



## Clinical trial results:

**A randomized phase II trial comparing pazopanib with doxorubicin as first line treatment in elderly patients with metastatic or advanced soft tissue sarcoma**

### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2011-004168-30   |
| Trial protocol           | DE BE            |
| Global end of trial date | 28 February 2017 |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 13 May 2022  |
| First version publication date | 13 May 2022  |

### Trial information

#### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | STS001 |
|-----------------------|--------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01861951 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |                                                                                   |
|------------------------------|-----------------------------------------------------------------------------------|
| Sponsor organisation name    | Hannover Medical School                                                           |
| Sponsor organisation address | Carl-Neuberg-Str. 1, Hannover, Germany, 30625                                     |
| Public contact               | Zentrum für Klinische Studien, Hannover Medical School,<br>EudraCT@mh-hannover.de |
| Scientific contact           | Zentrum für Klinische Studien, Hannover Medical School,<br>EudraCT@mh-hannover.de |

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:

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**Results analysis stage**

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|                                                      |                  |
|------------------------------------------------------|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 08 March 2018    |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 28 February 2017 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 28 February 2017 |
| Was the trial ended prematurely?                     | No               |

Notes:

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**General information about the trial**

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Main objective of the trial:

Primary objective:

To show that progression-free survival (PFS) in the pazopanib group is not inferior to that in the doxorubicin group

Key secondary objectives:

- To show that the proportion of patients with neutrophil granulocytopenia grade 4 is smaller in the pazopanib group than in the doxorubicin group
- To show that the proportion of patients with febrile neutropenia is smaller in the pazopanib group than in the doxorubicin group

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Protection of trial subjects:

The clinical trial was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and with the standards of International Conference on Harmonisation (ICH) Good Clinical Practice (GCP).

A continuous risk assessment was performed during the study.

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Background therapy:

Use of concomitant medication with doxorubicin and pazopanib were handled according to the summary of product characteristics (SmPC)/investigator's brochure (IB).

Patients have received full supportive care during the study, including transfusion of blood and blood products, and treatment with antibiotics, analgesics, erythropoietin, or bisphosphonates, when appropriate. Anti-emetics (such as prochlorperazine, lorazepam, ondansetron, or other 5-HT antagonists) were administered prophylactically in the event of nausea. Anti-diarrheals such as loperamide were administered as needed in the event of diarrhea. Although acetaminophen at doses of  $\leq 2$  g/day was permitted, it should have been used with caution in subjects with impaired liver function.

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Evidence for comparator:

As a result of the heterogeneity of soft tissue sarcomas (STS), finding an effective anti-tumor agent has been difficult. For decades, doxorubicin has formed the backbone of systemic treatment of a wide range of cancers including hematological malignancies, many types of carcinoma, and unresectable or metastatic STS. Hematological toxicity is frequently associated with doxorubicin treatment. Due to its aggressiveness it is usually not suited for elderly patients. Finding a drug with similar efficacy, but less adverse effects is particularly important for this patient group.

The aim of the clinical trial was to compare pazopanib with doxorubicin in elderly patients with metastatic or advanced STS. We tested the hypothesis whether pazopanib treatment has comparable efficacy to doxorubicin treatment while offering better tolerability in elderly patients with metastatic or advanced STS.

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|                                                           |                 |
|-----------------------------------------------------------|-----------------|
| Actual start date of recruitment                          | 12 October 2012 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | No              |

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Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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|                                      |              |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Belgium: 12  |
| Country: Number of subjects enrolled | Germany: 108 |
| Worldwide total number of subjects   | 120          |
| EEA total number of subjects         | 120          |

Notes:

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**Subjects enrolled per age group**

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|                                           |    |
|-------------------------------------------|----|
| 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)                      | 22 |
| From 65 to 84 years                       | 96 |
| 85 years and over                         | 2  |

## Subject disposition

### Recruitment

Recruitment details:

Subjects were enrolled at a total of 14 study sites in Germany and Belgium (Germany: 13 study sites, Belgium: 1 study site).

First patient first visit: 12-Oct-2012

Last patient first visit: 18-Mar-2016

Last patient last visit: 28-Feb-2017

### Pre-assignment

Screening details:

A total of 120 patients were randomized. 39 patients were randomized to Doxorubicin (Arm A) and 81 patients to Pazopanib (Arm B). 118 patients received at least one dose of study drug. Two patients in Arm A did not receive any study drug (one patient withdrew consent and one patient were excluded by investigator's decision).

### Period 1

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

### Arms

|                              |                     |
|------------------------------|---------------------|
| Are arms mutually exclusive? | Yes                 |
| <b>Arm title</b>             | Doxorubicin (Arm A) |

Arm description:

Participants randomized to receive Doxorubicin 75 mg/m<sup>2</sup> body surface area (BSA), intravenous (i.v.), day 1 (d1), every 3 weeks (q3wk). Participants received a maximum of 6 cycles of study treatment. The duration of the study intervention was 18 weeks or until disease progression, treatment failure, or death due to any cause, whichever occurred first.

|                                        |                                       |
|----------------------------------------|---------------------------------------|
| Arm type                               | Active comparator                     |
| Investigational medicinal product name | Doxorubicin                           |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

Doxorubicin 75 mg/m<sup>2</sup> BSA, d1, q3wk, maximum of 6 cycles

Duration of the study intervention: 18 weeks or until disease progression, treatment failure, or death due to any cause, whichever occurred first

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | Pazopanib (Arm B) |
|------------------|-------------------|

Arm description:

Participants randomized to receive Pazopanib 800 mg, per oral (p.o.), daily. Participants received Pazopanib continuously until disease progression, treatment failure, or death due to any cause, whichever occurred first.

|                                        |                    |
|----------------------------------------|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Pazopanib          |
| Investigational medicinal product code |                    |
| Other name                             | Votrient®          |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

Pazopanib 800 mg (2 x 400 mg or 4 x 200 mg), p.o., daily

Duration of the study intervention: Participants received Pazopanib continuously until disease

progression, treatment failure, or death due to any cause, whichever occurred first.

| <b>Number of subjects in period 1</b> | Doxorubicin (Arm A) | Pazopanib (Arm B) |
|---------------------------------------|---------------------|-------------------|
| Started                               | 39                  | 81                |
| Completed                             | 15                  | 3                 |
| Not completed                         | 24                  | 78                |
| Adverse event, serious fatal          | -                   | 1                 |
| Consent withdrawn by subject          | 5                   | 2                 |
| Physician decision                    | 2                   | 2                 |
| Adverse event, non-fatal              | 3                   | 18                |
| Unknown                               | 2                   | 4                 |
| Progressive disease                   | 12                  | 51                |

## Baseline characteristics

### Reporting groups

Reporting group title

Overall trial

Reporting group description: -

| Reporting group values                                | Overall trial | Total |  |
|-------------------------------------------------------|---------------|-------|--|
| Number of subjects                                    | 120           | 120   |  |
| Age categorical                                       |               |       |  |
| Units: Subjects                                       |               |       |  |
| In utero                                              |               | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks) |               | 0     |  |
| Newborns (0-27 days)                                  |               | 0     |  |
| Infants and toddlers (28 days-23<br>months)           |               | 0     |  |
| Children (2-11 years)                                 |               | 0     |  |
| Adolescents (12-17 years)                             |               | 0     |  |
| Adults (18-64 years)                                  |               | 0     |  |
| From 65-84 years                                      |               | 0     |  |
| 85 years and over                                     |               | 0     |  |
| Age continuous                                        |               |       |  |
| Units: years                                          |               |       |  |
| median                                                | 71            |       |  |
| full range (min-max)                                  | 60 to 88      | -     |  |
| Gender categorical                                    |               |       |  |
| Units: Subjects                                       |               |       |  |
| Female                                                | 59            | 59    |  |
| Male                                                  | 61            | 61    |  |

## End points

### End points reporting groups

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Doxorubicin (Arm A) |
|-----------------------|---------------------|

Reporting group description:

Participants randomized to receive Doxorubicin 75 mg/m<sup>2</sup> body surface area (BSA), intravenous (i.v.), day 1 (d1), every 3 weeks (q3wk). Participants received a maximum of 6 cycles of study treatment. The duration of the study intervention was 18 weeks or until disease progression, treatment failure, or death due to any cause, whichever occurred first.

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Pazopanib (Arm B) |
|-----------------------|-------------------|

Reporting group description:

Participants randomized to receive Pazopanib 800 mg, per oral (p.o.), daily. Participants received Pazopanib continuously until disease progression, treatment failure, or death due to any cause, whichever occurred first.

|                            |                                         |
|----------------------------|-----------------------------------------|
| Subject analysis set title | progression free survival rate (PFR) PP |
|----------------------------|-----------------------------------------|

|                           |              |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

The primary analysis will be performed on the PP population and, as a sensitivity analysis, on the ITT population. Consistency between results in the ITT analysis and PP analysis is needed to draw any conclusion regarding differences in progression-free survival. For progression-free survival a Cox-regression model will be used to calculate the hazard ratio of pazopanib and doxorubicin (pazopanib/doxorubicin) and the respective two-sided 95% CI. If the upper limit of the two-sided 95% CI in the PP-population is smaller than 1.8, non-inferiority will be concluded. Additionally, Kaplan-Meier curves will be drawn.

### Primary: Progression-free survival PP population

|                 |                                         |
|-----------------|-----------------------------------------|
| End point title | Progression-free survival PP population |
|-----------------|-----------------------------------------|

End point description:

inter-quartile range (Q1-Q3) was not available in the primary study report

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

End point timeframe:

time from date of randomization until the date of first objective documentation of disease progression, treatment failure, or death due to any cause, whichever occurs first

| End point values                 | Doxorubicin (Arm A) | Pazopanib (Arm B) | progression free survival rate (PFR) PP |  |
|----------------------------------|---------------------|-------------------|-----------------------------------------|--|
| Subject group type               | Reporting group     | Reporting group   | Subject analysis set                    |  |
| Number of subjects analysed      | 39                  | 81                | 120                                     |  |
| Units: month                     |                     |                   |                                         |  |
| median (confidence interval 95%) | 5.3 (1.7 to 8.2)    | 4.4 (2.7 to 6.0)  | 4.4 (1.7 to 8.2)                        |  |

### Statistical analyses

|                            |                  |
|----------------------------|------------------|
| Statistical analysis title | Primary analysis |
|----------------------------|------------------|

|                   |                                         |
|-------------------|-----------------------------------------|
| Comparison groups | Doxorubicin (Arm A) v Pazopanib (Arm B) |
|-------------------|-----------------------------------------|

|                                         |                                |
|-----------------------------------------|--------------------------------|
| Number of subjects included in analysis | 120                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | non-inferiority <sup>[1]</sup> |
| Method                                  | Regression, Cox                |
| Parameter estimate                      | Hazard ratio (HR)              |
| Point estimate                          | 1                              |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 0.65                           |
| upper limit                             | 1.53                           |
| Variability estimate                    | Standard deviation             |

Notes:

[1] - The upper limit of the 95%-CI was lower than the predefined non-inferiority margin of 1.8. Thus, non-inferiority of Pazopanib regarding PFS could be concluded.

## Secondary: Neutrophil granulocytopenia grade 4

|                 |                                     |
|-----------------|-------------------------------------|
| End point title | Neutrophil granulocytopenia grade 4 |
|-----------------|-------------------------------------|

End point description:

Key secondary analysis was performed in the ITT population. Descriptive results for neutropenia grade 4 and febrile neutropenia during the study indicated a strong difference between Doxorubicin and Pazopanib. Some events have been observed prior to randomization (excluded from analysis) or after progression (excluded from analysis in case of occurrence of neutropenia after start of another anticancer agent). Considering events during the study, neutropenia grade 4 and febrile neutropenia were only observed in the Doxorubicin group. A total of 28 neutropenia of CTC grade 4 occurred in 22 Doxorubicin patients (56.4%), and a total of 4 febrile neutropenia in 4 Doxorubicin patients (10.3%). Most patients experienced only one event. Neutropenia predominantly occurred 2 weeks after start of treatment. Superiority testing with chi-square tests showed significant results for the first key-secondary endpoint neutropenia grade 4 ( $p < 0.0001$ ) as well as for febrile neutropenia ( $p = 0.003$ ).

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

End point timeframe:

during study; from randomization until progression/ death

| End point values            | Doxorubicin (Arm A) | Pazopanib (Arm B) |  |  |
|-----------------------------|---------------------|-------------------|--|--|
| Subject group type          | Reporting group     | Reporting group   |  |  |
| Number of subjects analysed | 39                  | 81                |  |  |
| Units: number               | 22                  | 0                 |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Febrile neutropenia

|                 |                     |
|-----------------|---------------------|
| End point title | Febrile neutropenia |
|-----------------|---------------------|

End point description:

Key secondary analysis was performed in the ITT population. Descriptive results for neutropenia grade 4 and febrile neutropenia during the study indicated a strong difference between Doxorubicin and Pazopanib. Some events have been observed prior to randomization (excluded from analysis) or after progression (excluded from analysis in case of occurrence of neutropenia after start of another

anticancer agent). Considering events during the study, neutropenia grade 4 and febrile neutropenia were only observed in the Doxorubicin group. A total of 28 neutropenia of CTC grade 4 occurred in 22 Doxorubicin patients (56.4%), and a total of 4 febrile neutropenia in 4 Doxorubicin patients (10.3%). Most patients experienced only one event. Neutropenia predominantly occurred 2 weeks after start of treatment. Superiority testing with chi-square tests showed significant results for the first key-secondary endpoint neutropenia grade 4 ( $p < 0.0001$ ) as well as for febrile neutropenia ( $p = 0.003$ ).

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

End point timeframe:

during study; from randomization until progression/ death

| <b>End point values</b>     | Doxorubicin<br>(Arm A) | Pazopanib<br>(Arm B) |  |  |
|-----------------------------|------------------------|----------------------|--|--|
| Subject group type          | Reporting group        | Reporting group      |  |  |
| Number of subjects analysed | 39                     | 81                   |  |  |
| Units: number               | 4                      | 0                    |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

The AE documentation period for this trial begins upon first administration of the IMP(s) and ends 28 days after the last application of the IMP.

Adverse event reporting additional description:

Numbers in the non-serious adverse events section reflect all adverse events occurring during the study (non-serious and serious).

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 20.0 |
|--------------------|------|

### Reporting groups

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Pazopanib (Arm B) |
|-----------------------|-------------------|

Reporting group description: -

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Doxorubicin (Arm A) |
|-----------------------|---------------------|

Reporting group description: -

| Serious adverse events                                              | Pazopanib (Arm B) | Doxorubicin (Arm A) |  |
|---------------------------------------------------------------------|-------------------|---------------------|--|
| Total subjects affected by serious adverse events                   |                   |                     |  |
| subjects affected / exposed                                         | 45 / 81 (55.56%)  | 13 / 37 (35.14%)    |  |
| number of deaths (all causes)                                       | 10                | 1                   |  |
| number of deaths resulting from adverse events                      |                   |                     |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                     |  |
| Neoplasm progression                                                |                   |                     |  |
| subjects affected / exposed                                         | 2 / 81 (2.47%)    | 0 / 37 (0.00%)      |  |
| occurrences causally related to treatment / all                     | 0 / 2             | 0 / 0               |  |
| deaths causally related to treatment / all                          | 0 / 3             | 0 / 0               |  |
| Vascular disorders                                                  |                   |                     |  |
| Hypertensive crisis                                                 |                   |                     |  |
| subjects affected / exposed                                         | 1 / 81 (1.23%)    | 1 / 37 (2.70%)      |  |
| occurrences causally related to treatment / all                     | 0 / 1             | 1 / 1               |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0               |  |
| Lymphoedema                                                         |                   |                     |  |
| subjects affected / exposed                                         | 1 / 81 (1.23%)    | 0 / 37 (0.00%)      |  |
| occurrences causally related to treatment / all                     | 0 / 1             | 0 / 0               |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0               |  |
| Shock haemorrhagic                                                  |                   |                     |  |

|                                                      |                |                |  |
|------------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                          | 1 / 81 (1.23%) | 0 / 37 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 1          | 0 / 0          |  |
| Thrombosis                                           |                |                |  |
| subjects affected / exposed                          | 1 / 81 (1.23%) | 0 / 37 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Surgical and medical procedures                      |                |                |  |
| Catheter management                                  |                |                |  |
| subjects affected / exposed                          | 1 / 81 (1.23%) | 0 / 37 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Surgery                                              |                |                |  |
| subjects affected / exposed                          | 0 / 81 (0.00%) | 1 / 37 (2.70%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| General disorders and administration site conditions |                |                |  |
| Disease progression                                  |                |                |  |
| subjects affected / exposed                          | 1 / 81 (1.23%) | 0 / 37 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 1          | 0 / 0          |  |
| General physical health deterioration                |                |                |  |
| subjects affected / exposed                          | 7 / 81 (8.64%) | 1 / 37 (2.70%) |  |
| occurrences causally related to treatment / all      | 3 / 7          | 1 / 1          |  |
| deaths causally related to treatment / all           | 0 / 3          | 0 / 0          |  |
| Impaired healing                                     |                |                |  |
| subjects affected / exposed                          | 1 / 81 (1.23%) | 0 / 37 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Pain                                                 |                |                |  |
| subjects affected / exposed                          | 2 / 81 (2.47%) | 0 / 37 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| Pyrexia                                         |                |                |  |
| subjects affected / exposed                     | 2 / 81 (2.47%) | 1 / 37 (2.70%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders |                |                |  |
| Acute respiratory distress syndrome             |                |                |  |
| subjects affected / exposed                     | 0 / 81 (0.00%) | 1 / 37 (2.70%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 1 / 1          |  |
| Haemothorax                                     |                |                |  |
| subjects affected / exposed                     | 1 / 81 (1.23%) | 0 / 37 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Obliterative bronchiolitis                      |                |                |  |
| subjects affected / exposed                     | 1 / 81 (1.23%) | 0 / 37 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pleural effusion                                |                |                |  |
| subjects affected / exposed                     | 1 / 81 (1.23%) | 0 / 37 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| Pneumothorax                                    |                |                |  |
| subjects affected / exposed                     | 3 / 81 (3.70%) | 0 / 37 (0.00%) |  |
| occurrences causally related to treatment / all | 3 / 4          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pneumonia aspiration                            |                |                |  |
| subjects affected / exposed                     | 1 / 81 (1.23%) | 0 / 37 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pulmonary embolism                              |                |                |  |
| subjects affected / exposed                     | 1 / 81 (1.23%) | 0 / 37 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| Investigations                                  |                |                |  |
| Alanine aminotransferase increased              |                |                |  |
| subjects affected / exposed                     | 4 / 81 (4.94%) | 0 / 37 (0.00%) |  |
| occurrences causally related to treatment / all | 4 / 4          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Aspartate aminotransferase increased            |                |                |  |
| subjects affected / exposed                     | 1 / 81 (1.23%) | 0 / 37 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Blood creatinine increased                      |                |                |  |
| subjects affected / exposed                     | 1 / 81 (1.23%) | 0 / 37 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hepatic enzyme increased                        |                |                |  |
| subjects affected / exposed                     | 2 / 81 (2.47%) | 0 / 37 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Transaminases increased                         |                |                |  |
| subjects affected / exposed                     | 3 / 81 (3.70%) | 0 / 37 (0.00%) |  |
| occurrences causally related to treatment / all | 4 / 4          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Injury, poisoning and procedural complications  |                |                |  |
| Cervical vertebral fracture                     |                |                |  |
| subjects affected / exposed                     | 1 / 81 (1.23%) | 0 / 37 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Seroma                                          |                |                |  |
| subjects affected / exposed                     | 2 / 81 (2.47%) | 0 / 37 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cardiac disorders                               |                |                |  |
| Acute myocardial infarction                     |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 81 (0.00%) | 1 / 37 (2.70%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Atrial fibrillation                             |                |                |  |
| subjects affected / exposed                     | 1 / 81 (1.23%) | 0 / 37 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Nervous system disorders                        |                |                |  |
| Cerebrovascular accident                        |                |                |  |
| subjects affected / exposed                     | 1 / 81 (1.23%) | 1 / 37 (2.70%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cerebellar syndrome                             |                |                |  |
| subjects affected / exposed                     | 1 / 81 (1.23%) | 0 / 37 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Syncope                                         |                |                |  |
| subjects affected / exposed                     | 0 / 81 (0.00%) | 1 / 37 (2.70%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Blood and lymphatic system disorders            |                |                |  |
| Anaemia                                         |                |                |  |
| subjects affected / exposed                     | 0 / 81 (0.00%) | 1 / 37 (2.70%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Febrile neutropenia                             |                |                |  |
| subjects affected / exposed                     | 0 / 81 (0.00%) | 2 / 37 (5.41%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 2 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Neutropenia                                     |                |                |  |
| subjects affected / exposed                     | 1 / 81 (1.23%) | 0 / 37 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Eye disorders                                   |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| Macular hole                                    |                |                |  |
| subjects affected / exposed                     | 1 / 81 (1.23%) | 0 / 37 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastrointestinal disorders                      |                |                |  |
| Duodenal ulcer perforation                      |                |                |  |
| subjects affected / exposed                     | 1 / 81 (1.23%) | 0 / 37 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastrointestinal haemorrhage                    |                |                |  |
| subjects affected / exposed                     | 1 / 81 (1.23%) | 1 / 37 (2.70%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastric haemorrhage                             |                |                |  |
| subjects affected / exposed                     | 1 / 81 (1.23%) | 0 / 37 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Intestinal perforation                          |                |                |  |
| subjects affected / exposed                     | 1 / 81 (1.23%) | 0 / 37 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Stomatitis                                      |                |                |  |
| subjects affected / exposed                     | 0 / 81 (0.00%) | 1 / 37 (2.70%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Subileus                                        |                |                |  |
| subjects affected / exposed                     | 0 / 81 (0.00%) | 1 / 37 (2.70%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 2 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hepatobiliary disorders                         |                |                |  |
| Hepatotoxicity                                  |                |                |  |
| subjects affected / exposed                     | 2 / 81 (2.47%) | 0 / 37 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| Hypertransaminasaemia                           |                |                |  |
| subjects affected / exposed                     | 3 / 81 (3.70%) | 0 / 37 (0.00%) |  |
| occurrences causally related to treatment / all | 3 / 3          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Renal and urinary disorders                     |                |                |  |
| Acute kidney injury                             |                |                |  |
| subjects affected / exposed                     | 0 / 81 (0.00%) | 1 / 37 (2.70%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Musculoskeletal and connective tissue disorders |                |                |  |
| Back pain                                       |                |                |  |
| subjects affected / exposed                     | 2 / 81 (2.47%) | 0 / 37 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Spinal column stenosis                          |                |                |  |
| subjects affected / exposed                     | 1 / 81 (1.23%) | 0 / 37 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Infections and infestations                     |                |                |  |
| Clostridium difficile infection                 |                |                |  |
| subjects affected / exposed                     | 0 / 81 (0.00%) | 1 / 37 (2.70%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Erysipelas                                      |                |                |  |
| subjects affected / exposed                     | 0 / 81 (0.00%) | 1 / 37 (2.70%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Device related infection                        |                |                |  |
| subjects affected / exposed                     | 0 / 81 (0.00%) | 1 / 37 (2.70%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Infection                                       |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 1 / 81 (1.23%) | 0 / 37 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| Infected seroma                                 |                |                |  |
| subjects affected / exposed                     | 2 / 81 (2.47%) | 0 / 37 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Neutropenic sepsis                              |                |                |  |
| subjects affected / exposed                     | 0 / 81 (0.00%) | 1 / 37 (2.70%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pneumonia                                       |                |                |  |
| subjects affected / exposed                     | 3 / 81 (3.70%) | 0 / 37 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 3          | 0 / 0          |  |
| deaths causally related to treatment / all      | 1 / 1          | 0 / 0          |  |
| Sepsis                                          |                |                |  |
| subjects affected / exposed                     | 0 / 81 (0.00%) | 1 / 37 (2.70%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Urosepsis                                       |                |                |  |
| subjects affected / exposed                     | 1 / 81 (1.23%) | 0 / 37 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Urinary tract infection                         |                |                |  |
| subjects affected / exposed                     | 1 / 81 (1.23%) | 2 / 37 (5.41%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 1 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Wound infection                                 |                |                |  |
| subjects affected / exposed                     | 1 / 81 (1.23%) | 0 / 37 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Metabolism and nutrition disorders              |                |                |  |
| Hyponatraemia                                   |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 1 / 81 (1.23%) | 0 / 37 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hypokalaemia                                    |                |                |  |
| subjects affected / exposed                     | 1 / 81 (1.23%) | 0 / 37 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

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

| <b>Non-serious adverse events</b>                                   | Pazopanib (Arm B) | Doxorubicin (Arm A) |  |
|---------------------------------------------------------------------|-------------------|---------------------|--|
| Total subjects affected by non-serious adverse events               |                   |                     |  |
| subjects affected / exposed                                         | 80 / 81 (98.77%)  | 37 / 37 (100.00%)   |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                     |  |
| Neoplasm progression                                                |                   |                     |  |
| subjects affected / exposed                                         | 3 / 81 (3.70%)    | 0 / 37 (0.00%)      |  |
| occurrences (all)                                                   | 3                 | 0                   |  |
| Tumour pain                                                         |                   |                     |  |
| subjects affected / exposed                                         | 3 / 81 (3.70%)    | 0 / 37 (0.00%)      |  |
| occurrences (all)                                                   | 4                 | 0                   |  |
| Vascular disorders                                                  |                   |                     |  |
| Hypertensive crisis                                                 |                   |                     |  |
| subjects affected / exposed                                         | 1 / 81 (1.23%)    | 1 / 37 (2.70%)      |  |
| occurrences (all)                                                   | 1                 | 1                   |  |
| Hypotension                                                         |                   |                     |  |
| subjects affected / exposed                                         | 0 / 81 (0.00%)    | 1 / 37 (2.70%)      |  |
| occurrences (all)                                                   | 0                 | 1                   |  |
| Lymphoedema                                                         |                   |                     |  |
| subjects affected / exposed                                         | 2 / 81 (2.47%)    | 0 / 37 (0.00%)      |  |
| occurrences (all)                                                   | 2                 | 0                   |  |
| Haematoma                                                           |                   |                     |  |
| subjects affected / exposed                                         | 1 / 81 (1.23%)    | 0 / 37 (0.00%)      |  |
| occurrences (all)                                                   | 1                 | 0                   |  |
| Hypertension                                                        |                   |                     |  |

|                                                                                                                                    |                        |                     |  |
|------------------------------------------------------------------------------------------------------------------------------------|------------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                                                   | 30 / 81 (37.04%)<br>38 | 3 / 37 (8.11%)<br>3 |  |
| Thrombophlebitis superficial<br>subjects affected / exposed<br>occurrences (all)                                                   | 0 / 81 (0.00%)<br>0    | 1 / 37 (2.70%)<br>1 |  |
| Shock haemorrhagic<br>subjects affected / exposed<br>occurrences (all)                                                             | 1 / 81 (1.23%)<br>1    | 0 / 37 (0.00%)<br>0 |  |
| Thrombosis<br>subjects affected / exposed<br>occurrences (all)                                                                     | 1 / 81 (1.23%)<br>1    | 1 / 37 (2.70%)<br>1 |  |
| Surgical and medical procedures<br>Catheter management<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 81 (1.23%)<br>1    | 0 / 37 (0.00%)<br>0 |  |
| Surgery<br>subjects affected / exposed<br>occurrences (all)                                                                        | 0 / 81 (0.00%)<br>0    | 1 / 37 (2.70%)<br>1 |  |
| General disorders and administration<br>site conditions<br>Disease progression<br>subjects affected / exposed<br>occurrences (all) | 3 / 81 (3.70%)<br>3    | 0 / 37 (0.00%)<br>0 |  |
| Chills<br>subjects affected / exposed<br>occurrences (all)                                                                         | 1 / 81 (1.23%)<br>1    | 0 / 37 (0.00%)<br>0 |  |
| Chest pain<br>subjects affected / exposed<br>occurrences (all)                                                                     | 1 / 81 (1.23%)<br>1    | 2 / 37 (5.41%)<br>2 |  |
| Chest discomfort<br>subjects affected / exposed<br>occurrences (all)                                                               | 1 / 81 (1.23%)<br>1    | 0 / 37 (0.00%)<br>0 |  |
| Asthenia<br>subjects affected / exposed<br>occurrences (all)                                                                       | 2 / 81 (2.47%)<br>2    | 0 / 37 (0.00%)<br>0 |  |
| Influenza like illness                                                                                                             |                        |                     |  |

|                                       |                  |                  |
|---------------------------------------|------------------|------------------|
| subjects affected / exposed           | 1 / 81 (1.23%)   | 2 / 37 (5.41%)   |
| occurrences (all)                     | 1                | 2                |
| Impaired healing                      |                  |                  |
| subjects affected / exposed           | 1 / 81 (1.23%)   | 0 / 37 (0.00%)   |
| occurrences (all)                     | 1                | 0                |
| General physical health deterioration |                  |                  |
| subjects affected / exposed           | 11 / 81 (13.58%) | 1 / 37 (2.70%)   |
| occurrences (all)                     | 12               | 1                |
| Gait disturbance                      |                  |                  |
| subjects affected / exposed           | 1 / 81 (1.23%)   | 0 / 37 (0.00%)   |
| occurrences (all)                     | 1                | 0                |
| Fatigue                               |                  |                  |
| subjects affected / exposed           | 47 / 81 (58.02%) | 24 / 37 (64.86%) |
| occurrences (all)                     | 59               | 29               |
| Drug intolerance                      |                  |                  |
| subjects affected / exposed           | 0 / 81 (0.00%)   | 1 / 37 (2.70%)   |
| occurrences (all)                     | 0                | 1                |
| Localised oedema                      |                  |                  |
| subjects affected / exposed           | 1 / 81 (1.23%)   | 0 / 37 (0.00%)   |
| occurrences (all)                     | 1                | 0                |
| Oedema peripheral                     |                  |                  |
| subjects affected / exposed           | 5 / 81 (6.17%)   | 3 / 37 (8.11%)   |
| occurrences (all)                     | 8                | 3                |
| Mucosal inflammation                  |                  |                  |
| subjects affected / exposed           | 10 / 81 (12.35%) | 9 / 37 (24.32%)  |
| occurrences (all)                     | 10               | 10               |
| Pain                                  |                  |                  |
| subjects affected / exposed           | 10 / 81 (12.35%) | 1 / 37 (2.70%)   |
| occurrences (all)                     | 10               | 1                |
| Temperature intolerance               |                  |                  |
| subjects affected / exposed           | 1 / 81 (1.23%)   | 0 / 37 (0.00%)   |
| occurrences (all)                     | 1                | 0                |
| Sensation of blood flow               |                  |                  |
| subjects affected / exposed           | 1 / 81 (1.23%)   | 0 / 37 (0.00%)   |
| occurrences (all)                     | 1                | 0                |
| Pyrexia                               |                  |                  |

|                                                                                         |                        |                     |  |
|-----------------------------------------------------------------------------------------|------------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all)                                        | 3 / 81 (3.70%)<br>3    | 2 / 37 (5.41%)<br>5 |  |
| Peripheral swelling<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 81 (1.23%)<br>1    | 1 / 37 (2.70%)<br>1 |  |
| Reproductive system and breast disorders                                                |                        |                     |  |
| Balanoposthitis<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 81 (1.23%)<br>3    | 0 / 37 (0.00%)<br>0 |  |
| Pelvic pain<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 81 (0.00%)<br>0    | 1 / 37 (2.70%)<br>1 |  |
| Respiratory, thoracic and mediastinal disorders                                         |                        |                     |  |
| Acute respiratory distress syndrome<br>subjects affected / exposed<br>occurrences (all) | 0 / 81 (0.00%)<br>0    | 1 / 37 (2.70%)<br>1 |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)                            | 8 / 81 (9.88%)<br>8    | 3 / 37 (8.11%)<br>4 |  |
| Dysphonia<br>subjects affected / exposed<br>occurrences (all)                           | 7 / 81 (8.64%)<br>7    | 0 / 37 (0.00%)<br>0 |  |
| Cough<br>subjects affected / exposed<br>occurrences (all)                               | 11 / 81 (13.58%)<br>12 | 3 / 37 (8.11%)<br>3 |  |
| Dyspnoea exertional<br>subjects affected / exposed<br>occurrences (all)                 | 3 / 81 (3.70%)<br>3    | 0 / 37 (0.00%)<br>0 |  |
| Haemothorax<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 81 (1.23%)<br>1    | 0 / 37 (0.00%)<br>0 |  |
| Haemoptysis<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 81 (1.23%)<br>1    | 0 / 37 (0.00%)<br>0 |  |
| Epistaxis                                                                               |                        |                     |  |

|                             |                |                |  |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 5 / 81 (6.17%) | 0 / 37 (0.00%) |  |
| occurrences (all)           | 5              | 0              |  |
| Pneumonia aspiration        |                |                |  |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 37 (0.00%) |  |
| occurrences (all)           | 1              | 0              |  |
| Pleural effusion            |                |                |  |
| subjects affected / exposed | 1 / 81 (1.23%) | 2 / 37 (5.41%) |  |
| occurrences (all)           | 1              | 3              |  |
| Oropharyngeal pain          |                |                |  |
| subjects affected / exposed | 1 / 81 (1.23%) | 1 / 37 (2.70%) |  |
| occurrences (all)           | 1              | 1              |  |
| Pneumothorax                |                |                |  |
| subjects affected / exposed | 3 / 81 (3.70%) | 0 / 37 (0.00%) |  |
| occurrences (all)           | 4              | 0              |  |
| Hiccups                     |                |                |  |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 37 (2.70%) |  |
| occurrences (all)           | 0              | 1              |  |
| Obliterative bronchiolitis  |                |                |  |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 37 (0.00%) |  |
| occurrences (all)           | 1              | 0              |  |
| Pulmonary embolism          |                |                |  |
| subjects affected / exposed | 1 / 81 (1.23%) | 1 / 37 (2.70%) |  |
| occurrences (all)           | 1              | 1              |  |
| Psychiatric disorders       |                |                |  |
| Agitation                   |                |                |  |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 37 (0.00%) |  |
| occurrences (all)           | 1              | 0              |  |
| Anxiety                     |                |                |  |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 37 (0.00%) |  |
| occurrences (all)           | 1              | 0              |  |
| Depressed mood              |                |                |  |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 37 (2.70%) |  |
| occurrences (all)           | 0              | 1              |  |
| Depression                  |                |                |  |
| subjects affected / exposed | 3 / 81 (3.70%) | 1 / 37 (2.70%) |  |
| occurrences (all)           | 3              | 1              |  |

|                                      |                 |                |  |
|--------------------------------------|-----------------|----------------|--|
| Insomnia                             |                 |                |  |
| subjects affected / exposed          | 1 / 81 (1.23%)  | 0 / 37 (0.00%) |  |
| occurrences (all)                    | 1               | 0              |  |
| Mental disorder                      |                 |                |  |
| subjects affected / exposed          | 1 / 81 (1.23%)  | 0 / 37 (0.00%) |  |
| occurrences (all)                    | 1               | 0              |  |
| Sleep disorder                       |                 |                |  |
| subjects affected / exposed          | 4 / 81 (4.94%)  | 2 / 37 (5.41%) |  |
| occurrences (all)                    | 4               | 2              |  |
| Product issues                       |                 |                |  |
| Device fastener issue                |                 |                |  |
| subjects affected / exposed          | 1 / 81 (1.23%)  | 0 / 37 (0.00%) |  |
| occurrences (all)                    | 1               | 0              |  |
| Investigations                       |                 |                |  |
| Alanine aminotransferase increased   |                 |                |  |
| subjects affected / exposed          | 9 / 81 (11.11%) | 1 / 37 (2.70%) |  |
| occurrences (all)                    | 9               | 1              |  |
| Amylase increased                    |                 |                |  |
| subjects affected / exposed          | 1 / 81 (1.23%)  | 0 / 37 (0.00%) |  |
| occurrences (all)                    | 1               | 0              |  |
| Blood bilirubin increased            |                 |                |  |
| subjects affected / exposed          | 4 / 81 (4.94%)  | 0 / 37 (0.00%) |  |
| occurrences (all)                    | 6               | 0              |  |
| Blood creatinine increased           |                 |                |  |
| subjects affected / exposed          | 4 / 81 (4.94%)  | 0 / 37 (0.00%) |  |
| occurrences (all)                    | 4               | 0              |  |
| Blood urea increased                 |                 |                |  |
| subjects affected / exposed          | 1 / 81 (1.23%)  | 0 / 37 (0.00%) |  |
| occurrences (all)                    | 1               | 0              |  |
| Blood alkaline phosphatase increased |                 |                |  |
| subjects affected / exposed          | 4 / 81 (4.94%)  | 0 / 37 (0.00%) |  |
| occurrences (all)                    | 4               | 0              |  |
| Aspartate aminotransferase increased |                 |                |  |
| subjects affected / exposed          | 8 / 81 (9.88%)  | 0 / 37 (0.00%) |  |
| occurrences (all)                    | 8               | 0              |  |
| Breath sounds abnormal               |                 |                |  |

|                                                   |                  |                 |  |
|---------------------------------------------------|------------------|-----------------|--|
| subjects affected / exposed                       | 1 / 81 (1.23%)   | 0 / 37 (0.00%)  |  |
| occurrences (all)                                 | 1                | 0               |  |
| C-reactive protein increased                      |                  |                 |  |
| subjects affected / exposed                       | 1 / 81 (1.23%)   | 1 / 37 (2.70%)  |  |
| occurrences (all)                                 | 1                | 1               |  |
| Hepatic enzyme increased                          |                  |                 |  |
| subjects affected / exposed                       | 3 / 81 (3.70%)   | 1 / 37 (2.70%)  |  |
| occurrences (all)                                 | 3                | 1               |  |
| Lipase increased                                  |                  |                 |  |
| subjects affected / exposed                       | 1 / 81 (1.23%)   | 0 / 37 (0.00%)  |  |
| occurrences (all)                                 | 1                | 0               |  |
| Lymphocyte count decreased                        |                  |                 |  |
| subjects affected / exposed                       | 1 / 81 (1.23%)   | 0 / 37 (0.00%)  |  |
| occurrences (all)                                 | 1                | 0               |  |
| Neutrophil count decreased                        |                  |                 |  |
| subjects affected / exposed                       | 0 / 81 (0.00%)   | 5 / 37 (13.51%) |  |
| occurrences (all)                                 | 0                | 7               |  |
| Platelet count decreased                          |                  |                 |  |
| subjects affected / exposed                       | 4 / 81 (4.94%)   | 0 / 37 (0.00%)  |  |
| occurrences (all)                                 | 4                | 0               |  |
| Respiratory sinus arrhythmia<br>magnitude         |                  |                 |  |
| subjects affected / exposed                       | 1 / 81 (1.23%)   | 0 / 37 (0.00%)  |  |
| occurrences (all)                                 | 1                | 0               |  |
| Transaminases increased                           |                  |                 |  |
| subjects affected / exposed                       | 3 / 81 (3.70%)   | 0 / 37 (0.00%)  |  |
| occurrences (all)                                 | 5                | 0               |  |
| White blood cell count decreased                  |                  |                 |  |
| subjects affected / exposed                       | 1 / 81 (1.23%)   | 2 / 37 (5.41%)  |  |
| occurrences (all)                                 | 1                | 3               |  |
| Weight decreased                                  |                  |                 |  |
| subjects affected / exposed                       | 10 / 81 (12.35%) | 2 / 37 (5.41%)  |  |
| occurrences (all)                                 | 10               | 2               |  |
| Injury, poisoning and procedural<br>complications |                  |                 |  |

|                                                                                 |                     |                     |  |
|---------------------------------------------------------------------------------|---------------------|---------------------|--|
| Wound dehiscence<br>subjects affected / exposed<br>occurrences (all)            | 0 / 81 (0.00%)<br>0 | 1 / 37 (2.70%)<br>1 |  |
| Wound complication<br>subjects affected / exposed<br>occurrences (all)          | 0 / 81 (0.00%)<br>0 | 1 / 37 (2.70%)<br>1 |  |
| Seroma<br>subjects affected / exposed<br>occurrences (all)                      | 2 / 81 (2.47%)<br>3 | 0 / 37 (0.00%)<br>0 |  |
| Rib fracture<br>subjects affected / exposed<br>occurrences (all)                | 1 / 81 (1.23%)<br>1 | 0 / 37 (0.00%)<br>0 |  |
| Incisional hernia<br>subjects affected / exposed<br>occurrences (all)           | 1 / 81 (1.23%)<br>1 | 0 / 37 (0.00%)<br>0 |  |
| Cervical vertebral fracture<br>subjects affected / exposed<br>occurrences (all) | 1 / 81 (1.23%)<br>1 | 0 / 37 (0.00%)<br>0 |  |
| Cardiac disorders                                                               |                     |                     |  |
| Atrial fibrillation<br>subjects affected / exposed<br>occurrences (all)         | 2 / 81 (2.47%)<br>2 | 0 / 37 (0.00%)<br>0 |  |
| Aortic valve stenosis<br>subjects affected / exposed<br>occurrences (all)       | 1 / 81 (1.23%)<br>1 | 0 / 37 (0.00%)<br>0 |  |
| Acute myocardial infarction<br>subjects affected / exposed<br>occurrences (all) | 0 / 81 (0.00%)<br>0 | 1 / 37 (2.70%)<br>1 |  |
| Bradycardia<br>subjects affected / exposed<br>occurrences (all)                 | 2 / 81 (2.47%)<br>2 | 0 / 37 (0.00%)<br>0 |  |
| Cardiac failure<br>subjects affected / exposed<br>occurrences (all)             | 1 / 81 (1.23%)<br>1 | 0 / 37 (0.00%)<br>0 |  |
| Cardiovascular disorder                                                         |                     |                     |  |

|                             |                 |                |  |
|-----------------------------|-----------------|----------------|--|
| subjects affected / exposed | 0 / 81 (0.00%)  | 1 / 37 (2.70%) |  |
| occurrences (all)           | 0               | 1              |  |
| Ventricular arrhythmia      |                 |                |  |
| subjects affected / exposed | 0 / 81 (0.00%)  | 1 / 37 (2.70%) |  |
| occurrences (all)           | 0               | 1              |  |
| Tachyarrhythmia             |                 |                |  |
| subjects affected / exposed | 0 / 81 (0.00%)  | 1 / 37 (2.70%) |  |
| occurrences (all)           | 0               | 1              |  |
| Nervous system disorders    |                 |                |  |
| Dizziness                   |                 |                |  |
| subjects affected / exposed | 4 / 81 (4.94%)  | 1 / 37 (2.70%) |  |
| occurrences (all)           | 5               | 1              |  |
| Disturbance in attention    |                 |                |  |
| subjects affected / exposed | 0 / 81 (0.00%)  | 1 / 37 (2.70%) |  |
| occurrences (all)           | 0               | 1              |  |
| Cerebrovascular accident    |                 |                |  |
| subjects affected / exposed | 1 / 81 (1.23%)  | 1 / 37 (2.70%) |  |
| occurrences (all)           | 1               | 1              |  |
| Cerebellar syndrome         |                 |                |  |
| subjects affected / exposed | 1 / 81 (1.23%)  | 0 / 37 (0.00%) |  |
| occurrences (all)           | 1               | 0              |  |
| Ageusia                     |                 |                |  |
| subjects affected / exposed | 0 / 81 (0.00%)  | 1 / 37 (2.70%) |  |
| occurrences (all)           | 0               | 1              |  |
| Hemiparesis                 |                 |                |  |
| subjects affected / exposed | 1 / 81 (1.23%)  | 0 / 37 (0.00%) |  |
| occurrences (all)           | 1               | 0              |  |
| Headache                    |                 |                |  |
| subjects affected / exposed | 9 / 81 (11.11%) | 1 / 37 (2.70%) |  |
| occurrences (all)           | 9               | 1              |  |
| Head discomfort             |                 |                |  |
| subjects affected / exposed | 0 / 81 (0.00%)  | 1 / 37 (2.70%) |  |
| occurrences (all)           | 0               | 1              |  |
| Facial paralysis            |                 |                |  |
| subjects affected / exposed | 1 / 81 (1.23%)  | 0 / 37 (0.00%) |  |
| occurrences (all)           | 1               | 0              |  |

|                                      |                  |                 |  |
|--------------------------------------|------------------|-----------------|--|
| Dysgeusia                            |                  |                 |  |
| subjects affected / exposed          | 14 / 81 (17.28%) | 3 / 37 (8.11%)  |  |
| occurrences (all)                    | 14               | 3               |  |
| Hypoaesthesia                        |                  |                 |  |
| subjects affected / exposed          | 1 / 81 (1.23%)   | 0 / 37 (0.00%)  |  |
| occurrences (all)                    | 1                | 0               |  |
| Dysarthria                           |                  |                 |  |
| subjects affected / exposed          | 1 / 81 (1.23%)   | 0 / 37 (0.00%)  |  |
| occurrences (all)                    | 1                | 0               |  |
| Neuralgia                            |                  |                 |  |
| subjects affected / exposed          | 1 / 81 (1.23%)   | 1 / 37 (2.70%)  |  |
| occurrences (all)                    | 1                | 1               |  |
| Syncope                              |                  |                 |  |
| subjects affected / exposed          | 0 / 81 (0.00%)   | 1 / 37 (2.70%)  |  |
| occurrences (all)                    | 0                | 1               |  |
| Polyneuropathy                       |                  |                 |  |
| subjects affected / exposed          | 1 / 81 (1.23%)   | 0 / 37 (0.00%)  |  |
| occurrences (all)                    | 1                | 0               |  |
| Phantom pain                         |                  |                 |  |
| subjects affected / exposed          | 1 / 81 (1.23%)   | 0 / 37 (0.00%)  |  |
| occurrences (all)                    | 1                | 0               |  |
| Peroneal nerve palsy                 |                  |                 |  |
| subjects affected / exposed          | 1 / 81 (1.23%)   | 0 / 37 (0.00%)  |  |
| occurrences (all)                    | 1                | 0               |  |
| Paraesthesia                         |                  |                 |  |
| subjects affected / exposed          | 4 / 81 (4.94%)   | 0 / 37 (0.00%)  |  |
| occurrences (all)                    | 5                | 0               |  |
| Orthostatic intolerance              |                  |                 |  |
| subjects affected / exposed          | 0 / 81 (0.00%)   | 1 / 37 (2.70%)  |  |
| occurrences (all)                    | 0                | 1               |  |
| Blood and lymphatic system disorders |                  |                 |  |
| Leukopenia                           |                  |                 |  |
| subjects affected / exposed          | 7 / 81 (8.64%)   | 8 / 37 (21.62%) |  |
| occurrences (all)                    | 15               | 11              |  |
| Febrile neutropenia                  |                  |                 |  |

|                             |                  |                  |  |
|-----------------------------|------------------|------------------|--|
| subjects affected / exposed | 0 / 81 (0.00%)   | 3 / 37 (8.11%)   |  |
| occurrences (all)           | 0                | 3                |  |
| Anaemia                     |                  |                  |  |
| subjects affected / exposed | 8 / 81 (9.88%)   | 9 / 37 (24.32%)  |  |
| occurrences (all)           | 10               | 13               |  |
| Lymphopenia                 |                  |                  |  |
| subjects affected / exposed | 0 / 81 (0.00%)   | 1 / 37 (2.70%)   |  |
| occurrences (all)           | 0                | 1                |  |
| Neutropenia                 |                  |                  |  |
| subjects affected / exposed | 8 / 81 (9.88%)   | 11 / 37 (29.73%) |  |
| occurrences (all)           | 13               | 20               |  |
| Thrombocytopenia            |                  |                  |  |
| subjects affected / exposed | 11 / 81 (13.58%) | 3 / 37 (8.11%)   |  |
| occurrences (all)           | 19               | 3                |  |
| Ear and labyrinth disorders |                  |                  |  |
| Hypoacusis                  |                  |                  |  |
| subjects affected / exposed | 1 / 81 (1.23%)   | 0 / 37 (0.00%)   |  |
| occurrences (all)           | 1                | 0                |  |
| Vertigo                     |                  |                  |  |
| subjects affected / exposed | 2 / 81 (2.47%)   | 2 / 37 (5.41%)   |  |
| occurrences (all)           | 2                | 2                |  |
| Eye disorders               |                  |                  |  |
| Eye haemorrhage             |                  |                  |  |
| subjects affected / exposed | 1 / 81 (1.23%)   | 0 / 37 (0.00%)   |  |
| occurrences (all)           | 1                | 0                |  |
| Visual acuity reduced       |                  |                  |  |
| subjects affected / exposed | 0 / 81 (0.00%)   | 1 / 37 (2.70%)   |  |
| occurrences (all)           | 0                | 1                |  |
| Macular hole                |                  |                  |  |
| subjects affected / exposed | 1 / 81 (1.23%)   | 0 / 37 (0.00%)   |  |
| occurrences (all)           | 1                | 0                |  |
| Lacrimation increased       |                  |                  |  |
| subjects affected / exposed | 1 / 81 (1.23%)   | 0 / 37 (0.00%)   |  |
| occurrences (all)           | 1                | 0                |  |
| Visual impairment           |                  |                  |  |

|                             |                  |                 |  |
|-----------------------------|------------------|-----------------|--|
| subjects affected / exposed | 0 / 81 (0.00%)   | 1 / 37 (2.70%)  |  |
| occurrences (all)           | 0                | 1               |  |
| Gastrointestinal disorders  |                  |                 |  |
| Diarrhoea                   |                  |                 |  |
| subjects affected / exposed | 35 / 81 (43.21%) | 5 / 37 (13.51%) |  |
| occurrences (all)           | 41               | 5               |  |
| Abdominal distension        |                  |                 |  |
| subjects affected / exposed | 0 / 81 (0.00%)   | 1 / 37 (2.70%)  |  |
| occurrences (all)           | 0                | 1               |  |
| Abdominal pain              |                  |                 |  |
| subjects affected / exposed | 7 / 81 (8.64%)   | 0 / 37 (0.00%)  |  |
| occurrences (all)           | 8                | 0               |  |
| Abdominal pain upper        |                  |                 |  |
| subjects affected / exposed | 5 / 81 (6.17%)   | 0 / 37 (0.00%)  |  |
| occurrences (all)           | 5                | 0               |  |
| Abdominal wall haemorrhage  |                  |                 |  |
| subjects affected / exposed | 1 / 81 (1.23%)   | 0 / 37 (0.00%)  |  |
| occurrences (all)           | 1                | 0               |  |
| Anal fissure                |                  |                 |  |
| subjects affected / exposed | 1 / 81 (1.23%)   | 0 / 37 (0.00%)  |  |
| occurrences (all)           | 1                | 0               |  |
| Anorectal discomfort        |                  |                 |  |
| subjects affected / exposed | 1 / 81 (1.23%)   | 0 / 37 (0.00%)  |  |
| occurrences (all)           | 1                | 0               |  |
| Constipation                |                  |                 |  |
| subjects affected / exposed | 7 / 81 (8.64%)   | 5 / 37 (13.51%) |  |
| occurrences (all)           | 8                | 5               |  |
| Dry mouth                   |                  |                 |  |
| subjects affected / exposed | 2 / 81 (2.47%)   | 1 / 37 (2.70%)  |  |
| occurrences (all)           | 2                | 1               |  |
| Duodenal ulcer perforation  |                  |                 |  |
| subjects affected / exposed | 1 / 81 (1.23%)   | 0 / 37 (0.00%)  |  |
| occurrences (all)           | 1                | 0               |  |
| Dyspepsia                   |                  |                 |  |
| subjects affected / exposed | 1 / 81 (1.23%)   | 2 / 37 (5.41%)  |  |
| occurrences (all)           | 1                | 2               |  |

|                                    |                  |                  |
|------------------------------------|------------------|------------------|
| Dysphagia                          |                  |                  |
| subjects affected / exposed        | 1 / 81 (1.23%)   | 0 / 37 (0.00%)   |
| occurrences (all)                  | 1                | 0                |
| Epulis                             |                  |                  |
| subjects affected / exposed        | 0 / 81 (0.00%)   | 1 / 37 (2.70%)   |
| occurrences (all)                  | 0                | 1                |
| Eructation                         |                  |                  |
| subjects affected / exposed        | 0 / 81 (0.00%)   | 1 / 37 (2.70%)   |
| occurrences (all)                  | 0                | 1                |
| Flatulence                         |                  |                  |
| subjects affected / exposed        | 3 / 81 (3.70%)   | 0 / 37 (0.00%)   |
| occurrences (all)                  | 3                | 0                |
| Gastric haemorrhage                |                  |                  |
| subjects affected / exposed        | 1 / 81 (1.23%)   | 0 / 37 (0.00%)   |
| occurrences (all)                  | 1                | 0                |
| Gastritis                          |                  |                  |
| subjects affected / exposed        | 1 / 81 (1.23%)   | 1 / 37 (2.70%)   |
| occurrences (all)                  | 1                | 1                |
| Gastrointestinal haemorrhage       |                  |                  |
| subjects affected / exposed        | 1 / 81 (1.23%)   | 2 / 37 (5.41%)   |
| occurrences (all)                  | 1                | 2                |
| Gastrooesophageal reflux disease   |                  |                  |
| subjects affected / exposed        | 0 / 81 (0.00%)   | 1 / 37 (2.70%)   |
| occurrences (all)                  | 0                | 1                |
| Intestinal perforation             |                  |                  |
| subjects affected / exposed        | 1 / 81 (1.23%)   | 0 / 37 (0.00%)   |
| occurrences (all)                  | 1                | 0                |
| Lower gastrointestinal haemorrhage |                  |                  |
| subjects affected / exposed        | 1 / 81 (1.23%)   | 0 / 37 (0.00%)   |
| occurrences (all)                  | 1                | 0                |
| Nausea                             |                  |                  |
| subjects affected / exposed        | 35 / 81 (43.21%) | 18 / 37 (48.65%) |
| occurrences (all)                  | 40               | 25               |
| Oesophagitis                       |                  |                  |
| subjects affected / exposed        | 0 / 81 (0.00%)   | 1 / 37 (2.70%)   |
| occurrences (all)                  | 0                | 1                |

|                                        |                  |                  |  |
|----------------------------------------|------------------|------------------|--|
| Vomiting                               |                  |                  |  |
| subjects affected / exposed            | 16 / 81 (19.75%) | 7 / 37 (18.92%)  |  |
| occurrences (all)                      | 18               | 9                |  |
| Subileus                               |                  |                  |  |
| subjects affected / exposed            | 0 / 81 (0.00%)   | 1 / 37 (2.70%)   |  |
| occurrences (all)                      | 0                | 2                |  |
| Stomatitis                             |                  |                  |  |
| subjects affected / exposed            | 3 / 81 (3.70%)   | 7 / 37 (18.92%)  |  |
| occurrences (all)                      | 3                | 13               |  |
| Retroperitoneal haematoma              |                  |                  |  |
| subjects affected / exposed            | 0 / 81 (0.00%)   | 1 / 37 (2.70%)   |  |
| occurrences (all)                      | 0                | 1                |  |
| Regurgitation                          |                  |                  |  |
| subjects affected / exposed            | 0 / 81 (0.00%)   | 1 / 37 (2.70%)   |  |
| occurrences (all)                      | 0                | 1                |  |
| Hepatobiliary disorders                |                  |                  |  |
| Hepatotoxicity                         |                  |                  |  |
| subjects affected / exposed            | 2 / 81 (2.47%)   | 0 / 37 (0.00%)   |  |
| occurrences (all)                      | 2                | 0                |  |
| Hypertransaminasaemia                  |                  |                  |  |
| subjects affected / exposed            | 3 / 81 (3.70%)   | 0 / 37 (0.00%)   |  |
| occurrences (all)                      | 3                | 0                |  |
| Jaundice                               |                  |                  |  |
| subjects affected / exposed            | 1 / 81 (1.23%)   | 0 / 37 (0.00%)   |  |
| occurrences (all)                      | 1                | 0                |  |
| Skin and subcutaneous tissue disorders |                  |                  |  |
| Alopecia                               |                  |                  |  |
| subjects affected / exposed            | 2 / 81 (2.47%)   | 20 / 37 (54.05%) |  |
| occurrences (all)                      | 2                | 21               |  |
| Decubitus ulcer                        |                  |                  |  |
| subjects affected / exposed            | 1 / 81 (1.23%)   | 0 / 37 (0.00%)   |  |
| occurrences (all)                      | 1                | 0                |  |
| Dry skin                               |                  |                  |  |
| subjects affected / exposed            | 3 / 81 (3.70%)   | 0 / 37 (0.00%)   |  |
| occurrences (all)                      | 3                | 0                |  |
| Erythema                               |                  |                  |  |

|                                            |                |                |
|--------------------------------------------|----------------|----------------|
| subjects affected / exposed                | 2 / 81 (2.47%) | 0 / 37 (0.00%) |
| occurrences (all)                          | 2              | 0              |
| Hair colour changes                        |                |                |
| subjects affected / exposed                | 5 / 81 (6.17%) | 0 / 37 (0.00%) |
| occurrences (all)                          | 5              | 0              |
| Intertrigo                                 |                |                |
| subjects affected / exposed                | 1 / 81 (1.23%) | 0 / 37 (0.00%) |
| occurrences (all)                          | 1              | 0              |
| Nail dystrophy                             |                |                |
| subjects affected / exposed                | 1 / 81 (1.23%) | 0 / 37 (0.00%) |
| occurrences (all)                          | 1              | 0              |
| Night sweats                               |                |                |
| subjects affected / exposed                | 2 / 81 (2.47%) | 1 / 37 (2.70%) |
| occurrences (all)                          | 2              | 1              |
| Palmar-plantar erythrodysesthesia syndrome |                |                |
| subjects affected / exposed                | 2 / 81 (2.47%) | 0 / 37 (0.00%) |
| occurrences (all)                          | 2              | 0              |
| Rash                                       |                |                |
| subjects affected / exposed                | 5 / 81 (6.17%) | 1 / 37 (2.70%) |
| occurrences (all)                          | 5              | 1              |
| Xeroderma                                  |                |                |
| subjects affected / exposed                | 1 / 81 (1.23%) | 0 / 37 (0.00%) |
| occurrences (all)                          | 1              | 0              |
| Skin lesion                                |                |                |
| subjects affected / exposed                | 1 / 81 (1.23%) | 0 / 37 (0.00%) |
| occurrences (all)                          | 1              | 0              |
| Skin hypopigmentation                      |                |                |
| subjects affected / exposed                | 1 / 81 (1.23%) | 0 / 37 (0.00%) |
| occurrences (all)                          | 1              | 0              |
| Skin fissures                              |                |                |
| subjects affected / exposed                | 1 / 81 (1.23%) | 0 / 37 (0.00%) |
| occurrences (all)                          | 1              | 0              |
| Skin exfoliation                           |                |                |
| subjects affected / exposed                | 2 / 81 (2.47%) | 0 / 37 (0.00%) |
| occurrences (all)                          | 2              | 0              |

|                                                                         |                        |                     |  |
|-------------------------------------------------------------------------|------------------------|---------------------|--|
| Scar pain<br>subjects affected / exposed<br>occurrences (all)           | 1 / 81 (1.23%)<br>1    | 0 / 37 (0.00%)<br>0 |  |
| Renal and urinary disorders                                             |                        |                     |  |
| Bladder discomfort<br>subjects affected / exposed<br>occurrences (all)  | 1 / 81 (1.23%)<br>1    | 0 / 37 (0.00%)<br>0 |  |
| Acute kidney injury<br>subjects affected / exposed<br>occurrences (all) | 0 / 81 (0.00%)<br>0    | 1 / 37 (2.70%)<br>1 |  |
| Urinary retention<br>subjects affected / exposed<br>occurrences (all)   | 0 / 81 (0.00%)<br>0    | 1 / 37 (2.70%)<br>1 |  |
| Polyuria<br>subjects affected / exposed<br>occurrences (all)            | 1 / 81 (1.23%)<br>1    | 0 / 37 (0.00%)<br>0 |  |
| Nocturia<br>subjects affected / exposed<br>occurrences (all)            | 1 / 81 (1.23%)<br>1    | 0 / 37 (0.00%)<br>0 |  |
| Leukocyturia<br>subjects affected / exposed<br>occurrences (all)        | 1 / 81 (1.23%)<br>1    | 0 / 37 (0.00%)<br>0 |  |
| Haematuria<br>subjects affected / exposed<br>occurrences (all)          | 0 / 81 (0.00%)<br>0    | 1 / 37 (2.70%)<br>1 |  |
| Dysuria<br>subjects affected / exposed<br>occurrences (all)             | 0 / 81 (0.00%)<br>0    | 1 / 37 (2.70%)<br>1 |  |
| Endocrine disorders                                                     |                        |                     |  |
| Hyperthyroidism<br>subjects affected / exposed<br>occurrences (all)     | 1 / 81 (1.23%)<br>1    | 1 / 37 (2.70%)<br>1 |  |
| Hypothyroidism<br>subjects affected / exposed<br>occurrences (all)      | 11 / 81 (13.58%)<br>11 | 0 / 37 (0.00%)<br>0 |  |
| Musculoskeletal and connective tissue disorders                         |                        |                     |  |

|                             |                |                |
|-----------------------------|----------------|----------------|
| Flank pain                  |                |                |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 37 (0.00%) |
| occurrences (all)           | 2              | 0              |
| Coccydynia                  |                |                |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 37 (0.00%) |
| occurrences (all)           | 1              | 0              |
| Clubbing                    |                |                |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 37 (2.70%) |
| occurrences (all)           | 0              | 1              |
| Bone pain                   |                |                |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 37 (0.00%) |
| occurrences (all)           | 1              | 0              |
| Back pain                   |                |                |
| subjects affected / exposed | 5 / 81 (6.17%) | 0 / 37 (0.00%) |
| occurrences (all)           | 6              | 0              |
| Groin pain                  |                |                |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 37 (0.00%) |
| occurrences (all)           | 1              | 0              |
| Arthralgia                  |                |                |
| subjects affected / exposed | 2 / 81 (2.47%) | 2 / 37 (5.41%) |
| occurrences (all)           | 2              | 2              |
| Muscular weakness           |                |                |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 37 (0.00%) |
| occurrences (all)           | 1              | 0              |
| Musculoskeletal chest pain  |                |                |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 37 (0.00%) |
| occurrences (all)           | 1              | 0              |
| Musculoskeletal pain        |                |                |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 37 (0.00%) |
| occurrences (all)           | 1              | 0              |
| Muscle tightness            |                |                |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 37 (0.00%) |
| occurrences (all)           | 1              | 0              |
| Muscle spasms               |                |                |
| subjects affected / exposed | 5 / 81 (6.17%) | 0 / 37 (0.00%) |
| occurrences (all)           | 5              | 0              |

|                                 |                  |                |  |
|---------------------------------|------------------|----------------|--|
| Limb discomfort                 |                  |                |  |
| subjects affected / exposed     | 1 / 81 (1.23%)   | 0 / 37 (0.00%) |  |
| occurrences (all)               | 1                | 0              |  |
| Myalgia                         |                  |                |  |
| subjects affected / exposed     | 2 / 81 (2.47%)   | 1 / 37 (2.70%) |  |
| occurrences (all)               | 2                | 1              |  |
| Pain in extremity               |                  |                |  |
| subjects affected / exposed     | 10 / 81 (12.35%) | 2 / 37 (5.41%) |  |
| occurrences (all)               | 12               | 3              |  |
| Spinal pain                     |                  |                |  |
| subjects affected / exposed     | 2 / 81 (2.47%)   | 0 / 37 (0.00%) |  |
| occurrences (all)               | 2                | 0              |  |
| Spinal column stenosis          |                  |                |  |
| subjects affected / exposed     | 1 / 81 (1.23%)   | 0 / 37 (0.00%) |  |
| occurrences (all)               | 1                | 0              |  |
| Infections and infestations     |                  |                |  |
| Clostridium difficile infection |                  |                |  |
| subjects affected / exposed     | 0 / 81 (0.00%)   | 1 / 37 (2.70%) |  |
| occurrences (all)               | 0                | 1              |  |
| Candida infection               |                  |                |  |
| subjects affected / exposed     | 0 / 81 (0.00%)   | 2 / 37 (5.41%) |  |
| occurrences (all)               | 0                | 2              |  |
| Bronchitis                      |                  |                |  |
| subjects affected / exposed     | 0 / 81 (0.00%)   | 1 / 37 (2.70%) |  |
| occurrences (all)               | 0                | 1              |  |
| Acinetobacter infection         |                  |                |  |
| subjects affected / exposed     | 0 / 81 (0.00%)   | 1 / 37 (2.70%) |  |
| occurrences (all)               | 0                | 1              |  |
| Abscess                         |                  |                |  |
| subjects affected / exposed     | 1 / 81 (1.23%)   | 0 / 37 (0.00%) |  |
| occurrences (all)               | 1                | 0              |  |
| Cystitis                        |                  |                |  |
| subjects affected / exposed     | 1 / 81 (1.23%)   | 0 / 37 (0.00%) |  |
| occurrences (all)               | 1                | 0              |  |
| Infection                       |                  |                |  |

|                             |                |                |
|-----------------------------|----------------|----------------|
| subjects affected / exposed | 2 / 81 (2.47%) | 0 / 37 (0.00%) |
| occurrences (all)           | 2              | 0              |
| Infected seroma             |                |                |
| subjects affected / exposed | 2 / 81 (2.47%) | 0 / 37 (0.00%) |
| occurrences (all)           | 2              | 0              |
| Herpes virus infection      |                |                |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 37 (2.70%) |
| occurrences (all)           | 0              | 1              |
| Gastroenteritis             |                |                |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 37 (2.70%) |
| occurrences (all)           | 0              | 1              |
| Erysipelas                  |                |                |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 37 (2.70%) |
| occurrences (all)           | 0              | 1              |
| Device related infection    |                |                |
| subjects affected / exposed | 0 / 81 (0.00%) | 2 / 37 (5.41%) |
| occurrences (all)           | 0              | 2              |
| Pneumonia staphylococcal    |                |                |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 37 (2.70%) |
| occurrences (all)           | 0              | 1              |
| Pneumonia                   |                |                |
| subjects affected / exposed | 4 / 81 (4.94%) | 1 / 37 (2.70%) |
| occurrences (all)           | 4              | 1              |
| Pharyngitis                 |                |                |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 37 (0.00%) |
| occurrences (all)           | 1              | 0              |
| Oral candidiasis            |                |                |
| subjects affected / exposed | 0 / 81 (0.00%) | 2 / 37 (5.41%) |
| occurrences (all)           | 0              | 2              |
| Oesophageal candidiasis     |                |                |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 37 (0.00%) |
| occurrences (all)           | 1              | 0              |
| Respiratory tract infection |                |                |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 37 (0.00%) |
| occurrences (all)           | 2              | 0              |
| Neutropenic sepsis          |                |                |

|                                         |                |                 |  |
|-----------------------------------------|----------------|-----------------|--|
| subjects affected / exposed             | 0 / 81 (0.00%) | 1 / 37 (2.70%)  |  |
| occurrences (all)                       | 0              | 1               |  |
| Sepsis                                  |                |                 |  |
| subjects affected / exposed             | 0 / 81 (0.00%) | 1 / 37 (2.70%)  |  |
| occurrences (all)                       | 0              | 1               |  |
| Streptococcal infection                 |                |                 |  |
| subjects affected / exposed             | 0 / 81 (0.00%) | 1 / 37 (2.70%)  |  |
| occurrences (all)                       | 0              | 1               |  |
| Viral upper respiratory tract infection |                |                 |  |
| subjects affected / exposed             | 1 / 81 (1.23%) | 0 / 37 (0.00%)  |  |
| occurrences (all)                       | 1              | 0               |  |
| Urosepsis                               |                |                 |  |
| subjects affected / exposed             | 1 / 81 (1.23%) | 0 / 37 (0.00%)  |  |
| occurrences (all)                       | 1              | 0               |  |
| Urinary tract infection                 |                |                 |  |
| subjects affected / exposed             | 4 / 81 (4.94%) | 4 / 37 (10.81%) |  |
| occurrences (all)                       | 5              | 4               |  |
| Upper respiratory tract infection       |                |                 |  |
| subjects affected / exposed             | 0 / 81 (0.00%) | 1 / 37 (2.70%)  |  |
| occurrences (all)                       | 0              | 1               |  |
| Tonsillitis                             |                |                 |  |
| subjects affected / exposed             | 0 / 81 (0.00%) | 1 / 37 (2.70%)  |  |
| occurrences (all)                       | 0              | 1               |  |
| Subcutaneous abscess                    |                |                 |  |
| subjects affected / exposed             | 0 / 81 (0.00%) | 1 / 37 (2.70%)  |  |
| occurrences (all)                       | 0              | 1               |  |
| Wound infection                         |                |                 |  |
| subjects affected / exposed             | 1 / 81 (1.23%) | 0 / 37 (0.00%)  |  |
| occurrences (all)                       | 1              | 0               |  |
| Metabolism and nutrition disorders      |                |                 |  |
| Hypercalcaemia                          |                |                 |  |
| subjects affected / exposed             | 0 / 81 (0.00%) | 1 / 37 (2.70%)  |  |
| occurrences (all)                       | 0              | 1               |  |
| Fluid retention                         |                |                 |  |
| subjects affected / exposed             | 0 / 81 (0.00%) | 1 / 37 (2.70%)  |  |
| occurrences (all)                       | 0              | 2               |  |

|                             |                  |                  |
|-----------------------------|------------------|------------------|
| Dehydration                 |                  |                  |
| subjects affected / exposed | 1 / 81 (1.23%)   | 1 / 37 (2.70%)   |
| occurrences (all)           | 1                | 1                |
| Decreased appetite          |                  |                  |
| subjects affected / exposed | 28 / 81 (34.57%) | 10 / 37 (27.03%) |
| occurrences (all)           | 32               | 12               |
| Hyperglycaemia              |                  |                  |
| subjects affected / exposed | 1 / 81 (1.23%)   | 1 / 37 (2.70%)   |
| occurrences (all)           | 1                | 1                |
| Hypoalbuminaemia            |                  |                  |
| subjects affected / exposed | 1 / 81 (1.23%)   | 0 / 37 (0.00%)   |
| occurrences (all)           | 1                | 0                |
| Hyponatraemia               |                  |                  |
| subjects affected / exposed | 2 / 81 (2.47%)   | 0 / 37 (0.00%)   |
| occurrences (all)           | 2                | 0                |
| Hypomagnesaemia             |                  |                  |
| subjects affected / exposed | 0 / 81 (0.00%)   | 1 / 37 (2.70%)   |
| occurrences (all)           | 0                | 1                |
| Hypokalaemia                |                  |                  |
| subjects affected / exposed | 3 / 81 (3.70%)   | 2 / 37 (5.41%)   |
| occurrences (all)           | 3                | 3                |
| Hypocalcaemia               |                  |                  |
| subjects affected / exposed | 1 / 81 (1.23%)   | 0 / 37 (0.00%)   |
| occurrences (all)           | 1                | 0                |
| Hypophosphataemia           |                  |                  |
| subjects affected / exposed | 0 / 81 (0.00%)   | 1 / 37 (2.70%)   |
| occurrences (all)           | 0                | 1                |
| Magnesium deficiency        |                  |                  |
| subjects affected / exposed | 1 / 81 (1.23%)   | 0 / 37 (0.00%)   |
| occurrences (all)           | 1                | 0                |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                                                                                                       |
|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 23 August 2012    | SA No. 1 covered the following major changes: additional assessment of vital signs after week 2, 3, 6, 9, 12, 15, 19, 26, and every 6 weeks as part of the extension study; adjustment of tumor imaging methods |
| 27 September 2013 | SA No. 2 covered the following major changes: changes due to update of Investigator's Brochure of pazopanib                                                                                                     |
| 27 March 2015     | SA No. 3 covered the following major changes: clarification of study duration and end                                                                                                                           |
| 09 November 2015  | SA No. 4 covered the following major changes: 6-months prolongation of recruiting time                                                                                                                          |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

None reported

Notes:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/27387325>

<http://www.ncbi.nlm.nih.gov/pubmed/32840417>