Clinical trial results:
A phase II trial to assess the activity and safety of TH-302 in combination with sunitinib in patients with well- and moderately-differentiated metastatic pancreatic neuroendocrine tumors (pNET) previously untreated

Summary

EudraCT number	2014-004072-30
Trial protocol	ES
Global end of trial date	10 January 2020

Results information

Result version number	v1 (current)
This version publication date	01 July 2020
First version publication date	01 July 2020
Summary attachment (see zip file)	ICH3 summary (GETNE-1408 - CLINICAL STUDY REPORTS SUMMARY.pdf)

Trial information

Trial identification

Sponsor protocol code	GETNE-1408

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02402062
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Grupo Español de Tumores Neuroendocrinos y Endocrinos (GETNE)
Sponsor organisation address	C/ Pau Alsina 68 esc B entlo. 5, Barcelona, Spain, 08024
Public contact	Dr. Jaume Capdevila Castillón, Grupo Español de Tumores Neuroendocrinos y Endocrinos (GETNE), getne@getne.org
Scientific contact	Dr. Enrique Grande, Medical Oncology. Hospital Ramon y Cajal, egrande@oncologiahrc.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	22 May 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 January 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the safety and activity of TH-302 in combination with sunitinib in patients with a well- or moderately-differentiated metastatic pancreatic neuroendocrine tumour (pNET). Efficacy assessed by Objective Response Rate (ORR).

Protection of trial subjects:

The Sponsor provides compliance with the principles originated from the Helsinki declaration, the Good Clinical Practice requirements from the International Conference of Harmonization (ICH) for the conduct of clinical trials and the local current legislation (European Directive 2001/20/EC)(Real Decreto de Ensayos Clínicos 223/2004).
The Sponsor guarantees compliance with the principles established in the Organic Law for Protection of Personal Data 15/1999 and to facilitate the exercise of rights of access, rectification, cancellation and opposition.

To ensure patient safety the experimental treatment will be temporarily interrupted until resolution of toxicity ≤ grade 2.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 May 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: 17
Worldwide total number of subjects	17
EEA total number of subjects	17

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)	10
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between May/2015 and May/2018, 21 patients were screened and finally 17 were included. 4 patients were excluded because screening failure.

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	21[1]
Number of subjects completed	17

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Not meeting inclusion criteria: 4

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: 4 patients were screened but did not match inclusion criteria so they were not included in the study.

Period 1

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

Arms

Arm title	Experimental arm

Arm description:

Treatment with TH-302 administered at 340 mg/m2 by intravenous infusion on days 8 and 22 in combination with Sunitinib given orally at doses of 37.5 mg per day continuously in 28-day cycles.

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

Dosage and administration details:

Sunitinib given orally at doses of 37.5 mg per day continuously. The treatment was maintained until disease progression, unacceptable toxicity, non-compliance with the protocol, the patient’s withdrawal of informed consent or at the discretion of the investigator.

Investigational medicinal product name	TH-302
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

TH-302 administered at 340 mg/m2 by intravenous infusion on days 8 and 22 of 28 days cycle. The treatment was maintained until disease progression, unacceptable toxicity, non-compliance with the protocol, the patient’s withdrawal of informed consent or at the discretion of the investigator.

Number of subjects in period 1	Experimental arm
Started	17
Completed	17

Period 2

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

Arms

Arm title	Experimental arm

Arm description:

Treatment with TH-302 administered at 340 mg/m2 by intravenous infusion on days 8 and 22 in combination with Sunitinib given orally at doses of 37.5 mg per day continuously in 28-day cycles.

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

Dosage and administration details:

Sunitinib given orally at doses of 37.5 mg per day continuously. The treatment was maintained until disease progression, unacceptable toxicity, non-compliance with the protocol, the patient’s withdrawal of informed consent or at the discretion of the investigator.

Investigational medicinal product name	TH-302
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

TH-302 administered at 340 mg/m2 by intravenous infusion on days 8 and 22 of 28 days cycle. The treatment was maintained until disease progression, unacceptable toxicity, non-compliance with the protocol, the patient’s withdrawal of informed consent or at the discretion of the investigator.

Number of subjects in period 2	Experimental arm
Started	17
Completed	7
Not completed	10
Adverse event, serious fatal	1
Adverse event, non-fatal	4
Lack of efficacy	5

Baseline characteristics

Reporting groups	
Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	17	17	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
median	60.78		
standard deviation	± 10.78	-	
Gender categorical Units: Subjects			
Female	6	6	
Male	11	11	
ECOG PS			
The ECOG scale is a practical way to measure the quality of life of a patient exclusively with cancer or cancer.			
Units: Subjects			
grade 0	11	11	
grade 1	6	6	
Ethnicity Units: Subjects			
White	17	17	
Electrocardiogram (ECG) Units: Subjects			
QT interval longer than 450ms	17	17	
Left ventricular ejection fraction (LVEF) Units: Subjects			
higher than 50%	17	17	
Abbreviated Charlson comorbidity index Units: Subjects			
index 2	11	11	
index 3	4	4	
index 4	2	2	

Peripheral arterial disease Units: Subjects			
Yes	1	1	
No	16	16	
Diabetes Units: Subjects			
Yes	5	5	
No	12	12	
Tumor histological grade Units: Subjects			
grade 2	15	15	
grade 1	2	2	
Ki-67 index Units: Subjects			
>10%	8	8	
>2%-5%	5	5	
>5%-10%	4	4	
Mitosis 10 HPF Units: Subjects			
Unknown	6	6	
<2	6	6	
2-20	5	5	
Primary tumor surgery Units: Subjects			
Yes	6	6	
No	11	11	
Tumor stage at diagnosis Units: Subjects			
II	3	3	
III	1	1	
IV	13	13	
Tumor relapse location Units: Subjects			
Hepatic	12	12	
unknown	4	4	
Extra-hepatic	1	1	
Somatostanine analogues prior the trial Units: Subjects			
Yes	7	7	
No	10	10	
Baseline concomitant medication Units: Subjects			
Yes	16	16	
No	1	1	
Weight Units: kilogram(s)			
arithmetic mean	70.97		
standard deviation	± 15.01	-	
Height Units: centimeter			
arithmetic mean	166.71		

standard deviation	± 7.74	-	
Body mass index (BMI)			
Units: kg/m2			
arithmetic mean	25.46		
standard deviation	± 4.75	-	
Body surface area (BSA)			
Units: m2			
arithmetic mean	1.79		
standard deviation	± 0.20	-	
Blood pressure systolic (BPs)			
Units: mmHg			
arithmetic mean	134.82		
standard deviation	± 10.95	-	
Blood pressure diastolic (BPd)			
Units: mmHg			
arithmetic mean	79.12		
standard deviation	± 7.42	-	
Haemoglobin			
Units: g/dL			
arithmetic mean	13.82		
standard deviation	± 1.21	-	
White blood cells			
Units: x109/L			
arithmetic mean	6.22		
standard deviation	± 2.17	-	
Absolute neutrophil count			
Units: x109/L			
arithmetic mean	4.52		
standard deviation	± 1.84	-	
Absolute Lymphocytes count			
Units: x109/L			
arithmetic mean	1.69		
standard deviation	± 0.41	-	
Platelet count			
Units: x109/L			
arithmetic mean	202.94		
standard deviation	± 77.34	-	
Sodium			
Units: mmol/L			
arithmetic mean	139.22		
standard deviation	± 3.06	-	
Potassium			
Units: mmol/L			
arithmetic mean	4.35		
standard deviation	± 0.35	-	
Calcium			
Units: mmol/L			
arithmetic mean	9.18		
standard deviation	± 1.83	-	
Magnesium			
Units: mmol/L			
arithmetic mean	1.9		

standard deviation	± 0.38	-	
Glucose			
Units: mmol/L			
arithmetic mean	133.44		
standard deviation	± 59.92	-	
Creatinine			
Units: mg/dL			
arithmetic mean	0.76		
standard deviation	± 0.17	-	
Aspartate AST (SGOT)			
Units: u/L			
arithmetic mean	48.95		
standard deviation	± 40.18	-	
Alanine transaminase ALT (SGPT)			
Units: u/L			
arithmetic mean	69.63		
standard deviation	± 61.12	-	
AST (SGOT)/ ALT (SGPT) (baseline)			
Units: Arbitrary units			
arithmetic mean	0.83		
standard deviation	± 0.30	-	
Total bilirubin			
Units: mg/dL			
arithmetic mean	0.86		
standard deviation	± 0.58	-	
Gamma-glutamyltransferase (GGT)			
Units: u/L			
arithmetic mean	351.25		
standard deviation	± 488.76	-	
Alkaline phosphatase (AP)			
Units: u/L			
arithmetic mean	201.64		
standard deviation	± 183.95	-	
Albumin			
Units: mg/dL			
arithmetic mean	4.28		
standard deviation	± 0.43	-	
Lactate dehydrogenase (LDH)			
Units: u/L			
arithmetic mean	216.88		
standard deviation	± 83.41	-	
CG a tumor marker			
Units: ng/L			
arithmetic mean	474.41		
standard deviation	± 626.35	-	
Enolase 1			
Units: ng/mL			
arithmetic mean	31.92		
standard deviation	± 31.08	-	
Time between diagnosis (anatomical pathology) and treatment initiation (date 1 cycle 1) in months			

Units: Months			
arithmetic mean	14.12		
standard deviation	± 22.72	-	
Time between diagnosis (anatomical pathology) and surgery in months			
Units: Months			
arithmetic mean	1.1		
standard deviation	± 2.94	-	
Time between diagnosis (anatomical pathology) and CT relapse in months			
Units: Months			
arithmetic mean	8.9		
standard deviation	± 13.77	-	

End points

End points reporting groups

Reporting group title	Experimental arm
Reporting group description:	
Treatment with TH-302 administered at 340 mg/m2 by intravenous infusion on days 8 and 22 in combination with Sunitinib given orally at doses of 37.5 mg per day continuously in 28-day cycles.	
Reporting group title	Experimental arm
Reporting group description:	
Treatment with TH-302 administered at 340 mg/m2 by intravenous infusion on days 8 and 22 in combination with Sunitinib given orally at doses of 37.5 mg per day continuously in 28-day cycles.	

Primary: Overal response rate (ORR)

End point title	Overal response rate (ORR)[1]
End point description:	
ORR will be evaluated according to the RECIST v 1.1 criteria that will be carried out every 8 weeks, regardless of delays in treatment secondary to treatment toxicity. ORR is defined as the percentage of patients in whom a complete response is confirmed (CR) or a partial response (RP) according to RECIST criteria, in relation to the total population analyzed. An answer is confirmed in those patients in whom this response persists in a test of repeat image ≥4 weeks after initial response documentation.	
End point type	Primary
End point timeframe:	
every 8 weeks since start of treatment	

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: This study had only one treatment arm, so no comparison between groups was assessed. The main aim was to characterize the outcomes in the population of study when treated with TH302 and sunitinib combination.

End point values	Experimental arm			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: Patients				
CR or PR	3			
No CR or PR	14			

Statistical analyses

No statistical analyses for this end point

Primary: Best response (not confirmed)

End point title	Best response (not confirmed)[2]
End point description:	
Best response to treatment achieved following RECIST v1.1 criteria. The best response is not confirmed in the following evaluation timepoints.	
End point type	Primary

End point timeframe:

Every 8 weeks from start of treatment.

Notes:

[2] - 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: This study had only one treatment arm, so no comparison between groups was assessed. The main aim was to characterize the outcomes in the population of study when treated with TH302 and sunitinib combination.

End point values	Experimental arm			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: Patients				
CR	1			
PR	3			
SD	11			
PD	1			
NE	1			

Statistical analyses

No statistical analyses for this end point

Primary: Confirmed response for objective response rate

End point title	Confirmed response for objective response rate[3]

End point description:

End point type	Primary

End point timeframe:

Every 8 weeks from start of treatment

Notes:

[3] - 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: This study had only one treatment arm, so no comparison between groups was assessed. The main aim was to characterize the outcomes in the population of study when treated with TH302 and sunitinib combination.

End point values	Experimental arm			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: Patients				
CR	1			
PR	2			
SD	11			
PD	1			
NE	2			

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 is defined as the time between the start of the study treatment until the date of the first objective evidence of radiological progression or death of the patient due to any cause; whichever happen first.

End point type	Secondary

End point timeframe:

every 8 weeks

End point values	Experimental arm			
Subject group type	Reporting group			
Number of subjects analysed	17[4]			
Units: months				
median (confidence interval 95%)	10.38 (2.66 to 18.1)			

Notes:

[4] - 11 events recorded along the study. 6 censored.

Attachments (see zip file)	Kaplan Meier graph for PFS/PFS GETNE1408.png

Statistical analyses

No statistical analyses for this end point

Secondary: Time to progression

End point title	Time to progression

End point description:

Time to progression is defined as the time between the start of the study treatment until the date of the first objective evidence of radiological progression.

End point type	Secondary

End point timeframe:

Every 8 weeks from the treatment start until disease progression, patient death or withdrawal, whichever occurs first.

End point values	Experimental arm			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: months				
median (full range (min-max))	5.32 (1.69 to 13.55)			

Statistical analyses

No statistical analyses for this end point

Secondary: Response duration (RD)

End point title	Response duration (RD)

End point description:

RD is defined as the time between the start from the first objective response documentation (CR or PR) which is subsequently confirmed, until the first objective evidence of radiological progression or death from any cause.
RD will be calculated only in the subgroup of patients with objective response (CR + PR).

End point type	Secondary

End point timeframe:

Every 8 weeks from the start of treatment until disease progression, patient death or withdrawal, whichever occurs first.

End point values	Experimental arm			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: months				
median (full range (min-max))	18.48 (4.20 to 38.31)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

OS is defined as the time between the start of study treatment until the date of death due to any cause.
If it is not possible to obtain confirmation of death, survival will be censored with the date of the last visit that the patient is known to be alive.

End point type	Secondary

End point timeframe:

Every 8 weeks from the start of treatment until patient death or withdrawal, whichever occurs first.

End point values	Experimental arm			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: months				
arithmetic mean (confidence interval 95%)	32.32 (25.12 to 39.53)			

Attachments (see zip file)	Kaplan Meier graph for OS/OS GETNE1408.png

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The security assessment period was between the date of the signed informed consent and up to 28 days after the last dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Experimental arm

Reporting group description:

Treatment with TH-302 administered at 340 mg/m2 by intravenous infusion on days 8 and 22 in combination with Sunitinib given orally at doses of 37.5 mg per day continuously in 28-day cycles.

Serious adverse events	Experimental arm		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 17 (17.65%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	1		
General disorders and administration site conditions			
Fever			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Alanine aminotransferase increased			

subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Biliary duct obstruction			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Pancreatitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		

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

Non-serious adverse events	Experimental arm		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 17 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 17 (35.29%)		
occurrences (all)	6		
Vascular disorders - Other, brachial vein thrombosis			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	14 / 17 (82.35%)		
occurrences (all)	14		
General disorders and administration site conditions - Other, epigastralgia			
subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	3		
Fever			

subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	3		
Dizziness			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Abdominal pain			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Vaginal inflammation			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Reproductive system and breast disorders - Other, genital dryness			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Mucositis oral			
subjects affected / exposed	10 / 17 (58.82%)		
occurrences (all)	10		
Epistaxis			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders - thoracic pain			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 17 (23.53%)		
occurrences (all)	4		
Myalgia			

subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2		
Dysesthesia subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2		
Peripheral motor neuropathy subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Paresthesia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Blood and lymphatic system disorders			
Neutrophil count decreased subjects affected / exposed occurrences (all)	9 / 17 (52.94%) 9		
Platelet count decreased subjects affected / exposed occurrences (all)	5 / 17 (29.41%) 5		
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	3 / 17 (17.65%) 3		
Blood bilirubin increased subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2		
Anemia subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2		
White blood cell decreased subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Hypocalcemia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Bilirrubin increased subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		

Aspartate aminotransferase increased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Eye disorders			
Conjunctivitis			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	9 / 17 (52.94%)		
occurrences (all)	9		
Dyspepsia			
subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	3		
Gastroesophageal reflux disease			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Dysphagia			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Rectal hemorrhage			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Hemorrhoids			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Gastrointestinal disorders - Other, specify: aerophagia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Gastrointestinal disorders - Other, specify: acute gastroenteritis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Gastrointestinal disorders - Other, glossitis			

subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Gastrointestinal disorders - Other, Gingivitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Esophagitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Anal ulcer			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Anal pain			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	5 / 17 (29.41%)		
occurrences (all)	5		
Rash acneiform			
subjects affected / exposed	4 / 17 (23.53%)		
occurrences (all)	4		
Skin hypopigmentation			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders - Other, Erythema			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Skin induration			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Skin hyperpigmentation			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders - Other, specify: Unspecified Onycopathy			

subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders - Other, specify: Psoriasis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders - Other, Inguinal cutaneous toxicity			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders - Other, facial rash			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders - Other, eczematous facial rash			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Erythroderma			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Alopecia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Renal and urinary disorders			
Hematuria			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Infections and infestations			

Constipation subjects affected / exposed occurrences (all) Pharyngitis subjects affected / exposed occurrences (all) Nail infection subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2 1 / 17 (5.88%) 1 1 / 17 (5.88%) 1		
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all) Dysgeusia subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Pancreatitis subjects affected / exposed occurrences (all)	 7 / 17 (41.18%) 7 6 / 17 (35.29%) 6 5 / 17 (29.41%) 5 4 / 17 (23.53%) 4 1 / 17 (5.88%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 March 2015	Change in the labels of Sunitinib 37,5 mg y 25 mg
07 May 2015	Quality IMPD of TH-302 v4.0 from november 2014
04 August 2015	New version of the protocol v. 3.0 from June 8th, 2015
15 January 2016	New version of the protocol v. 4.0 from November 27th, 2015 New label of TH-302
13 January 2017	New version of the protocolo v. 5.0 from November 23rd, 2016 New version of the patient information sheet, v. 5.0 from November 23rd, 2016
25 October 2017	Change of principal investigator from the Ramón y Cajal Hospital
06 February 2018	Change of the information in the label of TH-302
12 February 2019	New version of the protocol and patient information sheet v. 6.0 of January 8, 2019

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported