Clinical trial results:
Phase II study of pazopanib in patients with progressive recurrent and/or metastatic salivary gland carcinoma

Summary

EudraCT number	2012-004408-36
Trial protocol	FR
Global end of trial date	09 October 2019

Results information

Result version number	v1 (current)
This version publication date	06 July 2023
First version publication date	06 July 2023

Trial information

Trial identification

Sponsor protocol code	HN02-UC-0130/1205

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02393820
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UNICANCER
Sponsor organisation address	101 rue de Tolbiac, Paris, France, 75013
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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	20 October 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to assess the efficacy of pazopanib for treating patients with recurrent and/or metastatic salivary gland cancers, in terms of the 6-month progression-free survival (PFS) rate.

Protection of trial subjects:

This study was conducted in accordance with the Declaration of Helsinki (1964) and subsequent amendments, ICH Good Clinical Practice (GCP) Guidelines (CPMP/ICH/135/95), the European Directive (2001/20/CE) and the applicable local regulatory requirements and laws.
Furthermore, independent Ethics Committees reviewed and gave favorable opinions to the study documents, including the initial protocol and all subsequent amendments, and all information and documents provided to subjects/patients.
Written informed consent was obtained from all patients prior to enrollment.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 August 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 63
Worldwide total number of subjects	63
EEA total number of subjects	63

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)	44
From 65 to 84 years	19
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

PACSA ORL02 was designed as a multicentric, open-label, single-arm, non-randomised phase II study in patients who were suffering from progressive recurrent and/or metastatic salivary gland cancers.
Patients with salivary adenoid cystic carcinomas (ACC) and non-ACC were included in the study.
Recruitment only in France.

Pre-assignment

Screening details:

Patients with relapse and/or metastatic salivary gland cancer : salivary adenoid cystic carcinomas (ACC) ans non-ACC.
Confirmed disease progression using 2 tumour assessments within the 6 months before inclusion. The tumour assessment confirming disease progression had to be within 2 months of inclusion.

Pre-assignment period milestones

Number of subjects started	63
Number of subjects completed	63

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Adenoid cystic carcinoma (ACC)

Arm description:

Salivary Glands Carcinoma were separated in two cohorts/sub-groups: Adenoid Cystic Carcinoma (ACC) and Non-Adenoid Cystic Carcinoma (Non ACC).
In this "Arm" we reported results from the ACC subgroup.

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

Dosage and administration details:

Pazopanib (Votrient®) was administered orally 800 mg once daily (4 x 200-mg tablets)

Arm title	Non-Adenoid Cystic Carcinoma (Non ACC)

Arm description:

Salivary Glands Carcinoma were separated in two cohorts/sub-groups: Adenoid Cystic Carcinoma (ACC) and Non-Adenoid Cystic Carcinoma (Non ACC).
In this "Arm" we reported results from the Non ACC subgroup.

Arm type	Experimental

Investigational medicinal product name	Pazopanib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Pazopanib (Votrient®) was administered orally 800 mg once daily (4 x 200-mg tablets)

Number of subjects in period 1	Adenoid cystic carcinoma (ACC)	Non-Adenoid Cystic Carcinoma (Non ACC)
Started	45	18
Completed	0	0
Not completed	45	18
Disease progression	28	12
Adverse event, non-fatal	6	4
Death	3	-
Other reason	1	1
Investigator decision	2	1
Protocol deviation	5	-

Baseline characteristics

Reporting groups

Reporting group title	Adenoid cystic carcinoma (ACC)

Reporting group description:

Salivary Glands Carcinoma were separated in two cohorts/sub-groups: Adenoid Cystic Carcinoma (ACC) and Non-Adenoid Cystic Carcinoma (Non ACC).
In this "Arm" we reported results from the ACC subgroup.

Reporting group title	Non-Adenoid Cystic Carcinoma (Non ACC)

Reporting group description:

Salivary Glands Carcinoma were separated in two cohorts/sub-groups: Adenoid Cystic Carcinoma (ACC) and Non-Adenoid Cystic Carcinoma (Non ACC).
In this "Arm" we reported results from the Non ACC subgroup.

Reporting group values	Adenoid cystic carcinoma (ACC)	Non-Adenoid Cystic Carcinoma (Non ACC)	Total
Number of subjects	45	18	63
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)	29	15	44
From 65-84 years	16	3	19
85 years and over	0	0	0
Age continuous Units: years			
median	58	59	
full range (min-max)	27 to 84	28 to 76	-
Gender categorical Units: Subjects			
Female	27	6	33
Male	18	12	30
Metastatic at diagnosis Units: Subjects			
Yes	6	1	7
No	39	17	56
Metastatic progression at enrolment Units: Subjects			
Yes	44	12	56
No	1	6	7
Loco-regional recurrence at enrolment, Units: Subjects			
Yes	19	15	34
No	26	3	29

Site of primary tumour: Major salivary glands Units: Subjects			
Yes	23	17	40
No	22	1	23
Site of primary tumour: Major and minor salivary glands Units: Subjects			
Yes	3	0	3
No	42	18	60
Site of primary tumour: Minor salivary glands Units: Subjects			
Yes	19	1	20
No	26	17	43

End points

End points reporting groups

Reporting group title	Adenoid cystic carcinoma (ACC)

Reporting group description:

Salivary Glands Carcinoma were separated in two cohorts/sub-groups: Adenoid Cystic Carcinoma (ACC) and Non-Adenoid Cystic Carcinoma (Non ACC).
In this "Arm" we reported results from the ACC subgroup.

Reporting group title	Non-Adenoid Cystic Carcinoma (Non ACC)

Reporting group description:

Salivary Glands Carcinoma were separated in two cohorts/sub-groups: Adenoid Cystic Carcinoma (ACC) and Non-Adenoid Cystic Carcinoma (Non ACC).
In this "Arm" we reported results from the Non ACC subgroup.

Primary: The 6-month progression-free survival (PFS) rate.

End point title	The 6-month progression-free survival (PFS) rate.[1]

End point description:

The primary endpoint was the 6-month progression-free survival (PFS) rate. Disease progression or death of any cause were considered as PFS events.
The PFS rates will be estimated and presented with the associated 95% CI.

End point type	Primary

End point timeframe:

6 weeks after treatment initiation

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 was not designed to compare ACC and Non-ACC population. Thus, statistical comparisons by hypothesis tests between groups were not planned.

End point values	Adenoid cystic carcinoma (ACC)	Non-Adenoid Cystic Carcinoma (Non ACC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	18		
Units: percent				
number (confidence interval 95%)				
Response rate	47 (33 to 61)	50 (29 to 71)		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary endpoint:Objective response rate (ORR)

End point title	Secondary endpoint:Objective response rate (ORR)

End point description:

The ORR was defined as the proportion of patients with complete (CR) or partial responses (PR),

according to RECIST v1.0.

End point type	Secondary

End point timeframe:

The tumour assessments, performed at baseline (within 14 days of starting treatment) and at 12 weeks (after 3 cycles of treatment), were used to assess the 12-week ORR.

End point values	Adenoid cystic carcinoma (ACC)	Non-Adenoid Cystic Carcinoma (Non ACC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	18		
Units: percent				
median (confidence interval 95%)				
median (confidence interval 95%)	2 (0 to 12)	6 (0 to 27)		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary: progression-free survival (PFS)

End point title	Secondary: progression-free survival (PFS)

End point description:

PFS was defined as the time interval between start of treatment and first document disease progression or death from any cause, whichever occurred first.
The tumour assessments, performed at baseline (within 14 days of starting treatment) and then every 12 weeks until disease progression, were used to assess PFS.

End point type	Secondary

End point timeframe:

The tumour assessments, performed at baseline (within 14 days of starting treatment) and then every 12 weeks until disease progression, were used to assess PFS.

End point values	Adenoid cystic carcinoma (ACC)	Non-Adenoid Cystic Carcinoma (Non ACC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	18		
Units: percent				
median (confidence interval 95%)				
median (confidence interval 95%)	5.93 (3.67 to 8.20)	6.74 (2.59 to 8.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary: Overall survival

End point title	Secondary: Overall survival

End point description:

OS was defined as the time interval between start of treatment and death from any cause, whichever occurred first.

End point type	Secondary

End point timeframe:

OS was defined as the time interval between start of treatment and death from any cause, whichever occurred first.

End point values	Adenoid cystic carcinoma (ACC)	Non-Adenoid Cystic Carcinoma (Non ACC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45[2]	18[3]		
Units: Months				
number (not applicable)				
median (confidence interval 95%)	17.0	0		

Notes:

[2] - The median OS was 17.0 months (95% CI: 10.7-not reached).

[3] - The median OS has not been reached.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From inclusion until 30 days after end of treatment (up to 1 year).

Adverse event reporting additional description:

Safety analysis

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16

Reporting groups

Reporting group title	Adenoid cystic carcinoma (ACC)

Reporting group description:

Salivary Glands Carcinoma were separated in two cohorts/sub-groups: Adenoid Cystic Carcinoma (ACC) and Non-Adenoid Cystic Carcinoma (Non ACC).
In this "Arm" we reported results from the ACC subgroup.

Reporting group title	Non-Adenoid Cystic Carcinoma (Non ACC)

Reporting group description:

Salivary Glands Carcinoma were separated in two cohorts/sub-groups: Adenoid Cystic Carcinoma (ACC) and Non-Adenoid Cystic Carcinoma (Non ACC).
In this "Arm" we reported results from the Non ACC subgroup.

Serious adverse events	Adenoid cystic carcinoma (ACC)	Non-Adenoid Cystic Carcinoma (Non ACC)	
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 49 (51.02%)	11 / 20 (55.00%)	
number of deaths (all causes)	17	6	
number of deaths resulting from adverse events	2	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 49 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumor progression			
subjects affected / exposed	1 / 49 (2.04%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
hypertension arterial			

subjects affected / exposed	1 / 49 (2.04%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischemic stroke			
subjects affected / exposed	1 / 49 (2.04%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 49 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 49 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Performance status decreased			
subjects affected / exposed	1 / 49 (2.04%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	1 / 49 (2.04%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 49 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchopneumopathy			
subjects affected / exposed	1 / 49 (2.04%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumopathy			
subjects affected / exposed	2 / 49 (4.08%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hemoptysis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 49 (2.04%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
biopsy of lung			
subjects affected / exposed	3 / 49 (6.12%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Elevated liver enzymes			
subjects affected / exposed	1 / 49 (2.04%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 49 (2.04%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Left ventricular systolic dysfunction			
subjects affected / exposed	0 / 49 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	1 / 49 (2.04%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	

Myocardial infarction			
subjects affected / exposed	1 / 49 (2.04%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain abscess			
subjects affected / exposed	1 / 49 (2.04%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocephalus			
subjects affected / exposed	1 / 49 (2.04%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 49 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 49 (2.04%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Epigastralgia			
subjects affected / exposed	0 / 49 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 49 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorder gastrointestinal			

subjects affected / exposed	1 / 49 (2.04%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Mucositis oral			
subjects affected / exposed	1 / 49 (2.04%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	2 / 49 (4.08%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Drug-induced hepatitis			
subjects affected / exposed	0 / 49 (0.00%)	2 / 20 (10.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cytolysis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin erosion			
subjects affected / exposed	0 / 49 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 49 (2.04%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 49 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
staphylococcus aureus skin infection			
subjects affected / exposed	0 / 49 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis of face			
subjects affected / exposed	1 / 49 (2.04%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	1 / 49 (2.04%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 49 (2.04%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Adenoid cystic carcinoma (ACC)	Non-Adenoid Cystic Carcinoma (Non ACC)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 49 (100.00%)	20 / 20 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumoral pain			
subjects affected / exposed	2 / 49 (4.08%)	4 / 20 (20.00%)	
occurrences (all)	2	27	
Vascular disorders			

Hot flushes			
subjects affected / exposed	5 / 49 (10.20%)	3 / 20 (15.00%)	
occurrences (all)	11	30	
Hypertension			
subjects affected / exposed	21 / 49 (42.86%)	8 / 20 (40.00%)	
occurrences (all)	165	43	
Hypotension			
subjects affected / exposed	4 / 49 (8.16%)	2 / 20 (10.00%)	
occurrences (all)	12	4	
Paleness			
subjects affected / exposed	2 / 49 (4.08%)	0 / 20 (0.00%)	
occurrences (all)	5	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	43 / 49 (87.76%)	13 / 20 (65.00%)	
occurrences (all)	324	119	
Pain			
subjects affected / exposed	6 / 49 (12.24%)	1 / 20 (5.00%)	
occurrences (all)	18	8	
Facial pain			
subjects affected / exposed	3 / 49 (6.12%)	1 / 20 (5.00%)	
occurrences (all)	4	7	
Thoracic pain			
subjects affected / exposed	11 / 49 (22.45%)	2 / 20 (10.00%)	
occurrences (all)	38	2	
Deterioration of general health status			
subjects affected / exposed	3 / 49 (6.12%)	1 / 20 (5.00%)	
occurrences (all)	3	1	
Fever			
subjects affected / exposed	8 / 49 (16.33%)	3 / 20 (15.00%)	
occurrences (all)	9	4	
Shivering			
subjects affected / exposed	3 / 49 (6.12%)	0 / 20 (0.00%)	
occurrences (all)	10	0	
Mucous inflammation			

subjects affected / exposed	19 / 49 (38.78%)	4 / 20 (20.00%)	
occurrences (all)	19	11	
Feeling of faintness			
subjects affected / exposed	2 / 49 (4.08%)	4 / 20 (20.00%)	
occurrences (all)	3	5	
Facial oedema			
subjects affected / exposed	5 / 49 (10.20%)	2 / 20 (10.00%)	
occurrences (all)	17	6	
Peripheral oedema			
subjects affected / exposed	7 / 49 (14.29%)	1 / 20 (5.00%)	
occurrences (all)	42	1	
Flu syndrome			
subjects affected / exposed	3 / 49 (6.12%)	1 / 20 (5.00%)	
occurrences (all)	4	1	
Xerosis			
subjects affected / exposed	5 / 49 (10.20%)	1 / 20 (5.00%)	
occurrences (all)	22	10	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	3 / 49 (6.12%)	4 / 20 (20.00%)	
occurrences (all)	13	5	
Dyspnoea			
subjects affected / exposed	13 / 49 (26.53%)	6 / 20 (30.00%)	
occurrences (all)	43	17	
Epistaxis			
subjects affected / exposed	15 / 49 (30.61%)	5 / 20 (25.00%)	
occurrences (all)	59	9	
Nasal obstruction			
subjects affected / exposed	2 / 49 (4.08%)	0 / 20 (0.00%)	
occurrences (all)	6	0	
Pneumothorax			
subjects affected / exposed	1 / 49 (2.04%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			

subjects affected / exposed	1 / 49 (2.04%)	2 / 20 (10.00%)	
occurrences (all)	7	11	
Cough			
subjects affected / exposed	13 / 49 (26.53%)	5 / 20 (25.00%)	
occurrences (all)	52	20	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	4 / 49 (8.16%)	4 / 20 (20.00%)	
occurrences (all)	7	8	
Depression			
subjects affected / exposed	3 / 49 (6.12%)	2 / 20 (10.00%)	
occurrences (all)	10	29	
Insomnia			
subjects affected / exposed	6 / 49 (12.24%)	5 / 20 (25.00%)	
occurrences (all)	26	17	
Sleep disorder			
subjects affected / exposed	0 / 49 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	40	
Nervous system disorders			
Ageusia			
subjects affected / exposed	2 / 49 (4.08%)	1 / 20 (5.00%)	
occurrences (all)	5	1	
Headache			
subjects affected / exposed	16 / 49 (32.65%)	10 / 20 (50.00%)	
occurrences (all)	45	49	
Dysgeusia			
subjects affected / exposed	10 / 49 (20.41%)	3 / 20 (15.00%)	
occurrences (all)	62	13	
Migraine			
subjects affected / exposed	2 / 49 (4.08%)	0 / 20 (0.00%)	
occurrences (all)	9	0	
Neuralgia			
subjects affected / exposed	2 / 49 (4.08%)	1 / 20 (5.00%)	
occurrences (all)	10	5	
Neuromyopathy			

subjects affected / exposed	2 / 49 (4.08%)	0 / 20 (0.00%)	
occurrences (all)	12	0	
Peripheral neuropathy			
subjects affected / exposed	5 / 49 (10.20%)	0 / 20 (0.00%)	
occurrences (all)	11	0	
Palm-chin reflex			
subjects affected / exposed	3 / 49 (6.12%)	2 / 20 (10.00%)	
occurrences (all)	21	3	
Burning sensation			
subjects affected / exposed	2 / 49 (4.08%)	0 / 20 (0.00%)	
occurrences (all)	8	0	
Dizziness			
subjects affected / exposed	8 / 49 (16.33%)	5 / 20 (25.00%)	
occurrences (all)	19	23	
Somnolence			
subjects affected / exposed	5 / 49 (10.20%)	2 / 20 (10.00%)	
occurrences (all)	12	13	
Equilibrium problems			
subjects affected / exposed	2 / 49 (4.08%)	1 / 20 (5.00%)	
occurrences (all)	10	38	
trembling			
subjects affected / exposed	0 / 49 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	6	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	3 / 49 (6.12%)	3 / 20 (15.00%)	
occurrences (all)	8	10	
Ear pain			
subjects affected / exposed	3 / 49 (6.12%)	1 / 20 (5.00%)	
occurrences (all)	15	1	
Vertigo			
subjects affected / exposed	2 / 49 (4.08%)	3 / 20 (15.00%)	
occurrences (all)	2	30	
Eye disorders			
Increased lachrymal secretion			

subjects affected / exposed	2 / 49 (4.08%)	1 / 20 (5.00%)	
occurrences (all)	14	9	
Conjunctivitis			
subjects affected / exposed	3 / 49 (6.12%)	0 / 20 (0.00%)	
occurrences (all)	7	0	
Eye pain			
subjects affected / exposed	2 / 49 (4.08%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Visual defects			
subjects affected / exposed	4 / 49 (8.16%)	1 / 20 (5.00%)	
occurrences (all)	4	1	
Periorbital oedema			
subjects affected / exposed	2 / 49 (4.08%)	0 / 20 (0.00%)	
occurrences (all)	22	0	
Visual problems			
subjects affected / exposed	5 / 49 (10.20%)	1 / 20 (5.00%)	
occurrences (all)	22	1	
Gastrointestinal disorders			
Apyalism			
subjects affected / exposed	2 / 49 (4.08%)	0 / 20 (0.00%)	
occurrences (all)	7	0	
Dry mouth			
subjects affected / exposed	3 / 49 (6.12%)	1 / 20 (5.00%)	
occurrences (all)	6	16	
Constipation			
subjects affected / exposed	16 / 49 (32.65%)	5 / 20 (25.00%)	
occurrences (all)	62	11	
Diarrhoea			
subjects affected / exposed	32 / 49 (65.31%)	6 / 20 (30.00%)	
occurrences (all)	259	51	
Abdominal distention			
subjects affected / exposed	2 / 49 (4.08%)	2 / 20 (10.00%)	
occurrences (all)	2	3	
Abdominal pain			
subjects affected / exposed	19 / 49 (38.78%)	9 / 20 (45.00%)	
occurrences (all)	19	9	

Mouth pain			
subjects affected / exposed	2 / 49 (4.08%)	0 / 20 (0.00%)	
occurrences (all)	10	0	
Painful teeth			
subjects affected / exposed	3 / 49 (6.12%)	1 / 20 (5.00%)	
occurrences (all)	13	10	
Dyspepsia			
subjects affected / exposed	2 / 49 (4.08%)	1 / 20 (5.00%)	
occurrences (all)	2	1	
Dysphagia			
subjects affected / exposed	7 / 49 (14.29%)	1 / 20 (5.00%)	
occurrences (all)	30	4	
Flatulence			
subjects affected / exposed	3 / 49 (6.12%)	1 / 20 (5.00%)	
occurrences (all)	5	1	
Haemorrhoids			
subjects affected / exposed	5 / 49 (10.20%)	2 / 20 (10.00%)	
occurrences (all)	7	16	
Nausea			
subjects affected / exposed	29 / 49 (59.18%)	12 / 20 (60.00%)	
occurrences (all)	117	21	
Ptyalism			
subjects affected / exposed	2 / 49 (4.08%)	0 / 20 (0.00%)	
occurrences (all)	3	0	
Gastro-oesophageal reflux			
subjects affected / exposed	8 / 49 (16.33%)	0 / 20 (0.00%)	
occurrences (all)	22	0	
Bleeding gums			
subjects affected / exposed	3 / 49 (6.12%)	0 / 20 (0.00%)	
occurrences (all)	9	0	
Stomatitis			
subjects affected / exposed	8 / 49 (16.33%)	0 / 20 (0.00%)	
occurrences (all)	17	0	
Vomiting			
subjects affected / exposed	12 / 49 (24.49%)	8 / 20 (40.00%)	
occurrences (all)	23	10	

Glossodynia			
subjects affected / exposed	0 / 49 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	5	
Hepatobiliary disorders			
Hepatocellular lesions			
subjects affected / exposed	4 / 49 (8.16%)	1 / 20 (5.00%)	
occurrences (all)	24	1	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	10 / 49 (20.41%)	2 / 20 (10.00%)	
occurrences (all)	72	36	
Hair colour changes			
subjects affected / exposed	11 / 49 (22.45%)	4 / 20 (20.00%)	
occurrences (all)	146	50	
Pruritis			
subjects affected / exposed	4 / 49 (8.16%)	1 / 20 (5.00%)	
occurrences (all)	14	2	
Rash			
subjects affected / exposed	6 / 49 (12.24%)	0 / 20 (0.00%)	
occurrences (all)	33	0	
Erythema			
subjects affected / exposed	4 / 49 (8.16%)	3 / 20 (15.00%)	
occurrences (all)	25	5	
Erythrose			
subjects affected / exposed	2 / 49 (4.08%)	0 / 20 (0.00%)	
occurrences (all)	10	0	
Skin pain			
subjects affected / exposed	2 / 49 (4.08%)	1 / 20 (5.00%)	
occurrences (all)	2	1	
Acral syndrome			
subjects affected / exposed	2 / 49 (4.08%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Dry skin			
subjects affected / exposed	6 / 49 (12.24%)	4 / 20 (20.00%)	
occurrences (all)	16	65	
Dysphonia			

subjects affected / exposed	4 / 49 (8.16%)	1 / 20 (5.00%)	
occurrences (all)	13	1	
Renal and urinary disorders			
Kidney failure			
subjects affected / exposed	2 / 49 (4.08%)	0 / 20 (0.00%)	
occurrences (all)	4	0	
Proteinuria			
subjects affected / exposed	1 / 49 (2.04%)	2 / 20 (10.00%)	
occurrences (all)	1	3	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	3 / 49 (6.12%)	1 / 20 (5.00%)	
occurrences (all)	7	2	
Hypothyroidism			
subjects affected / exposed	10 / 49 (20.41%)	5 / 20 (25.00%)	
occurrences (all)	26	16	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 49 (12.24%)	2 / 20 (10.00%)	
occurrences (all)	33	10	
Cervicalgia			
subjects affected / exposed	5 / 49 (10.20%)	2 / 20 (10.00%)	
occurrences (all)	19	3	
Muscle contractures			
subjects affected / exposed	12 / 49 (24.49%)	2 / 20 (10.00%)	
occurrences (all)	53	18	
Dorsalgia			
subjects affected / exposed	9 / 49 (18.37%)	1 / 20 (5.00%)	
occurrences (all)	26	1	
Jaw pain			
subjects affected / exposed	5 / 49 (10.20%)	2 / 20 (10.00%)	
occurrences (all)	15	6	
Musculo-skeletal pain			
subjects affected / exposed	3 / 49 (6.12%)	2 / 20 (10.00%)	
occurrences (all)	3	2	
Bone pain			

subjects affected / exposed	2 / 49 (4.08%)	2 / 20 (10.00%)	
occurrences (all)	8	6	
Pain of the extremities			
subjects affected / exposed	3 / 49 (6.12%)	3 / 20 (15.00%)	
occurrences (all)	12	7	
Muscle weakness			
subjects affected / exposed	2 / 49 (4.08%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Myalgia			
subjects affected / exposed	5 / 49 (10.20%)	3 / 20 (15.00%)	
occurrences (all)	26	5	
Trismus (lockjaw)			
subjects affected / exposed	2 / 49 (4.08%)	2 / 20 (10.00%)	
occurrences (all)	6	3	
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 49 (4.08%)	1 / 20 (5.00%)	
occurrences (all)	2	1	
Ear infection			
subjects affected / exposed	2 / 49 (4.08%)	0 / 20 (0.00%)	
occurrences (all)	3	0	
Dental infection			
subjects affected / exposed	2 / 49 (4.08%)	1 / 20 (5.00%)	
occurrences (all)	4	1	
Urinary tract infection			
subjects affected / exposed	3 / 49 (6.12%)	1 / 20 (5.00%)	
occurrences (all)	8	3	
Pulmonary infection			
subjects affected / exposed	3 / 49 (6.12%)	1 / 20 (5.00%)	
occurrences (all)	5	2	
Oral mycosis			
subjects affected / exposed	2 / 49 (4.08%)	0 / 20 (0.00%)	
occurrences (all)	5	0	
Rhinitis			
subjects affected / exposed	8 / 49 (16.33%)	1 / 20 (5.00%)	
occurrences (all)	31	7	

Gastroenteritis			
subjects affected / exposed	0 / 49 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Rhinolaryngitis			
subjects affected / exposed	0 / 49 (0.00%)	3 / 20 (15.00%)	
occurrences (all)	0	3	
Sinusitis			
subjects affected / exposed	1 / 49 (2.04%)	2 / 20 (10.00%)	
occurrences (all)	3	4	
Metabolism and nutrition disorders			
Diminished appetite			
subjects affected / exposed	19 / 49 (38.78%)	5 / 20 (25.00%)	
occurrences (all)	59	30	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 April 2013	-The surveillance of liver function during pazopanib treatment had been updated. Consequently, the protocol and informed consent forms were modified. -Details concerning the thoraco-abdominal-pelvic scan and the direct bilirubin testing required were clarified.
12 October 2013	-Modification of Annex 8 concerning the blood pressure measurements. The protocol was updated to indicated that 3 measures, with a minimum interval of 3 min, were to be made. The average of the 3 readings would be recorded. -Following the issuing of a SUSAR in another clinical study using pazopanib. The study documents were modified to indicate that the pazopanib tablet was to be ingested whole (not broken nor crushed) with water, at least an hour before or 2 h after breakfast. -The protocol contact details were updated. -Updating of the investigator list.
10 April 2014	-The study documents were updated following the release of version 10 (22-Feb-2013) of the investigator brochure (pazopanib). -The protocol contact details were updated. -Updating of the investigator list.
22 July 2014	-Clarification of the Inclusion criterion N°2 to clearly define disease progression. In addition, patients treated between diagnosis of disease progression and study inclusion were not eligible. -The ethics committee was provided with version 11 of the investigator brochure (pazopanib). The protocol did not require updating following the release of this new version. -Updating of the investigator list
18 February 2015	-Modification of the eligibility criteria: -Addition of inclusion criteria requiring normal thyroid function (TSH level >0.3 µU/mL but <6 µU/mL; free T4 levels >9 pmol/L but <29 pmol/L). -Addition of a non-inclusion criterion excluding patients with severe or uncontrolled general medical conditions that in the investigator's opinion would interfere with the study conduct. -Updating of the investigator brochure. -Updating of sponsor details.
24 March 2016	Updating of the investigator list.
03 August 2016	-The protocol was updated to allow the use of the commercial stock of pazopanib (bottles containing 30 tablets instead of 34 tablets). The dose remained unchanged at 200 mg/tablet. -Updating of the expected adverse events (annex 5 of the protocol). -Updating of the sponsor contact details
10 May 2017	Updating of the investigator list.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported