# 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<br>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:<br>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 | | | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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<br>occurrences (all) | 14 / 217 (6.45%)<br>20 | 12 / 225 (5.33%)<br>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.<br>• Included additional objectives for pharmacokinetics.<br>• Added data from phase 1 study CX-839-001 for patients treated with telaglenastat and cabozantinib.<br>• Added instructions for patients who discontinued either telaglenastat/placebo or cabozantinib.<br>• Clarified language for survival follow-up.<br>• Included 110826 (major metabolite of telaglenastat) and cabozantinib for PK analysis.<br>• Included other reportable information language and updated overdose and abuse definitions.<br>• 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: