Clinical trial results:
A phase II triAl of Cabozantinib for hepaTocellular carcInoma patients intOlerant to sorafenib treatment or first line treatment different to sorafeNib. (ACTION trial)

Summary

EudraCT number	2019-004991-20
Trial protocol	ES
Global end of trial date	22 February 2023

Results information

Result version number	v1 (current)
This version publication date	15 February 2024
First version publication date	15 February 2024

Trial information

Trial identification

Sponsor protocol code	ACTION

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04316182
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	FRCB - IDIBAPS (Fundació de Recerca Clínic Barcelona - Institut d'Investigacions Biomèdiques August Pi i Sunyer) – Hospital Clinic de Barcelona
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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	29 November 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 February 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety profile established by rate of adverse events (AE) with Common Terminology Criteria for Adverse Events (CTCAE)≥3 excluding palmar-plantar erythordysthesia, rate of related-AEs and rate of death. The rate of AEs leading to treatment discontinuation.

Protection of trial subjects:

All patients including in Safety set signed informed consent and meet the selection criteria.
To ensure patient safety, the following procedures were performed at all study visits during treatment: Physical examination, ECOG performance status, Vital signs, Assessment of AEs/SAEs, Concomitant medications, Serum chemistry, Hematology, Coagulation (PT, INR, PTT) and Urinalysis.
Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 July 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 24
Worldwide total number of subjects	24
EEA total number of subjects	24

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)	7

From 65 to 84 years	16
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The screened patients were 29 and 4 of them were screening failure. From all included subjects (25), 24 (96%) were included in Safety population. The excluded patient did not receive the study medication.

Pre-assignment

Screening details:

The screened patients were 29 and 4 of them were screening failure: one due to adverse event, one due to Investigator decision and two patients do not meet eligibility criteria. One patient did not receive the 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	Cabozantinib

Arm description:

Cabozantinib 60 mg/day.

Arm type	Experimental
Investigational medicinal product name	Cabozantinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Cabozantinib was initiated at full dose (60 mg/day) and the dose was modified upon development of adverse events according to the study protocol and continued until symptomatic tumor progression, unacceptable adverse events, patient decision or death.

Number of subjects in period 1	Cabozantinib
Started	24
Completed	24

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	24	24	
Age categorical Units: Subjects			
Adults (18-64 years)	7	7	
From 65-84 years	16	16	
85 years and over	1	1	
Age continuous Units: years			
arithmetic mean	69.67		
standard deviation	± 10.37	-	
Gender categorical Units: Subjects			
Female	9	9	
Male	15	15	
Race Units: Subjects			
Black or African American	1	1	
Latin or Hispanic	1	1	
White	22	22	
Tumor burden Units: Subjects			
Extrahepatic spread	3	3	
Multinodular	14	14	
Portal invasion	4	4	
Single or up to 3 nodules >= 3cm	3	3	
Cirrhosis Units: Subjects			
Yes	19	19	
No	5	5	
Vascular Invasion Units: Subjects			
Yes	8	8	
No	16	16	
ECOG Units: Subjects			
ECOG 0	20	20	
ECOG 1	4	4	
First line treatment Units: Subjects			
Atezolizumab+bevacizumab	3	3	
Lenvatinib	1	1	

Nivolumab+ipilimumab	1	1	
Sorafenib	18	18	
Tislelizumab	1	1	
Worst type of progression Units: Subjects			
Extrahepatic growth	2	2	
Intrahepatic growth	8	8	
New extrahepatic lesion	1	1	
New intrahepatic lesion	11	11	
NA	2	2	
Worst first progression pattrern Units: Subjects			
Extrahepatic growth	2	2	
Intrahepatic growth	7	7	
New extrahepatic lesion	3	3	
New intrahepatic lesion	10	10	
NA	2	2	

Subject analysis sets

Subject analysis set title	Overall
Subject analysis set type	Full analysis

Subject analysis set description:
Patients who received study intervention

Reporting group values	Overall		
Number of subjects	24		
Age categorical Units: Subjects			
Adults (18-64 years)	7		
From 65-84 years	16		
85 years and over	1		
Age continuous Units: years			
arithmetic mean	69.67		
standard deviation	± 10.37		
Gender categorical Units: Subjects			
Female	9		
Male	15		
Race Units: Subjects			
Black or African American	1		
Latin or Hispanic	1		
White	22		
Tumor burden Units: Subjects			
Extrahepatic spread	3		
Multinodular	14		
Portal invasion	4		
Single or up to 3 nodules >= 3cm	3		

