subjects who received at least one dose of lenvatinib.

End point type	Secondary

End point timeframe:

From the date of beginning of lenvatinib administration up to date of death from any cause (up to Month 27)

End point values	Lenvatinib 24 mg			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: months				
median (confidence interval 95%)	3.2 (2.8 to 8.2)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signature of informed consent form up to 28 days after last dose of study drug (up to Month 27)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Lenvatinib 24 mg

Reporting group description:

Subjects received lenvatinib 24 mg (two 10-mg capsules and one 4-mg capsule), orally, once daily in a 28-days treatment cycle up to disease progression, development of unacceptable toxicity, lost to follow up, withdrawal of consent, subject's choice, pregnancy, or study termination by sponsor (approximately 27 months).

Serious adverse events	Lenvatinib 24 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 34 (73.53%)		
number of deaths (all causes)	27		
number of deaths resulting from adverse events	14		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	10 / 34 (29.41%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 10		
Malignant pleural effusion			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to peritoneum			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	4 / 34 (11.76%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		

Laryngeal oedema				
subjects affected / exposed	1 / 34 (2.94%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	1 / 34 (2.94%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	1 / 34 (2.94%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	1 / 34 (2.94%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	3 / 34 (8.82%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	1 / 34 (2.94%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Tracheal fistula				
subjects affected / exposed	1 / 34 (2.94%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Confusional state				
subjects affected / exposed	1 / 34 (2.94%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural				

complications			
Accidental overdose			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiopulmonary failure			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Presyncope			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Abdominal lymphadenopathy			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Agranulocytosis			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anal fistula			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dysphagia			

subjects affected / exposed	2 / 34 (5.88%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Odynophagia			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess neck			

subjects affected / exposed	1 / 34 (2.94%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Anal abscess				
subjects affected / exposed	1 / 34 (2.94%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Arthritis infective				
subjects affected / exposed	1 / 34 (2.94%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bacterial sepsis				
subjects affected / exposed	1 / 34 (2.94%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Perirectal abscess				
subjects affected / exposed	1 / 34 (2.94%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 34 (2.94%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelitis				
subjects affected / exposed	1 / 34 (2.94%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	1 / 34 (2.94%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Metabolism and nutrition disorders				
Dehydration				

subjects affected / exposed	2 / 34 (5.88%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Lenvatinib 24 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 34 (94.12%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant pleural effusion			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	3		
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Vascular disorders			
Bloody discharge			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	18 / 34 (52.94%)		
occurrences (all)	34		
Hypotension			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Inferior vena cava dilatation			

subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Vena cava thrombosis			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 34 (14.71%)		
occurrences (all)	8		
Cyst			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Facial pain			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	11 / 34 (32.35%)		
occurrences (all)	14		
Injection site bruising			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Localised oedema			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Mucosal inflammation			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Pain			

subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	4		
Immune system disorders			
Contrast media reaction			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Bronchial secretion retention			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	4 / 34 (11.76%)		
occurrences (all)	5		
Dry throat			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Dysphonia			
subjects affected / exposed	5 / 34 (14.71%)		
occurrences (all)	8		
Dyspnoea			
subjects affected / exposed	4 / 34 (11.76%)		
occurrences (all)	5		
Dyspnoea exertional			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	4 / 34 (11.76%)		
occurrences (all)	5		
Haemoptysis			
subjects affected / exposed	6 / 34 (17.65%)		
occurrences (all)	8		
Hypoxia			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Nasal congestion			

subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Nasal obstruction			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	6 / 34 (17.65%)		
occurrences (all)	10		
Pleuritic pain			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	3		
Pneumonia aspiration			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Pneumonitis			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Pneumothorax			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Pulmonary haemorrhage			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Respiratory tract congestion			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Sputum increased			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Depressed mood			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		

Depression			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	3 / 34 (8.82%)		
occurrences (all)	3		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	3		
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 34 (8.82%)		
occurrences (all)	3		
Bilirubin conjugated increased			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 34 (8.82%)		
occurrences (all)	4		
Blood bilirubin increased			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Blood creatinine increased			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Blood phosphorus increased			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Blood thyroid stimulating hormone increased			
subjects affected / exposed	3 / 34 (8.82%)		
occurrences (all)	3		
C-reactive protein increased			

subjects affected / exposed	1 / 34 (2.94%)			
occurrences (all)	1			
Electrocardiogram QT prolonged				
subjects affected / exposed	2 / 34 (5.88%)			
occurrences (all)	2			
Gamma-glutamyltransferase increased				
subjects affected / exposed	2 / 34 (5.88%)			
occurrences (all)	4			
International normalised ratio increased				
subjects affected / exposed	3 / 34 (8.82%)			
occurrences (all)	3			
Liver function test abnormal				
subjects affected / exposed	1 / 34 (2.94%)			
occurrences (all)	1			
Lymphocyte count decreased				
subjects affected / exposed	4 / 34 (11.76%)			
occurrences (all)	5			
Oxygen saturation decreased				
subjects affected / exposed	1 / 34 (2.94%)			
occurrences (all)	1			
Platelet count decreased				
subjects affected / exposed	2 / 34 (5.88%)			
occurrences (all)	2			
Sputum normal				
subjects affected / exposed	1 / 34 (2.94%)			
occurrences (all)	1			
Troponin increased				
subjects affected / exposed	1 / 34 (2.94%)			
occurrences (all)	1			
Urine analysis abnormal				
subjects affected / exposed	1 / 34 (2.94%)			
occurrences (all)	2			
Urine leukocyte esterase positive				

subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	9 / 34 (26.47%)		
occurrences (all)	12		
White blood cell count decreased			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Contusion			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Fall			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Post procedural complication			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Post procedural swelling			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Postoperative delirium			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Stoma site pain			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Atrial tachycardia			

subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Hyperdynamic left ventricle			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Sinus tachycardia			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Nervous system disorders			
Amnesia			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Cervical radiculopathy			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	4 / 34 (11.76%)		
occurrences (all)	4		
Dysgeusia			
subjects affected / exposed	3 / 34 (8.82%)		
occurrences (all)	5		
Facial paralysis			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	5 / 34 (14.71%)		
occurrences (all)	6		
Hyperaesthesia			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Hypoaesthesia			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Jugular vein occlusion			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		

Lethargy subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Somnolence subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Syncope subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Tremor subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 2		
Increased tendency to bruise subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Leukocytosis subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Lymphopenia subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 3		
Thrombocytopenia subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	3 / 34 (8.82%) 3		
Vertigo subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Eye disorders			

Vision blurred			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Abdominal pain			
subjects affected / exposed	3 / 34 (8.82%)		
occurrences (all)	5		
Abdominal pain lower			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Abdominal pain upper			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	3		
Anal fistula			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	7 / 34 (20.59%)		
occurrences (all)	8		
Dental caries			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	8 / 34 (23.53%)		
occurrences (all)	13		
Diverticulum			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Dry mouth			
subjects affected / exposed	3 / 34 (8.82%)		
occurrences (all)	4		
Dyspepsia			

subjects affected / exposed	3 / 34 (8.82%)			
occurrences (all)	3			
Dysphagia				
subjects affected / exposed	7 / 34 (20.59%)			
occurrences (all)	10			
Gastrooesophageal reflux disease				
subjects affected / exposed	1 / 34 (2.94%)			
occurrences (all)	1			
Gingival pain				
subjects affected / exposed	2 / 34 (5.88%)			
occurrences (all)	4			
Gingival recession				
subjects affected / exposed	1 / 34 (2.94%)			
occurrences (all)	1			
Glossodynia				
subjects affected / exposed	2 / 34 (5.88%)			
occurrences (all)	6			
Haemorrhoids				
subjects affected / exposed	1 / 34 (2.94%)			
occurrences (all)	1			
Loose tooth				
subjects affected / exposed	1 / 34 (2.94%)			
occurrences (all)	1			
Mouth swelling				
subjects affected / exposed	1 / 34 (2.94%)			
occurrences (all)	1			
Mouth ulceration				
subjects affected / exposed	1 / 34 (2.94%)			
occurrences (all)	1			
Nausea				
subjects affected / exposed	11 / 34 (32.35%)			
occurrences (all)	17			
Odynophagia				
subjects affected / exposed	2 / 34 (5.88%)			
occurrences (all)	3			
Oesophageal stenosis				

subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Oral dysaesthesia			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Oral mucosal erythema			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Oral pain			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Pancreatitis			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Periodontal disease			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Proctalgia			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	10 / 34 (29.41%)		
occurrences (all)	13		
Tongue dry			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	6 / 34 (17.65%)		
occurrences (all)	9		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Cholelithiasis			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		

Cholestasis			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Gallbladder enlargement			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Dermatitis contact			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Dry skin			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Hyperkeratosis			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Macule			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	8 / 34 (23.53%)		
occurrences (all)	9		
Pruritus			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	3		
Pruritus generalised			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Rash			

subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Rash macular subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Rash maculo-papular subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 3		
Rash pruritic subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Skin discolouration subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Skin ulcer subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 2		
Renal and urinary disorders			
Acute kidney injury subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Haematuria subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Proteinuria subjects affected / exposed occurrences (all)	8 / 34 (23.53%) 15		
Pyelocaliectasis subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 2		
Endocrine disorders			
Hypothyroidism subjects affected / exposed occurrences (all)	6 / 34 (17.65%) 6		
Musculoskeletal and connective tissue disorders			

Arthralgia				
subjects affected / exposed	6 / 34 (17.65%)			
occurrences (all)	8			
Back pain				
subjects affected / exposed	4 / 34 (11.76%)			
occurrences (all)	5			
Bone pain				
subjects affected / exposed	1 / 34 (2.94%)			
occurrences (all)	1			
Bursitis				
subjects affected / exposed	1 / 34 (2.94%)			
occurrences (all)	1			
Coccydynia				
subjects affected / exposed	1 / 34 (2.94%)			
occurrences (all)	1			
Flank pain				
subjects affected / exposed	1 / 34 (2.94%)			
occurrences (all)	1			
Muscle spasms				
subjects affected / exposed	1 / 34 (2.94%)			
occurrences (all)	1			
Muscular weakness				
subjects affected / exposed	2 / 34 (5.88%)			
occurrences (all)	2			
Musculoskeletal chest pain				
subjects affected / exposed	1 / 34 (2.94%)			
occurrences (all)	1			
Musculoskeletal discomfort				
subjects affected / exposed	1 / 34 (2.94%)			
occurrences (all)	1			
Myalgia				
subjects affected / exposed	4 / 34 (11.76%)			
occurrences (all)	4			
Neck pain				
subjects affected / exposed	4 / 34 (11.76%)			
occurrences (all)	5			

Pain in extremity			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Infections and infestations			
Arthritis infective			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Oral candidiasis			
subjects affected / exposed	3 / 34 (8.82%)		
occurrences (all)	3		
Paronychia			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Perirectal abscess			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Sepsis			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Superinfection			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Tooth infection			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Urinary tract infection			

subjects affected / exposed	4 / 34 (11.76%)		
occurrences (all)	4		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	10 / 34 (29.41%)		
occurrences (all)	12		
Dehydration			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Hypercalcaemia			
subjects affected / exposed	3 / 34 (8.82%)		
occurrences (all)	3		
Hyperglycaemia			
subjects affected / exposed	5 / 34 (14.71%)		
occurrences (all)	5		
Hyperkalaemia			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Hyperuricaemia			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Hypoalbuminaemia			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Hypocalcaemia			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	4		
Hypoglycaemia			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Hypomagnesaemia			
subjects affected / exposed	3 / 34 (8.82%)		
occurrences (all)	3		

Hyponatraemia subjects affected / exposed occurrences (all)	9 / 34 (26.47%) 15		
Hypophagia subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		

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? Yes

Date	Interruption	Restart date
26 September 2018	Study enrollment was terminated since the overall response rate was 3% (only 1 out of 33 subjects had confirmed PR).	-

Notes:

Limitations and caveats

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

Study enrollment was terminated since the overall response rate was 3% (only 1 out of 33 subjects had confirmed PR).

Notes: