Clinical trial results:
A phase II study to evaluate the safety and efficacy of lenvatinib in patients with advanced grade 1/2 neuroendocrine neoplasmas of pancreatic and extrapancreatic origin.

Summary

EudraCT number	2015-001467-39
Trial protocol	ES AT IT
Global end of trial date	12 August 2020

Results information

Result version number	v1 (current)
This version publication date	14 March 2024
First version publication date	14 March 2024

Trial information

Trial identification

Sponsor protocol code	GETNE1509

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02678780
WHO universal trial number (UTN)	-
Other trial identifiers	Acronym: TALENT

Notes:

Sponsors

Sponsor organisation name	GETNE (Grupo Español Tumores Neuroendocrinos)
Sponsor organisation address	C/ París, 162, Pral. 1ª., Barcelona, Spain, 08036
Public contact	Dr. Jaume Capdevila, GETNE (Grupo Español Tumores Neuroendocrinos), 0034 934894350, jcapdevila@vhio.net
Scientific contact	Dr. Jaume Capdevila, GETNE (Grupo Español Tumores Neuroendocrinos), 0034 934894350, jcapdevila@vhio.net

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	03 June 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 August 2020
Global end of trial reached?	Yes
Global end of trial date	12 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective
To assess the efficacy of lenvatinib on tumor objective response rate in two independent cohorts of patients with advanced neuroendocrine tumors: patients with advanced/metastatic G1/G2 pancreatic neuroendocrine tumors after progression to a previous targeted agent (cohort A), and patients with advanced/metastatic G1/G2 neuroendocrine tumors of gastrointestinal tract after failure to somatostatin analogues therapy (cohort B).

Protection of trial subjects:

Patients will be discontinued of study drug in case of disease progression and/or unacceptable toxicity. Also in those cases where patient withdrawal of consent.
Subjects who discontinue study administration prior to disease progression continued to undergo disease assessment every 12 weeks until documentation of disease progression or start of another anticancer therapy, at which time the subject entered the follow-up period

Background therapy:

Cohort A (pancreatic origin) previously treated with targeted agents (with possibility of one line of chemotherapy) and cohort B (gastrointestinal origin) previously treated with somatostatin analogues. Both cohorts could maintain treatment with somatostatin analogues during the trial.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	21 October 2015
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	Spain: 53
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Italy: 39
Worldwide total number of subjects	111
EEA total number of subjects	98

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)	71
From 65 to 84 years	39
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The recruitment period was 18 months.
Recruitment Start: October 2015 (15/Oct/2015)
End of Recruitment Period: September 2017 (08/Sep/2017)

Pre-assignment

Screening details:

Screening phase occurred between Day -28 and Day -1 (approximately one month). The purpose of the screening period was to establish protocol eligibility. Subjects who complete the baseline visit and continued to meet the criteria for inclusion/exclusion began the treatment phase of this study.

Pre-assignment period milestones

Number of subjects started	123[1]
Intermediate milestone: Number of subjects	Allocated and received treatment: 111
Number of subjects completed	111

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screening failure: 12

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Total patients that started the pre-assignment period (=screening phase) were 123 patients (=123 patients that signed Informed Consent Form).
The enrolled patients are considered the ones that got over screening phase and started treatment phase.
There were 12 patients that finally were screening failure, so 111 patients are considered the ones enrolled in the trial (in the treatment phase, 55 in cohort A, 56 in cohort B).

Period 1

Period 1 title	Period 1 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort A

Arm description:

Patients with pancreatic neuroendocrine tumor

Arm type	Experimental
Investigational medicinal product name	Lenvatinib
Investigational medicinal product code	E7080
Other name	(LENVIMA™)
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

24 mg per day

Arm title	Cohort B

Arm description:	
Patients with gastrointestinal neuroendocrine tumor	
Arm type	Experimental
Investigational medicinal product name	Lenvatinib
Investigational medicinal product code	E7080
Other name	(LENVIMA™)
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

24 mg per day

Number of subjects in period 1	Cohort A	Cohort B
Started	55	56
Completed	28	28
Not completed	27	28
Consent withdrawn by subject	2	1
Death	1	1
Other	6	8
Sponsor discontinuation	7	4
Unacceptable toxicity	11	14

Baseline characteristics

Reporting groups	
Reporting group title	Cohort A
Reporting group description:	
Patients with pancreatic neuroendocrine tumor	
Reporting group title	Cohort B
Reporting group description:	
Patients with gastrointestinal neuroendocrine tumor	

Reporting group values	Cohort A	Cohort B	Total
Number of subjects	55	56	111
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	38	33	71
From 65-84 years	17	22	39
85 years and over	0	1	1
Gender categorical Units: Subjects			
Female	31	23	54
Male	24	33	57

End points

End points reporting groups

Reporting group title	Cohort A
Reporting group description:	
Patients with pancreatic neuroendocrine tumor	
Reporting group title	Cohort B
Reporting group description:	
Patients with gastrointestinal neuroendocrine tumor	

Primary: Overall response rate (ORR)

End point title	Overall response rate (ORR)[1]

End point description:

To assess the efficacy of lenvatinib on tumor objective response rate (ORR), complete (CR) and partial responses (PR) in two independent cohorts of patients with advanced/metastatic G1/G2 neuroendocrine tumors: patients with pancreatic neuroendocrine tumors after progression to a previous targeted agent (cohort A), and patients with neuroendocrine tumors of the gastrointestinal tract after failure to somatostatin analogues therapy (cohort B).
The ORR is defined as the proportion of subjects who have best overall response of CR or PR (by RECIST criteria): ORR= (CR+PR)/(Total of patients)

End point type	Primary

End point timeframe:

Tumor assessments will be performed during the screening phase and,the first assessment will be performed 6 weeks after the first dose,the second assessment will be performed 12 weeks after the first dose, then every 12 weeks during study treatment cycles

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The method to perfom caluclations are detailed in the description field of each endpoint.

End point values	Cohort A	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	55		
Units: Percentaje	44	16		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free survival (PFS)

End point title	Progression Free survival (PFS)

End point description:

PFS censoring rules will follow FDA guidance in 2007.

End point type	Secondary

End point timeframe:

Progression-free survival (PFS) is defined as the time from the date of treatment start (C1D1) to the date of first documentation of disease progression or death (whichever occurs first) using RECIST 1.1.

End point values	Cohort A	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	55		
Units: month				
number (confidence interval 95%)	15.53 (11.2 to 29.27)	15.67 (12.07 to 19.53)		

Statistical analyses

No statistical analyses for this end point

Secondary: Early tumor shrinkage (ETS) rate

End point title	Early tumor shrinkage (ETS) rate

End point description:

To calculate early tumor shrinkage (ETS) rate, patients were classified as responders/non-responders after a period of 6 weeks (first post-baseline tumor assessment). Those who achieved a 20% reduction in target lesions after the first 6 weeks of treatment were classified as responders.

End point type	Secondary

End point timeframe:

Early tumor shrinkage (ETS) rate defined as 20% reduction in target lesions after the first 6 weeks of treatment (first tumor assessment)

End point values	Cohort A	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	51		
Units: Percentage				
responders	38	10		
no responders	62	90		

Statistical analyses

No statistical analyses for this end point

Secondary: Deepness of response (DpR)

End point title	Deepness of response (DpR)

End point description:

percentage of result based in median
DpR of 100%: All target tumour lesions disappear (Tumour shrinkage)
DpR of 0%: No change (No tumour shrinkage)

End point type	Secondary

End point timeframe:

Deepness of response (DpR) defined as percentage of maximum tumor shrinkage observed at the nadir compared with baseline.

End point values	Cohort A	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	56		
Units: Percentage	26	15		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study consent through the termination visit and for 28 days following study drug discontinuation, whichever is longer.

Adverse event reporting additional description:

They were to be followed up until resolution or stabilization.The sponsor was to be notified of any SAE that the investigator considered to be relatedto study treatment.Deaths and life-threatening events should be reported immediately.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Cohort A

Reporting group description:

Patients with pancreatic neuroendocrine tumor

Reporting group title	Cohort B

Reporting group description:

Patients with gastrointestinal neuroendocrine tumor

Serious adverse events	Cohort A	Cohort B	
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 55 (41.82%)	24 / 56 (42.86%)	
number of deaths (all causes)	22	28	
number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign neoplasm of bladder			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral papilloma			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to large intestine			

subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Lymphoedema			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Colon operation			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			

subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Sinus bradycardia			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 55 (5.45%)	3 / 56 (5.36%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	3 / 55 (5.45%)	3 / 56 (5.36%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vomiting			
subjects affected / exposed	2 / 55 (3.64%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Colitis			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 55 (1.82%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mallory-Weiss syndrome			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastroduodenal haemorrhage			

subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal inflammation			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal toxicity			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Small intestinal perforation			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stenosis			

subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 55 (1.82%)	2 / 56 (3.57%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 55 (3.64%)	2 / 56 (3.57%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Febrile infection			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic infection			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	0 / 55 (0.00%)	2 / 56 (3.57%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal abscess			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			

Hyperamylasaemia			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Cohort A	Cohort B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 55 (100.00%)	56 / 56 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	43 / 55 (78.18%)	48 / 56 (85.71%)	
occurrences (all)	87	125	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	31 / 55 (56.36%)	32 / 56 (57.14%)	
occurrences (all)	136	124	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 November 2015	This amendment was made to adapt the current version of the protocol to the changes requested by the Medicines and Healthcare products Regulatory Agency (MHRA) of UK during study evaluation. Some sections were updated, including the eligibility criteria (inclusion criteria 17 related to anticonception and exclusion criteria 16 is more detailed related to hypersensitivity to study drug or active substances). Involving changes in the protocol (protocol v3.0) and in the Patient Information Sheet (PIS)
04 April 2016	Involving changes in the protocol (protocol v4.0) and in the PIS. This amendment was made due to the extension of sites and the update of an exclusion criteria (LVEF of 50%). Protocol v4.0 dated 04/Apr/2016 is the last and current version of the study protocol.
29 June 2017	Was submitted due to the update of the Summary of Product Characteristics (SmPC) of lenvatinib, which also involved an update of the security information in PIS. There were no changes in the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/33945297