Clinical trial results:
Phase II study of cabozantinib in patients with metastatic gastrointestinal stromal tumor (GIST) who progressed during neoadjuvant, adjuvant or palliative therapy with imatinib and sunitinib

Summary

EudraCT number	2014-000501-13
Trial protocol	BE DE HU GB
Global end of trial date	12 March 2021

Results information

Result version number	v2 (current)
This version publication date	20 March 2022
First version publication date	25 September 2021
Version creation reason	• Correction of full data set Correction of numbers needed

Trial information

Trial identification

Sponsor protocol code	1317-STBSG

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02216578
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	European Organisation for the Research and Treatment of Cancer (EORTC)
Sponsor organisation address	Avenue E. Mounierlaan 83/11, Brussels, Belgium, 1200
Public contact	Clinical Operations Department, European Organisation for the Research and Treatment of Cancer (EORTC), +32 2774, regulatory@eortc.be
Scientific contact	Clinical Operations Department, European Organisation for the Research and Treatment of Cancer (EORTC), +32 2774, regulatory@eortc.be

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	10 September 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 September 2019
Global end of trial reached?	Yes
Global end of trial date	12 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective is to assess the safety and activity of cabozantinib in patients with metastatic GIST who have previously progressed on imatinib and sunitinib and have not been exposed yet to other KIT- or PDGFR-directed tyrosine kinase inhibitors such as regorafenib or similar agents.

Protection of trial subjects:

The responsible investigator ensure that this study was conducted in agreement with either the Declaration of Helsinki (available on the World Medical Association web site (http://www.wma.net)) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient. The protocol had been written, and the study was conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP, available online at https://www.ema.europa.eu/documents/scientific-guideline/ich-e6-r1-guideline-good-clinicalpractice_en.pdf). The protocol was approved by the competent ethics committee(s) as required

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 October 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	France: 20
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Hungary: 7
Worldwide total number of subjects	50
EEA total number of subjects	50

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)	27
From 65 to 84 years	23
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 50 patients were registered by 11 institutions between February 28, 2017 and August 31, 2018.

Pre-assignment

Screening details:

Eligible patients aged at least 18 years, had ECOG performance status (PS) of 0-1 and adequate bone marrow and organ function prior to receiving the first dose of study treatmentn. Histologically confirmed diagnosis of GIST that is metastatic. Failure on prior therapy with imatinib and sunitinib.

Pre-assignment period milestones

Number of subjects started	50
Number of subjects completed	50

Period 1

Period 1 title	Overall period - Full patient population (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Arm I

Arm description:

Cabozantinib was provided by Exelixis Inc., Alameda (United States) as 60 mg and 20 mg yellow film-coated tablets. Tablets were taken once daily at a starting dose of 60 mg, and patients were instructed not to eat for at least 2 h before and at least 1 h after taking cabozantinib. One treatment cycle was defined as 21 d of continuous dosing. Treatment was continued until patients experienced no further benefit, became intolerant to the drug or wished to discontinue the treatment. Treatment beyond RECIST 1.1 progression was allowed.

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

Dosage and administration details:

Cabozantinib was adequately provided by Exelixis free of charge as 60-mg and 20-mg yellow film-coated tablets. The 60-mg tablets were oval and the 20-mg tablets were round. One cycle of treatment was defined as 21 days of continuous dosing. Cabozantinib tablets were administered once daily at a starting dose of 60 mg, and patients were instructed not to eat for at least 2 hours before and at least 1 hour after taking cabozantinib.

Number of subjects in period 1	Arm I
Started	50
Completed	0
Not completed	50
Still on treatment at analysis	4
Toxicity	4
Patient's decision	2
Lost to follow-up	1
Progression of disease	39

Baseline characteristics

Reporting groups

Reporting group title	Overall period - Full patient population

Reporting group description: -

Reporting group values	Overall period - Full patient population	Total	
Number of subjects	50	50	
Age categorical Units: Subjects			
Adults (18-64 years)	27	27	
From 65-84 years	23	23	
Age continuous Units: years			
median	63		
full range (min-max)	35 to 82	-	
Gender categorical Units: Subjects			
Female	20	20	
Male	30	30	
Prior treatment for metastatic disease - Imatinib received Units: Subjects			
Yes	50	50	
No	0	0	
Prior treatment for metastatic disease - Sunitinib received Units: Subjects			
Yes	50	50	
No	0	0	
Prior treatment for metastatic disease - Surgery done Units: Subjects			
Yes	47	47	
No	3	3	
Prior treatment for metastatic disease - Radiotherapy received Units: Subjects			
Yes	4	4	
No	46	46	
ECOG Performance Status Units: Subjects			
ECOG 0	38	38	
ECOG 1	12	12	

End points

End points reporting groups

Reporting group title	Arm I

Reporting group description:

Cabozantinib was provided by Exelixis Inc., Alameda (United States) as 60 mg and 20 mg yellow film-coated tablets. Tablets were taken once daily at a starting dose of 60 mg, and patients were instructed not to eat for at least 2 h before and at least 1 h after taking cabozantinib. One treatment cycle was defined as 21 d of continuous dosing. Treatment was continued until patients experienced no further benefit, became intolerant to the drug or wished to discontinue the treatment. Treatment beyond RECIST 1.1 progression was allowed.

Subject analysis set title	Decision rule - primary patient population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

This clinical trial had a sample size that required 41 patients eligible and evaluable (this last one meaning that the patient started the study treatment and had an image assessment as baseline) for the primary analysis. To allow for a sufficient number of patients to be assessable for the decision rule of the primary endpoint, the screening continue beyond those 41 (to a maximum of 50 patients - resulting in the final number of patients in the study). For the "Decision rule - primary patient population", the first 41 eligible and evaluable patients were considered.

Subject analysis set title	All patients
Subject analysis set type	Full analysis

Subject analysis set description:

All patients

Primary: Progression free survival (PFS) at 12 weeks

End point title	Progression free survival (PFS) at 12 weeks

End point description:

PFS at 12 weeks was measured as a binary variable. Patients will be considered as a "success" if this radiological evaluation indicates either CR, PR or SD as defined by RECIST v1.1 (see hereunder); all other cases will be considered as failures (including patients who have progressed or died before the week 12 assessment, patients with unknown progression status at week 12, or patients who started new anti-tumor therapy in the absence of progressive disease).

End point type	Primary

End point timeframe:

This will be based on the disease evaluation by the local investigator of the radiological images performed 12 weeks after start of treatment.

End point values	Decision rule - primary patient population	All patients		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	41	50		
Units: Subjects				
Success	24	30		
Failure	17	20		

Statistical analyses

Statistical analysis title	Primary endpoint - A'Hern one stage design

Statistical analysis description:

A'Hern one stage design was used considering the following decision rule: P0 was taken as 40% - success in ≤ 40% of the cases was considered as unacceptable. P1 was taken as 60%. If at least 21 out of 41 eligible and evaluable patients were progression-free at the week 12 assessment, the activity of cabozantinib in this trial would be deemed sufficient to warrant further exploration of the drug in metastatic GIST. Type I and type II errors were fixed at 10% (alpha = beta = 0.10).

Comparison groups	All patients v Decision rule - primary patient population
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.0126 [2]
Method	Exact test, binomial proportion, 1-sided
Parameter estimate	Proportion estimate
Point estimate	0.585
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	0.74

Notes:

[1] - For the primary endpoint, PFS rate at 12 weeks was estimated using the Clopper-Pearson method for the (95%) confidence limits estimation in the primary analysis population.
This is a single arm test - two arms were provided due to EUDRACT reporting system limitation. The primary test is performed in the decision rule population only.

[2] - The corresponding exact p-values for the binomial proportion test (considering P0 was taken as 40%) is 0.0126.

Secondary: Progression free survival (PFS)

End point title	Progression free survival (PFS)

End point description:

PFS was estimated by the Kaplan-Meier (KM) method. Median PFS was provided with its 95% confidence interval.

Patients alive and free from progression at the time of the analysis were censored at the date of last disease assessment.

End point type	Secondary

End point timeframe:

PFS was computed from the date of start of treatment to the first documented date of progression (by central review of the radiological images based on RECIST v1.1) or death, whatever the cause, whichever occurs first.

End point values	Arm I	All patients		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	50	50		
Units: Months				
median (confidence interval 95%)	5.5 (3.6 to 6.9)	5.5 (3.6 to 6.9)		

Statistical analyses

Statistical analysis title	PFS - Full patient population

Statistical analysis description:

PFS was computed from the date of start of treatment to the first documented date of progression (by central review of the radiological images based on RECIST v1.1) or death, whatever the cause, whichever occurs first. Patients alive and free from progression at the time of the analysis were censored at the date of last disease assessment. PFS was estimated by the Kaplan-Meier (KM) method. Median PFS was provided with its 95% confidence interval.

Comparison groups	Arm I v All patients
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	Median PFS estimate
Point estimate	5.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.6
upper limit	6.9

Notes:

[3] - This is a single arm assessment - two arms were provided due to EUDRACT reporting system limitation

Secondary: Overall survival - Full patient population

End point title	Overall survival - Full patient population

End point description:

OS was estimated by the Kaplan-Meier (KM) method. Median OS was provided with its 95% confidence interval.

End point type	Secondary

End point timeframe:

OS was computed from the date of start of treatment to the date of death (due to any cause). Patients alive at the time of analysis were censored at the date of last follow-up.

End point values	Arm I	All patients		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	50	50[4]		
Units: months				
median (confidence interval 95%)	18.2 (14.3 to 22.3)	18.2 (14.3 to 22.3)		

Notes:

[4] - This is a single arm test - two arms were provided due to EUDRACT reporting system limitation

Statistical analyses

Statistical analysis title	OS - Full patient population

Statistical analysis description:

OS was computed from the date of start of treatment to the date of death (due to any cause). Patients alive at the time of analysis were censored at the date of last follow-up. OS was estimated by the Kaplan-Meier (KM) method. Median OS was provided with its 95% confidence interval.

Comparison groups	Arm I v All patients

Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other[5]
Parameter estimate	Median OS estimate
Point estimate	18.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.3
upper limit	22.3

Notes:

[5] - This is a single arm test - two arms were provided due to EUDRACT reporting system limitation

Secondary: Objective response rate (ORR)

End point title	Objective response rate (ORR)

End point description:

Response criteria was essentially based on a set of measurable lesions identified at baseline as target lesions, and – together with other lesions that are denoted as non-target lesions – followed until disease progression.

End point type	Secondary

End point timeframe:

ORR (Complete response + Partial response) was based on the best response recorded from the start of treatment until treatment discontinuation based on RECIST v1.1.

End point values	Arm I	All patients		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	50	50		
Units: Subjects				
Yes	7	7		
No	43	43		

Statistical analyses

Statistical analysis title	ORR - Full patient population

Statistical analysis description:

ORR (Complete response + Partial response) was based on the best response recorded from the start of treatment until treatment discontinuation based on RECIST v1.1. Response criteria was essentially based on a set of measurable lesions identified at baseline as target lesions, and – together with other lesions that are denoted as non-target lesions – followed until disease progression.
ORR was estimated using the Clopper-Pearson method for the (95%) confidence limits estimation.

Comparison groups	Arm I v All patients
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other[6]
Parameter estimate	Proportion estimate
Point estimate	0.14

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	0.27

Notes:

[6] - This is a single arm test - two arms were provided due to EUDRACT reporting system limitation

Secondary: Clinical benefit rate (CBR)

End point title	Clinical benefit rate (CBR)

End point description:

End point type	Secondary

End point timeframe:

CBR (Complete response + Partial response + Stable disease) was based on the best response recorded from the start of treatment until treatment discontinuation based on RECIST v1.1.

End point values	Arm I	All patients		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	50	50		
Units: Subjects				
Yes	41	41		
No	9	9		

Statistical analyses

Statistical analysis title	CBR - Full patient population

Statistical analysis description:

CBR (Complete response + Partial response + Stable disease) was based on the best response recorded from the start of treatment until treatment discontinuation based on RECIST v1.1. CBR was estimated using the Clopper-Pearson method for the (95%) confidence limits estimation.

Comparison groups	Arm I v All patients
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other[7]
Parameter estimate	Proportion estimate
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	0.91

Notes:

[7] - This is a single arm test - two arms were provided due to EUDRACT reporting system limitation

Secondary: Total duration of treatment

End point title	Total duration of treatment

End point description:

Total duration of treatment was computed from the date of start of treatment to the date of discontinuation of treatment for any reason, including disease progression, treatment toxicity, and death. Patients alive and still on protocol treatment at the time of the analysis were censored at the date of last known treatment administration.

End point type	Secondary

End point timeframe:

Total duration of treatment was computed from the date of start of treatment to the date of discontinuation of treatment for any reason, including disease progression, treatment toxicity, and death.

End point values	Arm I	All patients		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	50	50		
Units: months				
median (confidence interval 95%)	5.3 (4.0 to 8.5)	5.3 (4.0 to 8.5)		

Attachments (see zip file)	Total treatment duration - 50 patients/1317_trtdur1.jpeg

Statistical analyses

Statistical analysis title	Total treatment duration - Full patient population

Statistical analysis description:

Total duration of treatment was computed from the date of start of treatment to the date of discontinuation of treatment for any reason, including disease progression, treatment toxicity, and death. Patients alive and still on protocol treatment at the time of the analysis were censored at the date of last known treatment administration. Total treatment duration was estimated by the Kaplan-Meier (KM) method. The median estimate was provided with its 95% confidence interval.

Comparison groups	Arm I v All patients
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other[8]
Parameter estimate	Median estimate
Point estimate	5.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	4
upper limit	8.5

Notes:

[8] - This is a single arm test - two arms were provided due to EUDRACT reporting system limitation

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Start from day -14 prior to the first administration of the investigational agent until total resolution of all adverse events (AEs) and discontinuation of treatment with cabozantinib. Persistent AEs will be followed for at least 30 days (+/- 3 days).

Adverse event reporting additional description:

CRF for AEs contains pre-specified items. Both AEs and SAEs are evaluated using CTC grading.
Note that AEs related to hematology and biochemistry lab values were not specifically collected and are not included in the table below.

Assessment type	Non-systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Arm I

Reporting group description:

Cabozantinib.

Serious adverse events	Arm I		
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 50 (32.00%)		
number of deaths (all causes)	25		
number of deaths resulting from adverse events	0		
Investigations			
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
DEEP VEIN THROMBOSIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
ATRIOVENTRICULAR BLOCK			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
ENCEPHALOPATHY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
ANAEMIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
GENERAL PHYSICAL HEALTH DETERIORATION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PYREXIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
ANAL FISTULA			

alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	2 / 50 (4.00%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
DIARRHOEA				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	3 / 50 (6.00%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
GASTRIC ULCER PERFORATION				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
INTESTINAL OBSTRUCTION				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
CHOLECYSTITIS				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
PULMONARY EMBOLISM				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
URINARY TRACT OBSTRUCTION				

alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
BACK PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
HERPES ZOSTER OTICUS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Arm I		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 50 (100.00%)		
Vascular disorders			
DEEP VEIN THROMBOPHLEBITIS OF LEFT LOWER LIMB			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
HEMATOMA			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
HOT FLASHES			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
HYPERTENSION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	23 / 50 (46.00%)		
occurrences (all)	125		
General disorders and administration site conditions			
ALTERATION GENERAL STATUS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
ALTERATION OF GENERAL HEALTH			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
CHILLS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
EDEMA FACE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
EDEMA LIMBS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
FATIGUE			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	26 / 50 (52.00%)		
occurrences (all)	54		
FEBRILE SYMPTOMS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
FEVER			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	4		
FLU LIKE SYMPTOMS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
NIGHT SWEATS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	5		
WORSENING OF GENERAL CONDITION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Reproductive system and breast disorders			
VAGINAL PROLAPSE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			

BRONCHIAL CONGESTION				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences (all)	1			
COUGH				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	3 / 50 (6.00%)			
occurrences (all)	4			
DRY NOSE MUCOSA				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences (all)	1			
DYSPNEA				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	3 / 50 (6.00%)			
occurrences (all)	4			
EPISTAXIS				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences (all)	1			
HOARSENESS				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	9 / 50 (18.00%)			
occurrences (all)	9			
PRODUCTIVE COUGH				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences (all)	1			
RHINITIS				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	2 / 50 (4.00%)			
occurrences (all)	2			
SNEEZING				
alternative dictionary used: CTCAE 4.0				

subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
SORE THROAT			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Psychiatric disorders			
INSOMNIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Investigations			
CPK INCREASED			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
ELECTROCARDIOGRAM QT CORRECTED INTERVAL PROLONGED			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
WEIGHT GAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
WEIGHT LOSS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	29 / 50 (58.00%)		
occurrences (all)	71		
Injury, poisoning and procedural complications			
OMBILICAL HERNIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Cardiac disorders			

ATRIOVENTRICULAR BLOCK COMPLETE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
TACHYCARDIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Nervous system disorders			
ATAXIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
COGNITIVE DISTURBANCE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
DIZZINESS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
ENCEPHALOPATHY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
DYSGEUSIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	8 / 50 (16.00%)		
occurrences (all)	8		
HEADACHE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	9		
NEURALGIA			
alternative dictionary used: CTCAE			

4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
PERIPHERAL MOTOR NEUROPATHY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	2		
PERIPHERAL SENSORY NEUROPATHY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
SYNCOPE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Ear and labyrinth disorders			
EAR PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
HEARING IMPAIRED			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
VERTIGO			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Eye disorders			
FULL THICKNESS MACULAR HOLE RIGHT			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
VISUAL ACUITY DECLINED			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
VITROMACULAR TRACTION LEFT EYE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
ABDOMINAL DISTENSION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
ABDOMINAL PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	14 / 50 (28.00%)		
occurrences (all)	17		
ANAL FISSURE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	4		
ANAL FISTULA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	3		
ANAL PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
BLOATING			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
ANUSITIS			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	1 / 50 (2.00%)			
occurrences (all)	1			
CONSTIPATION				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	2 / 50 (4.00%)			
occurrences (all)	2			
DENTAL ABSTRACTION				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences (all)	1			
DIARRHEA				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	39 / 50 (78.00%)			
occurrences (all)	109			
DRY MOUTH				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	3 / 50 (6.00%)			
occurrences (all)	3			
DYSPEPSIA				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	4 / 50 (8.00%)			
occurrences (all)	4			
ESOPHAGITIS				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences (all)	1			
FLATULENCE				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	3 / 50 (6.00%)			
occurrences (all)	3			
FOOD POISONING				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences (all)	1			

GASTRIC PERFORATION				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences (all)	1			
GASTROESOPHAGEAL REFLUX DISEASE				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	2 / 50 (4.00%)			
occurrences (all)	2			
HEMORRHOIDS				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	6 / 50 (12.00%)			
occurrences (all)	15			
INTESTINAL OBSTRUCTION				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences (all)	2			
MUCOSITIS ORAL				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	18 / 50 (36.00%)			
occurrences (all)	23			
NAUSEA				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	7 / 50 (14.00%)			
occurrences (all)	15			
ORAL DYSESTHESIA				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences (all)	1			
ORAL PAIN				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences (all)	1			
PAIN EPIGASTRIC				
alternative dictionary used: CTCAE 4.0				

subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
PERIODONTAL DISEASE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
STOMACH CRAMPS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
TOOTH DEVELOPMENT DISORDER			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
STOMACH PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	3		
TOOTHACHE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
VOMITING			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	5 / 50 (10.00%)		
occurrences (all)	6		
Hepatobiliary disorders			
BILE DUCT STENOSIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	2		
BILIARY TRACT OCCLUSION			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	1 / 50 (2.00%)			
occurrences (all)	1			
CHOLECYSTITIS				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences (all)	1			
HEPATIC CYTOLYSIS				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences (all)	3			
Skin and subcutaneous tissue disorders				
ALOPECIA				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences (all)	1			
DRY SKIN				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	4 / 50 (8.00%)			
occurrences (all)	4			
DRY SKIN (BODY)				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences (all)	1			
ECZEMATOUS RASH LEFT LOWER LEG				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences (all)	1			
DRY SKIN (FACE)				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences (all)	1			
ERYTHEMA MULTIFORME				
alternative dictionary used: CTCAE 4.0				

subjects affected / exposed	1 / 50 (2.00%)			
occurrences (all)	1			
ERYTHEMA OF THE RIGTH HAND II-IV FINGER				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences (all)	1			
HAIR DISCOLORATION				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	3 / 50 (6.00%)			
occurrences (all)	3			
HAIR HYPOPIGMENTATION				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	3 / 50 (6.00%)			
occurrences (all)	3			
HAND HYPERSENSITIVITY				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences (all)	1			
HORNY FEET				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences (all)	1			
PALMAR-PLANTAR ERYTHRODYSESTHESIA SYNDROME				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	32 / 50 (64.00%)			
occurrences (all)	51			
PERIORBITAL EDEMA				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences (all)	1			
PHOTOSENSITIVITY				
alternative dictionary used: CTCAE 4.0				

subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
PRURITUS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	2		
RASH			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
SCALP PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
RASH MACULO-PAPULAR			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	4		
Renal and urinary disorders			
CYSTITIS NONINFECTIVE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
DYSURIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
HEMATURIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
NEPHROTIC COLITIS			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
PROTEINURIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	9		
URINARY INFLAMMATION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
URINARY TRACT OBSTRUCTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
URINARY URGENCY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
URINE INFLAMMATION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Endocrine disorders			
HYPERTHYROIDISM			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
HYPOTHYROIDISM			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	10 / 50 (20.00%)		
occurrences (all)	12		
Musculoskeletal and connective tissue disorders			
ARTHRITIS			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	1 / 50 (2.00%)			
occurrences (all)	1			
ARTHRALGIA				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	6 / 50 (12.00%)			
occurrences (all)	9			
BACK PAIN				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences (all)	1			
BONE PAIN				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	2 / 50 (4.00%)			
occurrences (all)	2			
CRAMP IN THE CALF				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences (all)	1			
GENERALIZED MUSCLE WEAKNESS				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	2 / 50 (4.00%)			
occurrences (all)	2			
MUSCLE CRAMPS				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	2 / 50 (4.00%)			
occurrences (all)	2			
MYALGIA				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	7 / 50 (14.00%)			
occurrences (all)	9			
PAIN (ACHILLES HEEL)				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences (all)	2			

PAIN IN EXTREMITY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Infections and infestations			
BRONCHIAL INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
FLU			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
HERPES ZOSTER OTICUS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
INFECTION NOS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
MYCOBACTERIUM TUBERCULOSIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
TOOTH INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
RHINITIS INFECTIVE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Metabolism and nutrition disorders			

ANOREXIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	14 / 50 (28.00%)		
occurrences (all)	21		
DEHYDRATION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
HYPOKALEMIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
HYPOPHOSPHATEMIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	5 / 50 (10.00%)		
occurrences (all)	6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 April 2016	oAdministrative changes: Changes to sponsor signatory page EORTC: change of PM STBSG: change of chairman and secretary Update of reference pathologists Reformatting of all references for publications and one additional reference added as published recently Other administrative changes oStatistics part: The design of the study has been simplified from a two-stage to a one-stage setup. End-points have been clarified to be more comprehensive The end of study definition has been updated to reflect standard EORTC notation oScientific part: Further to document provided by Exelixis (master protocol template): Drug specific patient selection criteria, dose and schedule modification and drug specific side effects have been updated. The patient information sheet has been updated based on the Summary of product Characteristics (last update Feb 2016). Drop of translational imaging research project about Choi Criteria due to lack of interest and funding. Motivation/rationale: Simplify the statistical design of the study from a two-stage design without interruption of accrual to a one-stage A'Hern design. Taking into account 12 weeks for the primary endpoint assessment of the 18th patient and approximately 1 month for obtaining and validating the information, it would take up to 4 months to conclude whether to stop or proceed to the next stage of the study. With 5 patients expected to be entered in the study every month, an additional 20 patients would have been enrolled prior to reaching this decision, making the interim look futile. We propose to switch to a one-stage design. This proposal was justified based on the available pre-clinical data, in combination with the molecular targeting profile of cabozantinib, showing that it was very likely that the study drug would show a level of efficacy in GIST similar to that obtained by related compounds such as sunitinib and regorafenib, at the time, the only treatment approved by FDA and EMA for this indication.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32470848