Cirrhosis Units: Subjects			
Yes	19		
No	5		
Vascular Invasion Units: Subjects			
Yes	8		
No	16		
ECOG Units: Subjects			
ECOG 0	20		
ECOG 1	4		
First line treatment Units: Subjects			
Atezolizumab+bevacizumab	3		
Lenvatinib	1		
Nivolumab+ipilimumab	1		
Sorafenib	18		
Tislelizumab	1		
Worst type of progression Units: Subjects			
Extrahepatic growth	2		
Intrahepatic growth	8		
New extrahepatic lesion	1		
New intrahepatic lesion	11		
NA	2		
Worst first progression pattrern Units: Subjects			
Extrahepatic growth	2		
Intrahepatic growth	7		
New extrahepatic lesion	3		
New intrahepatic lesion	10		
NA	2		

End points

End points reporting groups

Reporting group title	Cabozantinib
Reporting group description: Cabozantinib 60 mg/day.	
Subject analysis set title	Overall
Subject analysis set type	Full analysis
Subject analysis set description: Patients who received study intervention	

Primary: Adverse event (CTCAE)>=3 excluding palmar-plantar erythordysthesia

End point title	Adverse event (CTCAE)>=3 excluding palmar-plantar erythordysthesia[1]
End point description: Patients with grade >=3 adverse events, excluding palmar-plantar erythrodysthesia.	
End point type	Primary
End point timeframe: At every study visit until end 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: Only descriptive analysis performed.

End point values	Overall			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: Patients				
Yes	16			
No	8			

Statistical analyses

No statistical analyses for this end point

Primary: Treatment-related adverse events

End point title	Treatment-related adverse events[2]
End point description: Patients with related adverse events.	
End point type	Primary
End point timeframe: At every study visit until end 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: Only descriptive analysis performed.

End point values	Overall			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: Patients				
Yes	24			
No	0			

Statistical analyses

No statistical analyses for this end point

Primary: Adverse event resulting in death.

End point title	Adverse event resulting in death.[3]

End point description:

Patients with adverse events resulting in death.

End point type	Primary

End point timeframe:

At every study visit until end 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: Only descriptive analysis performed.

End point values	Overall			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: Patients				
Yes	0			
No	24			

Statistical analyses

No statistical analyses for this end point

Primary: Adverse events leading to discontinuation

End point title	Adverse events leading to discontinuation[4]

End point description:

Patients with adverse events leading to discontinuation.

End point type	Primary

End point timeframe:

At every study visit until end of treatment.

Notes:

[4] - 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 analysis performed.

End point values	Overall			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: Patients				
Yes	3			
No	21			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

The time from the inclusion date to death from any cause.

End point type	Secondary

End point timeframe:

Every 3 months.

End point values	Overall			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: month				
median (confidence interval 95%)	11 (8 to 20)			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate

End point title	Objective response rate

End point description:

Defined as a partial or complete response at any time, i.e. the best response from inclusion along all follow-up.

End point type	Secondary

End point timeframe:

Every 8 weeks.

End point values	Overall			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: Percentage				
number (confidence interval 95%)				
Yes	8.3 (1.0 to 27.0)			
No	91.7 (73.0 to 99.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to progression

End point title	Time to progression

End point description:

The time from the inclusion date to progression.

End point type	Secondary

End point timeframe:

Every 8 weeks.

End point values	Overall			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: month				
median (confidence interval 95%)	6 (3 to 8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pattern of progression

End point title	Pattern of progression

End point description:

Patterns of progression:
- Intrahepatic growth (IHG): increased size of intrahepatic target lesions or progression of intrahepatic "non-target" lesions at baseline.
- New intrahepatic lesion (NIH): emergence of new intrahepatic lesions
- Extrahepatic growth (EHG): increased size of extrahepatic target lesions, progression of extrahepatic "non-target" lesions at baseline or progression of the existing vascular invasion.
- New extrahepatic lesion (NEL): emergence of new extrahepatic lesions or emergence of vascular invasion.

End point type	Secondary

End point timeframe:

Every 8 weeks

End point values	Overall			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: Percentage				
Intrahepatic growth (IHG)	44			
New intrahepatic lesion (NIH)	22			
Extrahepatic growth (EHG)	11			
New extrahepatic lesion (NEH)	22			

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of patients who develop new extra-hepatic spread

End point title	Rate of patients who develop new extra-hepatic spread

End point description:

Rate of patients who develop new extra-hepatic spread

End point type	Secondary

End point timeframe:

Every 8 weeks

End point values	Overall			
Subject group type	Subject analysis set			
Number of subjects analysed	18[5]			
Units: Percentage				
Yes	22			
No	78			

Notes:

[5] - 5 patients (of 23 progressed) died due to PD without having a corresponding radiological evaluation.

Statistical analyses

No statistical analyses for this end point

Secondary: Post-progression survival

End point title	Post-progression survival

End point description:

For those patients who progressed, the time from the progression date to death from any cause.

End point type	Secondary

End point timeframe:

Every 3 months

End point values	Overall			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: month				
median (confidence interval 95%)	5 (2 to 9999)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were evaluated at each study visit. AEs occurring after the subject signed the informed consent form until the end of the safety follow-up period were collected.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Overall

Reporting group description:

Screened patients who meet selection criteria and received study medication.

Serious adverse events	Overall		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 24 (33.33%)		
number of deaths (all causes)	15		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Rectal haemorrhage			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal ischaemia			

subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Peritonitis bacterial			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin infection			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
COVID-19			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Overall		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 24 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Vascular disorders			
Epistaxis			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	2		
Haematoma			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	16 / 24 (66.67%)		
occurrences (all)	27		
Orthostatic hypotension			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	6 / 24 (25.00%)		
occurrences (all)	21		
Chills			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Discomfort			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	12 / 24 (50.00%)		
occurrences (all)	17		
Granuloma			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		

Mucosal inflammation subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 3		
Oedema subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2		
Oedema peripheral subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 3		
Pain subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Pyrexia subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2		
Decreased appetite subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2		
Non-cardiac chest pain subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Illness subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Respiratory, thoracic and mediastinal disorders			
Aphonia subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Cough subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Dysphonia subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Dyspnoea			

subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Productive cough			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 24 (20.83%)		
occurrences (all)	16		
Amylase increased			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 24 (25.00%)		
occurrences (all)	13		
Blood bilirubin increased			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	3		
Blood lactate dehydrogenase increased			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	4		
Blood pressure ambulatory increased			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	2		
Blood thyroid stimulating hormone increased			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		

Haemoglobin decreased			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Haemoglobin increased			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Platelet count decreased			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Protein albumin ratio			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Transaminases increased			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	5		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Ligament sprain			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	2		
Contusion			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Wound			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Joint injury			

subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Limb injury			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	3		
Eyelid injury			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Encephalopathy			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	3		
Hepatic encephalopathy			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Radiculopathy			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Tension headache			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Leukopenia			

subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Neutropenia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Pancytopenia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	4		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Eye disorders			
Erythema of eyelid			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Abdominal pain			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	6		
Abdominal pain upper			
subjects affected / exposed	5 / 24 (20.83%)		
occurrences (all)	6		
Ascites			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		
Constipation			
subjects affected / exposed	6 / 24 (25.00%)		
occurrences (all)	7		
Diarrhoea			
subjects affected / exposed	12 / 24 (50.00%)		
occurrences (all)	31		
Dysgeusia			

subjects affected / exposed	1 / 24 (4.17%)			
occurrences (all)	1			
Dyspepsia				
subjects affected / exposed	5 / 24 (20.83%)			
occurrences (all)	6			
Dysphagia				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences (all)	1			
Faeces pale				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences (all)	1			
Gastrointestinal haemorrhage				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences (all)	1			
Haemorrhoids				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences (all)	1			
Intestinal ischaemia				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences (all)	1			
Nausea				
subjects affected / exposed	5 / 24 (20.83%)			
occurrences (all)	6			
Odynophagia				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences (all)	1			
Oesophagitis				
subjects affected / exposed	2 / 24 (8.33%)			
occurrences (all)	2			
Rectal haemorrhage				
subjects affected / exposed	2 / 24 (8.33%)			
occurrences (all)	4			
Tooth loss				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences (all)	1			
Vomiting				

subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	5		
Oral dysaesthesia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Oral disorder			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Pancreatic failure			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	2		
Hypoalbuminaemia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Jaundice			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Hair colour changes			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Hyperhidrosis			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Hyperkeratosis			

subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	15 / 24 (62.50%)		
occurrences (all)	46		
Prurigo			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
pruritus			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	7		
Rash			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		
Skin disorder			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Skin lesion			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	3		
Cellulite			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Sensitive skin			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Anal rash			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Urinary retention			

subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	4		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		
Back pain			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	7		
Muscle spasms			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Myalgia			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Torticollis			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	2		
Sacral pain			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	2		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	2		
Musculoskeletal discomfort			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	2		
Spinal pain			

subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Infections and infestations			
Cystitis			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Gingivitis			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Hordeolum			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Oral candidiasis			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Orchitis			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Postoperative wound infection			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Pyuria			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	2		
Oropharyngeal candidiasis			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		

Peri-implantitis			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
COVID-19			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	4		
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Hypomagnesaemia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	2		
Hyponatraemia			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	3		
Hypophosphataemia			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	3		
Early satiety			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Decreased appetite			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	8		
Hypophagia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 August 2020	Amendement 1: This amendment includes 2 new Quality of life Questionnaires, the alert card and patient diary.
15 July 2021	Amendment 2: This amendment extends the trial recruitment period for 1 year, updates the Reference Safety Information with Cabozantinib Investigator Brochure version 16.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported