



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
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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
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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
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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
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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
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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
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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Reporting groups

Reporting group title	Lenvatinib 24 mg
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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 occurrences (all)	2 / 34 (5.88%) 4		
Immune system disorders Contrast media reaction subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Respiratory, thoracic and mediastinal disorders Bronchial secretion retention subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Cough subjects affected / exposed occurrences (all)	4 / 34 (11.76%) 5		
Dry throat subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 2		
Dysphonia subjects affected / exposed occurrences (all)	5 / 34 (14.71%) 8		
Dyspnoea subjects affected / exposed occurrences (all)	4 / 34 (11.76%) 5		
Dyspnoea exertional subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Epistaxis subjects affected / exposed occurrences (all)	4 / 34 (11.76%) 5		
Haemoptysis subjects affected / exposed occurrences (all)	6 / 34 (17.65%) 8		
Hypoxia subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 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	1 / 34 (2.94%)		
occurrences (all)	1		
Somnolence			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Syncope			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	2		
Increased tendency to bruise			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Leukocytosis			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Lymphopenia			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	3		
Thrombocytopenia			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	3 / 34 (8.82%)		
occurrences (all)	3		
Vertigo			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Eye disorders			

Vision blurred subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Gastrointestinal disorders			
Abdominal distension subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Abdominal pain subjects affected / exposed occurrences (all)	3 / 34 (8.82%) 5		
Abdominal pain lower subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Abdominal pain upper subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 3		
Anal fistula subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Constipation subjects affected / exposed occurrences (all)	7 / 34 (20.59%) 8		
Dental caries subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Diarrhoea subjects affected / exposed occurrences (all)	8 / 34 (23.53%) 13		
Diverticulum subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Dry mouth subjects affected / exposed occurrences (all)	3 / 34 (8.82%) 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	1 / 34 (2.94%)		
occurrences (all)	1		
Rash macular			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Rash maculo-papular			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences (all)	3		
Rash pruritic			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Skin discolouration			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Skin ulcer			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	2		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Haematuria			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	1		
Proteinuria			
subjects affected / exposed	8 / 34 (23.53%)		
occurrences (all)	15		
Pyelocaliectasis			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	2		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	6 / 34 (17.65%)		
occurrences (all)	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 occurrences (all)	1 / 34 (2.94%) 1		
Infections and infestations			
Arthritis infective subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Oral candidiasis subjects affected / exposed occurrences (all)	3 / 34 (8.82%) 3		
Paronychia subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Perirectal abscess subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Pneumonia subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Sepsis subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Superinfection subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Tooth infection subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 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	9 / 34 (26.47%)		
occurrences (all)	15		
Hypophagia			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences (all)	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).
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Notes: