



Clinical trial results:

A phase II trial of Cabozantinib for hepatocellular carcinoma patients intolerant to sorafenib treatment or first line treatment different to sorafenib. (ACTION trial)

Summary

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

Results information

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

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | ACTION |
|-----------------------|--------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | FRCB - IDIBAPS (Fundació de Recerca Clínic Barcelona - Institut d'Investigacions Biomèdiques August Pi i Sunyer) - Hospital Clinic de Barcelona |
| Sponsor organisation address | C/Roselló149-153, Barcelona, Spain, 08026 |
| Public contact | Dr. Maria Reig, BCLC group. Liver Unit. ICMDM. CIBEREHD. IDIBAPS - Hospital Clinic Barcelona, +34 93 227 98 03, mreig1@clinic.cat |
| Scientific contact | Dr. Maria Reig, BCLC group. Liver Unit. ICMDM. CIBEREHD. IDIBAPS - Hospital Clinic Barcelona, +34 93 227 98 03, mreig1@clinic.cat |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 29 November 2023 |
| Is this the analysis of the primary completion data? | No |

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

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

All patients including in Safety set signed informed consent and meet the selection criteria.

To ensure patient safety, the following procedures were performed at all study visits during treatment: Physical examination, ECOG performance status, Vital signs, Assessment of AEs/SAEs, Concomitant medications, Serum chemistry, Hematology, Coagulation (PT, INR, PTT) and Urinalysis.

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

Notes:

Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 7 |

| | |
|---------------------|----|
| From 65 to 84 years | 16 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

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

Period 1

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

Arms

| | |
|-----------|--------------|
| Arm title | Cabozantinib |
|-----------|--------------|

Arm description:

Cabozantinib 60 mg/day.

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

Dosage and administration details:

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

| | |
|---------------------------------------|--------------|
| Number of subjects in period 1 | Cabozantinib |
| Started | 24 |
| Completed | 24 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Overall Study |
|-----------------------|---------------|

Reporting group description: -

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

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

Subject analysis sets

| | |
|---|---------------|
| Subject analysis set title | Overall |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Patients who received study intervention | |

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

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

End points

End points reporting groups

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

Primary: Adverse event (CTCAE) ≥ 3 excluding palmar-plantar erythrodysthesia

| | |
|--|--|
| End point title | Adverse event (CTCAE) ≥ 3 excluding palmar-plantar erythrodysthesia ^[1] |
| End point description: Patients with grade ≥ 3 adverse events, excluding palmar-plantar erythrodysthesia. | |
| End point type | Primary |
| End point timeframe: At every study visit until end of treatment. | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive analysis performed.

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

Statistical analyses

No statistical analyses for this end point

Primary: Treatment-related adverse events

| | |
|--|---|
| End point title | Treatment-related adverse events ^[2] |
| End point description: Patients with related adverse events. | |
| End point type | Primary |
| End point timeframe: At every study visit until end of treatment. | |

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive analysis performed.

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

Statistical analyses

No statistical analyses for this end point

Primary: Adverse event resulting in death.

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

End point description:

Patients with adverse events resulting in death.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

At every study visit until end of treatment.

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive analysis performed.

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

Statistical analyses

No statistical analyses for this end point

Primary: Adverse events leading to discontinuation

| | |
|-----------------|--|
| End point title | Adverse events leading to discontinuation ^[4] |
|-----------------|--|

End point description:

Patients with adverse events leading to discontinuation.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

At every study visit until end of treatment.

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive analysis performed.

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

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

| | |
|---|------------------|
| End point title | Overall Survival |
| End point description: The time from the inclusion date to death from any cause. | |
| End point type | Secondary |
| End point timeframe: Every 3 months. | |

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

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate

| | |
|---|-------------------------|
| End point title | Objective response rate |
| End point description: Defined as a partial or complete response at any time, i.e. the best response from inclusion along all follow-up. | |
| End point type | Secondary |
| End point timeframe: Every 8 weeks. | |

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

Statistical analyses

No statistical analyses for this end point

Secondary: Time to progression

| | |
|--|---------------------|
| End point title | Time to progression |
| End point description: The time from the inclusion date to progression. | |
| End point type | Secondary |
| End point timeframe: Every 8 weeks. | |

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

Statistical analyses

No statistical analyses for this end point

Secondary: Pattern of progression

| | |
|--|------------------------|
| End point title | Pattern of progression |
| End point description: Patterns of progression: - Intrahepatic growth (IHG): increased size of intrahepatic target lesions or progression of intrahepatic "non-target" lesions at baseline. - New intrahepatic lesion (NIH): emergence of new intrahepatic lesions - Extrahepatic growth (EHG): increased size of extrahepatic target lesions, progression of extrahepatic "non-target" lesions at baseline or progression of the existing vascular invasion. - New extrahepatic lesion (NEL): emergence of new extrahepatic lesions or emergence of vascular invasion. | |
| End point type | Secondary |
| End point timeframe: Every 8 weeks | |

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|------------------------|---|
| End point title | Rate of patients who develop new extra-hepatic spread |
| End point description: | Rate of patients who develop new extra-hepatic spread |
| End point type | Secondary |
| End point timeframe: | Every 8 weeks |

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

Secondary: Post-progression survival

| | |
|------------------------|--|
| End point title | Post-progression survival |
| End point description: | For those patients who progressed, the time from the progression date to death from any cause. |
| End point type | Secondary |
| End point timeframe: | Every 3 months |

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 21.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Overall |
|-----------------------|---------|

Reporting group description:

Screened patients who meet selection criteria and received study medication.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported