Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled Phase 2 Study Comparing CB-839 in Combination with Cabozantinib (CB-Cabo) vs. Placebo with Cabozantinib (Pbo-Cabo) in Patients with Advanced or Metastatic Renal Cell Carcinoma (RCC)

Summary

EudraCT number	2018-000363-91
Trial protocol	GB ES DE IT
Global end of trial date	16 July 2021

Results information

Result version number	v1 (current)
This version publication date	30 July 2022
First version publication date	30 July 2022

Trial information

Trial identification

Sponsor protocol code	CX-839-008

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03428217
WHO universal trial number (UTN)	-
Other trial identifiers	IND Number: 118397

Notes:

Sponsors

Sponsor organisation name	Calithera Biosciences, Inc.
Sponsor organisation address	343 Oyster Point Blvd, Suite 200, South San Francisco, CA, United States, 94080
Public contact	Study Director, Calithera Biosciences, Inc., +1 650-870-1000, clinicaltrials@calithera.com
Scientific contact	Study Director, Calithera Biosciences, Inc., +1 650-870-1000, clinicaltrials@calithera.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 July 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 July 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare blinded Independent Radiology Committee (IRC)-adjudicated progression free survival (PFS) of patients treated with CB-839 + cabozantinib (CB-Cabo) versus placebo + cabozantinib (Pbo-Cabo) for advanced or metastatic clear-cell RCC (ccRCC).

Protection of trial subjects:

The Investigator provided for the protection of the patients by following all applicable regulations. These regulations were available upon request from the Sponsor. The Informed Consent Form used during the informed consent process was reviewed by the Sponsor and approved by the institutional review board (IRB)/independent ethics committee (IEC).
Before any procedures specified in the protocol were performed, a patient:
- was informed of all pertinent aspects of the study and all elements of informed consent
- was given time to ask questions and time to consider the decision to participate
- voluntarily agreed to participate in the study
- signed and dated an IRB/IEC approved Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 April 2018
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	Germany: 23
Country: Number of subjects enrolled	Spain: 42
Country: Number of subjects enrolled	Australia: 25
Country: Number of subjects enrolled	France: 58
Country: Number of subjects enrolled	United Kingdom: 28
Country: Number of subjects enrolled	Italy: 37
Country: Number of subjects enrolled	New Zealand: 23
Country: Number of subjects enrolled	United States: 208
Worldwide total number of subjects	444
EEA total number of subjects	160

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)	269
From 65 to 84 years	175
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Eligible participants were randomized in a 1:1 ratio to either the Pbo-Cabo arm or the CB-Cabo arm. Randomization was stratified by prior treatment with PD-1/PD-L1 inhibitor therapy (yes vs. no) and the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) Prognostic Risk Group (favorable vs. intermediate vs. poor).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Test article (CB-839, 200 mg/tablet) or placebo tablets that were identical in appearance were administered orally.

Arms

Are arms mutually exclusive?	Yes
Arm title	Pbo-Cabo

Arm description:

Placebo twice daily (BID) + cabozantinib (60 mg once daily [QD]) administered orally on Days 1 through 28 of each 28-day cycle until disease progression per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) or unacceptable toxicity, whichever occurred first.

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

Dosage and administration details:

Placebo tablets were administered orally BID on Days 1 through 28 of each 28-day cycle. Dosing was not adjusted for body weight or surface area.

Investigational medicinal product name	cabozantinib
Investigational medicinal product code	
Other name	Cabometyx, Cabometriq
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Cabozantinib (20, 40, or 60 mg/tablets) was administered orally on Days 1 through 28 of each 28-day cycle. Subjects should not eat for at least 2 hr before and at least 1 hr after taking cabozantinib, and the QD dose of cabozantinib should occur at around the same time every day, preferably at bedtime.

Arm title	CB-Cabo

Arm description:

CB-839 800 mg BID + cabozantinib (60 mg QD) administered orally on Days 1 through 28 of each 28-day cycle until disease progression per RECIST v1.1 or unacceptable toxicity, whichever occurred first.

Arm type	Experimental

Investigational medicinal product name	CB-839
Investigational medicinal product code	
Other name	telaglenastat
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

CB-839 tablets were administered orally BID on Days 1 through 28 of each 28-day cycle. Dosing was not adjusted for body weight or surface area.

Investigational medicinal product name	cabozantinib
Investigational medicinal product code	
Other name	Cabometyx, Cabometriq
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Cabozantinib (20, 40, or 60 mg/tablets) was administered orally on Days 1 through 28 of each 28-day cycle. Subjects should not eat for at least 2 hr before and at least 1 hr after taking cabozantinib, and the QD dose of cabozantinib should occur at around the same time every day, preferably at bedtime.

Number of subjects in period 1	Pbo-Cabo	CB-Cabo
Started	223	221
Received at least 1 dose of study drug	221	221
Completed	0	0
Not completed	223	221
Consent withdrawn by subject	8	7
Death	89	93
Other, not specified	1	-
Study terminated by sponsor	124	118
Lost to follow-up	1	3

Baseline characteristics

Reporting groups	
Reporting group title	Pbo-Cabo
Reporting group description:	
Placebo twice daily (BID) + cabozantinib (60 mg once daily [QD]) administered orally on Days 1 through 28 of each 28-day cycle until disease progression per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) or unacceptable toxicity, whichever occurred first.	
Reporting group title	CB-Cabo
Reporting group description:	
CB-839 800 mg BID + cabozantinib (60 mg QD) administered orally on Days 1 through 28 of each 28-day cycle until disease progression per RECIST v1.1 or unacceptable toxicity, whichever occurred first.	

Reporting group values	Pbo-Cabo	CB-Cabo	Total
Number of subjects	223	221	444
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	61.7	60.6	
standard deviation	± 10.33	± 10.37	-
Gender categorical			
Units: Subjects			
Female	68	47	115
Male	155	174	329
Ethnicity			
Units: Subjects			
Not Hispanic or Latino	173	176	349
Unknown	36	34	70
Hispanic or Latino	14	11	25
Race			
Units: Subjects			
White	176	174	350
Not Reported	31	32	63
Other, Not Specified	3	9	12
Black or African American	6	3	9
Asian	6	2	8
Native Hawaiian or Other Pacific Islander	1	1	2
Stratification Factor: Prior PD-1/PD-L1 Inhibitor Therapy			
PD-1: programmed cell death protein 1 PD-L1: programmed cell death protein ligand 1			
Units: Subjects			
Yes	139	137	276
No	84	84	168
Stratification Factor: IMDC Category			
The International Metastatic renal cell carcinoma Database Consortium (IMDC) score is currently used as prognostic index to stratify patients with mRCC in 3 subgroups: good/favorable, intermediate and poor-risk groups.			

Units: Subjects			
Poor	35	35	70
Intermediate	149	147	296
Favorable	39	39	78

End points

End points reporting groups

Reporting group title	Pbo-Cabo
Reporting group description:	
Placebo twice daily (BID) + cabozantinib (60 mg once daily [QD]) administered orally on Days 1 through 28 of each 28-day cycle until disease progression per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) or unacceptable toxicity, whichever occurred first.	
Reporting group title	CB-Cabo
Reporting group description:	
CB-839 800 mg BID + cabozantinib (60 mg QD) administered orally on Days 1 through 28 of each 28-day cycle until disease progression per RECIST v1.1 or unacceptable toxicity, whichever occurred first.	
Subject analysis set title	Intent-to-Treat (ITT) Analysis Set: Pbo-Cabo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized participants	
Subject analysis set title	Intent-to-Treat (ITT) Analysis Set: CB-Cabo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized participants	

Primary: Progression-Free Survival (PFS) as Assessed by the Independent Radiology Committee (IRC)

End point title	Progression-Free Survival (PFS) as Assessed by the Independent Radiology Committee (IRC)

End point description:

PFS is defined as the time from randomization to the occurrence of disease progression as assessed by the IRC using RECIST v1.1 or death from any cause, whichever occurs first. Subjects not experiencing disease progression or death at the time of analysis of PFS will be censored at the date of the last evaluable radiographic disease assessment.
RECIST v1.1 criteria:
Complete Response (CR): Disappearance of all target lesions.
Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition, the sum must also demonstrate an absolute increase of at least 5 mm.
Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

End point type	Primary

End point timeframe:

Up to the primary analysis data cut-off date of 31 Aug 2020. Maximum duration of follow-up for PFS was 22.14 months.

End point values	Intent-to-Treat (ITT) Analysis Set: Pbo-Cabo	Intent-to-Treat (ITT) Analysis Set: CB-Cabo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	223	221		
Units: months				
median (confidence interval 95%)	9.33 (7.64 to 11.01)	9.17 (7.59 to 11.10)		

Statistical analyses

Statistical analysis title	Stratified Analysis 1
Statistical analysis description:	
Stratified Analysis 1: Stratified by prior programmed cell death protein 1/programmed cell death protein ligand 1 (PD-1/PDL1) inhibitor therapy (yes vs no) and International Metastatic Renal Cell Carcinoma Database (IMDC) prognostic risk group (favorable vs intermediate vs poor).	
Comparison groups	Intent-to-Treat (ITT) Analysis Set: Pbo-Cabo v Intent-to-Treat (ITT) Analysis Set: CB-Cabo
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6528
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.21

Statistical analysis title	Stratified Analysis 2
Statistical analysis description:	
Stratified by prior PD-1/PD-L1 inhibitor therapy [yes vs. no] and IMDC prognostic risk group [favorable vs. intermediate/poor].	
Comparison groups	Intent-to-Treat (ITT) Analysis Set: Pbo-Cabo v Intent-to-Treat (ITT) Analysis Set: CB-Cabo
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8193
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.24

	Stratified Analysis 3

Statistical analysis title	
Statistical analysis description:	
Stratified by the number of prior anti-angio cancer therapy [0 vs. >=1].	
Comparison groups	Intent-to-Treat (ITT) Analysis Set: Pbo-Cabo v Intent-to-Treat (ITT) Analysis Set: CB-Cabo
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8345
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.25

Statistical analysis title	Unstratified Analysis
Comparison groups	Intent-to-Treat (ITT) Analysis Set: Pbo-Cabo v Intent-to-Treat (ITT) Analysis Set: CB-Cabo
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9479
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.27

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
OS is defined as the time from randomization to death due to any cause. Estimated from Kaplan-Meier methodology. 95% confidence interval (CI) based on Brookmeyer-Crowley methodology.	
End point type	Secondary
End point timeframe:	
Up to the primary analysis data cut-off date of 31 Aug 2020. Maximum duration of follow-up for OS was 25.86 months.	

End point values	Intent-to-Treat (ITT) Analysis Set: Pbo-Cabo	Intent-to-Treat (ITT) Analysis Set: CB-Cabo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	223[1]	221[2]		
Units: months				
median (confidence interval 95%)	24.84 (21.59 to 99999)	22.24 (18.56 to 99999)		

Notes:

[1] - 99999=not estimable due to small number of events

[2] - 99999=not estimable due to small number of events

Statistical analyses

Statistical analysis title	Stratified Analysis 1

Statistical analysis description:

Stratified by prior PD-1/PD-L1 inhibitor therapy [yes vs. no] and IMDC prognostic risk group [favorable vs. intermediate vs. poor].

Comparison groups	Intent-to-Treat (ITT) Analysis Set: Pbo-Cabo v Intent-to-Treat (ITT) Analysis Set: CB-Cabo
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3867
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.6

Statistical analysis title	Stratified Analysis 2

Statistical analysis description:

Stratified by prior PD-1/PD-L1 inhibitor therapy [yes vs. no] and IMDC prognostic risk group [favorable vs. intermediate/poor].

Comparison groups	Intent-to-Treat (ITT) Analysis Set: Pbo-Cabo v Intent-to-Treat (ITT) Analysis Set: CB-Cabo
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3367
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.62

Statistical analysis title	Stratified Analysis 3
Statistical analysis description:	
Stratified by prior PD-1/PD-L1 inhibitor therapy [yes vs. no] and IMDC prognostic risk group [favorable vs. intermediate/poor].	
Comparison groups	Intent-to-Treat (ITT) Analysis Set: Pbo-Cabo v Intent-to-Treat (ITT) Analysis Set: CB-Cabo
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2416
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	1.69

Statistical analysis title	Unstratified Analysis
Comparison groups	Intent-to-Treat (ITT) Analysis Set: Pbo-Cabo v Intent-to-Treat (ITT) Analysis Set: CB-Cabo
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3043
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.64

Secondary: PFS as Assessed by the Investigator

End point title	PFS as Assessed by the Investigator

End point description:

PFS is defined as the time from randomization to the occurrence of disease progression as assessed by the IRC using RECIST v1.1 or death from any cause, whichever occurs first. Subjects not experiencing disease progression or death at the time of analysis of PFS will be censored at the date of the last evaluable radiographic disease assessment.
RECIST v1.1 criteria:
Complete Response (CR): Disappearance of all target lesions.
Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition, the sum must also demonstrate an absolute increase of at least 5 mm.
Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

End point type	Secondary

End point timeframe:

Up to the primary analysis data cut-off date of 31 Aug 2020. Maximum duration of follow-up for PFS was 22.64 months.

End point values	Intent-to-Treat (ITT) Analysis Set: Pbo-Cabo	Intent-to-Treat (ITT) Analysis Set: CB-Cabo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	223	221		
Units: months				
median (confidence interval 95%)	8.38 (6.34 to 9.79)	9.17 (7.49 to 9.46)		

Statistical analyses

Statistical analysis title	Stratified Analysis 1

Statistical analysis description:

Stratified by prior PD-1/PD-L1 inhibitor therapy [yes vs. no] and IMDC prognostic risk group [favorable vs. intermediate vs. poor].

Comparison groups	Intent-to-Treat (ITT) Analysis Set: Pbo-Cabo v Intent-to-Treat (ITT) Analysis Set: CB-Cabo
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9692
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.25

Statistical analysis title	Stratified Analysis 2

Statistical analysis description:

Stratified by prior PD-1/PD-L1 inhibitor therapy [yes vs. no] and IMDC prognostic risk group [favorable vs. intermediate/poor].

Comparison groups	Intent-to-Treat (ITT) Analysis Set: Pbo-Cabo v Intent-to-Treat (ITT) Analysis Set: CB-Cabo

Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9235
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.27

Statistical analysis title	Stratified Analysis 3
Statistical analysis description: Stratified by the number of prior anti-angio cancer therapy [0 vs. >=1].	
Comparison groups	Intent-to-Treat (ITT) Analysis Set: Pbo-Cabo v Intent-to-Treat (ITT) Analysis Set: CB-Cabo
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9549
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.26

Statistical analysis title	Unstratified Analysis
Comparison groups	Intent-to-Treat (ITT) Analysis Set: Pbo-Cabo v Intent-to-Treat (ITT) Analysis Set: CB-Cabo
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8193
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.29

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug through at least 28 days after last dose of all study treatments, or until initiation of a new anticancer therapy (if earlier). Overall median duration of safety follow-up was 280.0 days.

Adverse event reporting additional description:

Per protocol, Grade 5 disease progression events are excluded from these tables. Disease progression includes events in the preferred terms of disease progression and malignant neoplasm progression.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Pbo-Cabo

Reporting group description:

Placebo BID + cabozantinib (60 mg QD) administered orally on Days 1 through 28 of each 28-day cycle until disease progression per RECIST v1.1 or unacceptable toxicity, whichever occurred first.

Reporting group title	CB-Cabo

Reporting group description:

CB-839 800 mg BID + cabozantinib (60 mg QD) administered orally on Days 1 through 28 of each 28-day cycle until disease progression per RECIST v1.1 or unacceptable toxicity, whichever occurred first.

Serious adverse events	Pbo-Cabo	CB-Cabo	
Total subjects affected by serious adverse events			
subjects affected / exposed	74 / 217 (34.10%)	90 / 225 (40.00%)	
number of deaths (all causes)	10	14	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	1 / 217 (0.46%)	2 / 225 (0.89%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma pancreas			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			

subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant ascites			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastases to pelvis			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsil cancer			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 217 (0.46%)	2 / 225 (0.89%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			

subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Nerve block			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	2 / 217 (0.92%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fatigue			
subjects affected / exposed	0 / 217 (0.00%)	2 / 225 (0.89%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Malaise			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			

subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Pregnancy of partner			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	7 / 217 (3.23%)	5 / 225 (2.22%)	
occurrences causally related to treatment / all	4 / 7	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 217 (0.92%)	4 / 225 (1.78%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 217 (0.46%)	5 / 225 (2.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 217 (0.00%)	3 / 225 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary oedema			

subjects affected / exposed	2 / 217 (0.92%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax spontaneous			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 217 (0.92%)	2 / 225 (0.89%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Troponin I increased			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	1 / 217 (0.46%)	2 / 225 (0.89%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accidental overdose			
subjects affected / exposed	0 / 217 (0.00%)	2 / 225 (0.89%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic fracture			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 217 (0.46%)	2 / 225 (0.89%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 217 (0.46%)	2 / 225 (0.89%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acute coronary syndrome			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac ventricular thrombosis			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Aphasia			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar syndrome			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyskinesia			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Monoplegia			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Motor dysfunction			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			

subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 217 (0.46%)	2 / 225 (0.89%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	2 / 217 (0.92%)	6 / 225 (2.67%)	
occurrences causally related to treatment / all	2 / 2	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 217 (0.46%)	3 / 225 (1.33%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 217 (0.46%)	2 / 225 (0.89%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 217 (0.00%)	2 / 225 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 217 (0.92%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 217 (0.46%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 217 (0.00%)	2 / 225 (0.89%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			

subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoperitoneum			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia strangulated			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Melaena			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oesophageal food impaction			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			

subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Volvulus			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	3 / 217 (1.38%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	1 / 217 (0.46%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stenosis			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hyperbilirubinaemia			

subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash macular			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 217 (1.84%)	2 / 225 (0.89%)	
occurrences causally related to treatment / all	3 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteinuria			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			

subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary bladder haemorrhage			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 217 (0.46%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 217 (0.00%)	2 / 225 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 217 (0.46%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fracture pain			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin pain			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 217 (1.38%)	2 / 225 (0.89%)	
occurrences causally related to treatment / all	0 / 4	2 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 217 (1.38%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 217 (0.00%)	3 / 225 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess			
subjects affected / exposed	1 / 217 (0.46%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	1 / 217 (0.46%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			

subjects affected / exposed	2 / 217 (0.92%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth infection			
subjects affected / exposed	1 / 217 (0.46%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute sinusitis			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis infective			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			

subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint abscess			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraspinal abscess			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound abscess			
subjects affected / exposed	1 / 217 (0.46%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	3 / 217 (1.38%)	2 / 225 (0.89%)	
occurrences causally related to treatment / all	1 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	2 / 217 (0.92%)	3 / 225 (1.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	3 / 217 (1.38%)	2 / 225 (0.89%)	
occurrences causally related to treatment / all	2 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			

subjects affected / exposed	0 / 217 (0.00%)	2 / 225 (0.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 217 (0.46%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 217 (0.46%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	0 / 217 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Pbo-Cabo	CB-Cabo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	213 / 217 (98.16%)	222 / 225 (98.67%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	72 / 217 (33.18%)	82 / 225 (36.44%)	
occurrences (all)	95	97	
Hypotension			
subjects affected / exposed	13 / 217 (5.99%)	10 / 225 (4.44%)	
occurrences (all)	13	11	
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	109 / 217 (50.23%)	94 / 225 (41.78%)	
occurrences (all)	138	116	
Asthenia			
subjects affected / exposed	49 / 217 (22.58%)	49 / 225 (21.78%)	
occurrences (all)	56	66	
Mucosal inflammation			
subjects affected / exposed	36 / 217 (16.59%)	23 / 225 (10.22%)	
occurrences (all)	42	28	
Oedema peripheral			
subjects affected / exposed	21 / 217 (9.68%)	22 / 225 (9.78%)	
occurrences (all)	26	27	
Pyrexia			
subjects affected / exposed	15 / 217 (6.91%)	20 / 225 (8.89%)	
occurrences (all)	18	27	
Chest pain			
subjects affected / exposed	13 / 217 (5.99%)	9 / 225 (4.00%)	
occurrences (all)	15	11	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	41 / 217 (18.89%)	50 / 225 (22.22%)	
occurrences (all)	48	56	
Dysphonia			
subjects affected / exposed	41 / 217 (18.89%)	33 / 225 (14.67%)	
occurrences (all)	44	35	
Dyspnoea			
subjects affected / exposed	34 / 217 (15.67%)	30 / 225 (13.33%)	
occurrences (all)	42	38	
Oropharyngeal pain			
subjects affected / exposed	16 / 217 (7.37%)	20 / 225 (8.89%)	
occurrences (all)	17	24	
Epistaxis			
subjects affected / exposed	13 / 217 (5.99%)	21 / 225 (9.33%)	
occurrences (all)	15	23	
Psychiatric disorders			

Insomnia			
subjects affected / exposed	17 / 217 (7.83%)	21 / 225 (9.33%)	
occurrences (all)	18	22	
Anxiety			
subjects affected / exposed	12 / 217 (5.53%)	16 / 225 (7.11%)	
occurrences (all)	12	17	
Depression			
subjects affected / exposed	16 / 217 (7.37%)	7 / 225 (3.11%)	
occurrences (all)	17	7	
Investigations			
Weight decreased			
subjects affected / exposed	65 / 217 (29.95%)	77 / 225 (34.22%)	
occurrences (all)	75	89	
Alanine aminotransferase increased			
subjects affected / exposed	39 / 217 (17.97%)	63 / 225 (28.00%)	
occurrences (all)	53	90	
Aspartate aminotransferase increased			
subjects affected / exposed	40 / 217 (18.43%)	56 / 225 (24.89%)	
occurrences (all)	50	76	
Blood creatinine increased			
subjects affected / exposed	12 / 217 (5.53%)	24 / 225 (10.67%)	
occurrences (all)	17	29	
Blood alkaline phosphatase increased			
subjects affected / exposed	14 / 217 (6.45%)	15 / 225 (6.67%)	
occurrences (all)	17	19	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	12 / 217 (5.53%)	11 / 225 (4.89%)	
occurrences (all)	13	14	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	52 / 217 (23.96%)	41 / 225 (18.22%)	
occurrences (all)	59	45	
Headache			
subjects affected / exposed	32 / 217 (14.75%)	39 / 225 (17.33%)	
occurrences (all)	39	41	

Dizziness			
subjects affected / exposed	24 / 217 (11.06%)	23 / 225 (10.22%)	
occurrences (all)	28	30	
Paraesthesia			
subjects affected / exposed	12 / 217 (5.53%)	10 / 225 (4.44%)	
occurrences (all)	13	10	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	29 / 217 (13.36%)	28 / 225 (12.44%)	
occurrences (all)	34	40	
Thrombocytopenia			
subjects affected / exposed	14 / 217 (6.45%)	20 / 225 (8.89%)	
occurrences (all)	17	26	
Eye disorders			
Vision blurred			
subjects affected / exposed	14 / 217 (6.45%)	22 / 225 (9.78%)	
occurrences (all)	14	22	
Photophobia			
subjects affected / exposed	8 / 217 (3.69%)	26 / 225 (11.56%)	
occurrences (all)	8	34	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	160 / 217 (73.73%)	162 / 225 (72.00%)	
occurrences (all)	378	330	
Nausea			
subjects affected / exposed	118 / 217 (54.38%)	123 / 225 (54.67%)	
occurrences (all)	163	168	
Vomiting			
subjects affected / exposed	75 / 217 (34.56%)	77 / 225 (34.22%)	
occurrences (all)	138	123	
Constipation			
subjects affected / exposed	63 / 217 (29.03%)	69 / 225 (30.67%)	
occurrences (all)	72	81	
Stomatitis			
subjects affected / exposed	49 / 217 (22.58%)	47 / 225 (20.89%)	
occurrences (all)	58	54	
Abdominal pain			

subjects affected / exposed	39 / 217 (17.97%)	40 / 225 (17.78%)	
occurrences (all)	48	46	
Gastrooesophageal reflux disease			
subjects affected / exposed	24 / 217 (11.06%)	42 / 225 (18.67%)	
occurrences (all)	33	47	
Dyspepsia			
subjects affected / exposed	28 / 217 (12.90%)	35 / 225 (15.56%)	
occurrences (all)	32	47	
Abdominal pain upper			
subjects affected / exposed	25 / 217 (11.52%)	21 / 225 (9.33%)	
occurrences (all)	31	22	
Dry mouth			
subjects affected / exposed	21 / 217 (9.68%)	14 / 225 (6.22%)	
occurrences (all)	22	14	
Oral pain			
subjects affected / exposed	15 / 217 (6.91%)	9 / 225 (4.00%)	
occurrences (all)	15	11	
Flatulence			
subjects affected / exposed	9 / 217 (4.15%)	14 / 225 (6.22%)	
occurrences (all)	10	15	
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	87 / 217 (40.09%)	95 / 225 (42.22%)	
occurrences (all)	121	117	
Rash			
subjects affected / exposed	28 / 217 (12.90%)	40 / 225 (17.78%)	
occurrences (all)	37	50	
Pruritus			
subjects affected / exposed	20 / 217 (9.22%)	25 / 225 (11.11%)	
occurrences (all)	25	26	
Dry skin			
subjects affected / exposed	19 / 217 (8.76%)	19 / 225 (8.44%)	
occurrences (all)	19	20	
Alopecia			

subjects affected / exposed	15 / 217 (6.91%)	16 / 225 (7.11%)	
occurrences (all)	15	16	
Hair colour changes			
subjects affected / exposed	11 / 217 (5.07%)	20 / 225 (8.89%)	
occurrences (all)	11	21	
Rash maculo-papular			
subjects affected / exposed	14 / 217 (6.45%)	13 / 225 (5.78%)	
occurrences (all)	15	13	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	17 / 217 (7.83%)	28 / 225 (12.44%)	
occurrences (all)	24	39	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	56 / 217 (25.81%)	66 / 225 (29.33%)	
occurrences (all)	67	69	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	37 / 217 (17.05%)	43 / 225 (19.11%)	
occurrences (all)	43	53	
Arthralgia			
subjects affected / exposed	33 / 217 (15.21%)	33 / 225 (14.67%)	
occurrences (all)	42	51	
Pain in extremity			
subjects affected / exposed	27 / 217 (12.44%)	28 / 225 (12.44%)	
occurrences (all)	34	30	
Muscle spasms			
subjects affected / exposed	24 / 217 (11.06%)	29 / 225 (12.89%)	
occurrences (all)	27	35	
Myalgia			
subjects affected / exposed	19 / 217 (8.76%)	11 / 225 (4.89%)	
occurrences (all)	24	14	
Musculoskeletal chest pain			
subjects affected / exposed	13 / 217 (5.99%)	14 / 225 (6.22%)	
occurrences (all)	18	17	
Muscular weakness			

subjects affected / exposed	9 / 217 (4.15%)	15 / 225 (6.67%)	
occurrences (all)	10	17	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	18 / 217 (8.29%)	23 / 225 (10.22%)	
occurrences (all)	33	40	
Upper respiratory tract infection			
subjects affected / exposed	12 / 217 (5.53%)	20 / 225 (8.89%)	
occurrences (all)	12	23	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	86 / 217 (39.63%)	83 / 225 (36.89%)	
occurrences (all)	111	101	
Hypomagnesaemia			
subjects affected / exposed	49 / 217 (22.58%)	48 / 225 (21.33%)	
occurrences (all)	66	82	
Hypophosphataemia			
subjects affected / exposed	38 / 217 (17.51%)	32 / 225 (14.22%)	
occurrences (all)	53	47	
Hypokalaemia			
subjects affected / exposed	27 / 217 (12.44%)	25 / 225 (11.11%)	
occurrences (all)	46	36	
Hyponatraemia			
subjects affected / exposed	30 / 217 (13.82%)	16 / 225 (7.11%)	
occurrences (all)	44	18	
Hypocalcaemia			
subjects affected / exposed	26 / 217 (11.98%)	18 / 225 (8.00%)	
occurrences (all)	32	25	
Hyperkalaemia			
subjects affected / exposed	16 / 217 (7.37%)	14 / 225 (6.22%)	
occurrences (all)	22	20	
Dehydration			
subjects affected / exposed	13 / 217 (5.99%)	15 / 225 (6.67%)	
occurrences (all)	21	24	
Hypoalbuminaemia			

subjects affected / exposed occurrences (all)	14 / 217 (6.45%) 20	12 / 225 (5.33%) 16	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 April 2020	• Updated emergency contacts and serious adverse event (SAE) reporting contact. • Included additional objectives for pharmacokinetics. • Added data from phase 1 study CX-839-001 for patients treated with telaglenastat and cabozantinib. • Added instructions for patients who discontinued either telaglenastat/placebo or cabozantinib. • Clarified language for survival follow-up. • Included 110826 (major metabolite of telaglenastat) and cabozantinib for PK analysis. • Included other reportable information language and updated overdose and abuse definitions. • Clarified assessment of blood urea nitrogen in the chemistry panel.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

At the time of the primary analysis (31 Aug 2020), the study did not meet the primary endpoint of improved PFS and the sponsor closed the study. The safety profile was consistent between the 2 groups of the study.

Notes: