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

## Summary

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

### Results information

| | |
|---|---|
| Result version number | v1 |
| This version publication date | 25 September 2021 |
| First version publication date | 25 September 2021 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | 1317-STBSG |

### Additional study identifiers

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

Notes:

### Sponsors

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

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 10 September 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 10 September 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 12 March 2021 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

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

Notes:

## Population of trial subjects

### Subjects enrolled per country

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

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |

| | |
|---|---|
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 27 |
| From 65 to 84 years | 23 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

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

### Pre-assignment

Screening details:

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

### Pre-assignment period milestones

| | |
|---|---|
| Number of subjects started | 50 |
| Number of subjects completed | 50 |

### Period 1

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

### Arms

| | |
|---|---|
| **Arm title** | Arm I |

Arm description:

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

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

Dosage and administration details:

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

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

## Baseline characteristics

### Reporting groups

| Reporting group title | Overall period - Full patient population |
|---|---|

Reporting group description: -

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

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Arm I |

Reporting group description:

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

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

Subject analysis set description:

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

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

Subject analysis set description:

All patients

### Primary: Progression free survival (PFS) at 12 weeks

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

End point description:

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

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

End point timeframe:

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

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

## Statistical analyses

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

Statistical analysis description:

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

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

Notes:

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

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

## Secondary: Progression free survival (PFS)

| End point title | Progression free survival (PFS) |
|---|---|

End point description:

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

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

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

## Statistical analyses

| Statistical analysis title | PFS - Full patient population |
|---|---|

Statistical analysis description:

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

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

Notes:

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

## Secondary: Overall survival - Full patient population

| End point title | Overall survival - Full patient population |
|---|---|

End point description:

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

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

Notes:

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

## Statistical analyses

| Statistical analysis title | OS - Full patient population |
|---|---|

Statistical analysis description:

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

| Comparison groups | Arm I v All patients |
|---|---|

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

Notes:

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

## Secondary: Objective response rate (ORR)

| | |
|---|---|
| End point title | Objective response rate (ORR) |

End point description:

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

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

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

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

## Statistical analyses

| Statistical analysis title | ORR - Full patient population |
|---|---|

Statistical analysis description:

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

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

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

Notes:

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

## Secondary: Clinical benefit rate (CBR)

| | |
|---|---|
| End point title | Clinical benefit rate (CBR) |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

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

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

### Statistical analyses

| **Statistical analysis title** | CBR - Full patient population |
|---|---|

Statistical analysis description:

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

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

Notes:

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

## Secondary: Total duration of treatment

| End point title | Total duration of treatment |
|---|---|

End point description:

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

| End point type | Secondary |
|---|---|

End point timeframe:

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

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

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

## Statistical analyses

| **Statistical analysis title** | Total treatment duration - Full patient population |
|---|---|

Statistical analysis description:

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

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

Notes:

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

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

| | |
|---|---|
| Assessment type | Non-systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | CTCAE |
| Dictionary version | 4.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Arm I |

Reporting group description:

Cabozantinib.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported

## Online references

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