



## Clinical trial results:

**A Phase 1b/2, multi-center, double-blind (principal investigators and study subjects blinded, sponsor unblinded), placebo-controlled, randomized, single-ascending dose study to assess the safety, pharmacokinetics, and pharmacodynamics of DS-1040B in subjects with acute ischemic stroke.**

### Summary

|                          |                      |
|--------------------------|----------------------|
| EudraCT number           | 2015-001824-43       |
| Trial protocol           | DE FR GB CZ ES SK IT |
| Global end of trial date | 13 August 2019       |

### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 17 August 2020 |
| First version publication date | 17 August 2020 |

### Trial information

#### Trial identification

|                       |               |
|-----------------------|---------------|
| Sponsor protocol code | DS1040-A-U103 |
|-----------------------|---------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02586233 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Daiichi Sankyo   |
| Sponsor organisation address | 211 Mt. Airy Road, Basking Ridge, United States, 07920   |
| Public contact               | Contact for Clinical Trial Information, Daiichi Sankyo Development Ltd, +1 908-992-6400, CTRinfo@dsi.com |
| Scientific contact           | Contact for Clinical Trial Information, Daiichi Sankyo Development Ltd, +1 908-992-6400, CTRinfo@dsi.com |

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |                |
|--|----------------|
| Analysis stage                                       | Final          |
| Date of interim/final analysis                       | 13 August 2019 |
| Is this the analysis of the primary completion data? | No             |
| Global end of trial reached?                         | Yes            |
| Global end of trial date                             | 13 August 2019 |
| Was the trial ended prematurely?                     | No             |

Notes:

## General information about the trial

Main objective of the trial:

To assess the safety and tolerability of DS-1040b (IV infusion over 6 hours) in subjects with AIS within 3 to 8 hours after stroke symptom onset

Protection of trial subjects:

This study was conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonisation consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/International Council for Harmonisation/135/95), the United States Food and Drug Administration GCP Regulations: Code of Federal Regulations Title 21, Parts 11, 50, 54, 56, and 312 as appropriate and other applicable local regulations.

Background therapy: -

Evidence for comparator: -

|   |                   |
|---|-------------------|
| Actual start date of recruitment                          | 01 September 2015 |
| Long term follow-up planned                               | No                |
| Independent data monitoring committee (IDMC) involvement? | No                |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                       |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Spain: 24             |
| Country: Number of subjects enrolled | United Kingdom: 3     |
| Country: Number of subjects enrolled | Czech Republic: 4     |
| Country: Number of subjects enrolled | France: 1             |
| Country: Number of subjects enrolled | Germany: 5            |
| Country: Number of subjects enrolled | United States: 46     |
| Country: Number of subjects enrolled | Taiwan: 13            |
| Country: Number of subjects enrolled | Australia: 4          |
| Country: Number of subjects enrolled | Korea, Republic of: 6 |
| Worldwide total number of subjects   | 106                   |
| EEA total number of subjects         | 37                    |

Notes:

### Subjects enrolled per age group

|   |   |
|---|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |

|  |    |
|--|----|
| Newborns (0-27 days)                     | 0  |
| Infants and toddlers (28 days-23 months) | 0  |
| Children (2-11 years)                    | 0  |
| Adolescents (12-17 years)                | 0  |
| Adults (18-64 years)                     | 55 |
| From 65 to 84 years                      | 49 |
| 85 years and over                        | 2  |

## Subject disposition

### Recruitment

Recruitment details:

A total of 106 participants who met all inclusion criteria and no exclusion criteria were randomized to treatment at a total of 78 clinic sites (46 in Europe, 19 in the United States, 7 in Asia, 5 in Australia, and 1 in Canada). Of the 106 participants randomized, 101 participants received treatment.

### Pre-assignment

Screening details:

The study consisted of 6, sequential, ascending-dose cohorts. Participants were randomized to either DS-1040b or placebo in a 3:1 ratio.

### Period 1

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

### Arms

|                              |                           |
|------------------------------|---------------------------|
| Are arms mutually exclusive? | Yes                       |
| <b>Arm title</b>             | Cohort 1: DS-1040b 0.6 mg |

Arm description:

Subjects who received a single intravenous infusion of DS-1040b 0.6 mg.

|  |                       |
|--|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | DS-1040b              |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Intravenous infusion of 0.6 mg to 9.6 mg over a 6-hour period

|                  |                           |
|------------------|---------------------------|
| <b>Arm title</b> | Cohort 2: DS-1040b 1.2 mg |
|------------------|---------------------------|

Arm description:

Subjects who received a single intravenous infusion of DS-1040b 1.2 mg.

|  |                       |
|--|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | DS-1040b              |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Intravenous infusion of 0.6 mg to 9.6 mg over a 6-hour period

|                  |                           |
|------------------|---------------------------|
| <b>Arm title</b> | Cohort 3: DS-1040b 2.4 mg |
|------------------|---------------------------|

Arm description:

Subjects who received a single intravenous infusion of DS-1040b 2.4 mg.

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|   |                           |
|---|---------------------------|
| Investigational medicinal product name                                  | DS-1040b                  |
| Investigational medicinal product code                                  |                           |
| Other name  |                           |
| Pharmaceutical forms  | Solution for infusion     |
| Routes of administration  | Intravenous use           |
| Dosage and administration details:                                      |                           |
| Intravenous infusion of 0.6 mg to 9.6 mg over a 6-hour period           |                           |
| <b>Arm title</b>  | Cohort 4: DS-1040 4.8 mg  |
| Arm description:  |                           |
| Subjects who received a single intravenous infusion of DS-1040b 4.8 mg. |                           |
| Arm type  | Experimental              |
| Investigational medicinal product name                                  | DS-1040b                  |
| Investigational medicinal product code                                  |                           |
| Other name  |                           |
| Pharmaceutical forms  | Solution for infusion     |
| Routes of administration  | Intravenous use           |
| Dosage and administration details:                                      |                           |
| Intravenous infusion of 0.6 mg to 9.6 mg over a 6-hour period           |                           |
| <b>Arm title</b>  | Cohort 5: DS-1040b 7.2 mg |
| Arm description:  |                           |
| Subjects who received a single intravenous infusion of DS-1040b 7.2 mg. |                           |
| Arm type  | Experimental              |
| Investigational medicinal product name                                  | DS-1040b                  |
| Investigational medicinal product code                                  |                           |
| Other name  |                           |
| Pharmaceutical forms  | Solution for infusion     |
| Routes of administration  | Intravenous use           |
| Dosage and administration details:                                      |                           |
| Intravenous infusion of 0.6 mg to 9.6 mg over a 6-hour period           |                           |
| <b>Arm title</b>  | Cohort 6: DS-1040b 9.6 mg |
| Arm description:  |                           |
| Subjects who received a single intravenous infusion of DS-1040b 9.6 mg. |                           |
| Arm type  | Experimental              |
| Investigational medicinal product name                                  | DS-1040b                  |
| Investigational medicinal product code                                  |                           |
| Other name  |                           |
| Pharmaceutical forms  | Solution for infusion     |
| Routes of administration  | Intravenous use           |
| Dosage and administration details:                                      |                           |
| Intravenous infusion of 0.6 mg to 9.6 mg over a 6-hour period           |                           |
| <b>Arm title</b>  | Placebo                   |
| Arm description:  |                           |
| Subjects who received a single intravenous infusion of placebo.         |                           |
| Arm type  | Placebo                   |
| Investigational medicinal product name                                  | 0.9% sodium chloride      |
| Investigational medicinal product code                                  |                           |
| Other name  |                           |
| Pharmaceutical forms  | Solution for infusion     |
| Routes of administration  | Intravenous use           |

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**Dosage and administration details:**

Intravenous infusion over 6-hour period

| <b>Number of subjects in period 1</b>        | Cohort 1: DS-1040b<br>0.6 mg | Cohort 2: DS-1040b<br>1.2 mg | Cohort 3: DS-1040b<br>2.4 mg |
|--|------------------------------|------------------------------|------------------------------|
| Started                                      | 7                            | 7                            | 13                           |
| Completed                                    | 7                            | 5                            | 13                           |
| Not completed                                | 0                            | 2                            | 0                            |
| Randomized, but did not receive<br>treatment | -                            | 1                            | -                            |
| Death  | -                            | 1                            | -                            |

| <b>Number of subjects in period 1</b>        | Cohort 4: DS-1040<br>4.8 mg | Cohort 5: DS-1040b<br>7.2 mg | Cohort 6: DS-1040b<br>9.6 mg |
|--|-----------------------------|------------------------------|------------------------------|
| Started                                      | 17                          | 18                           | 18                           |
| Completed                                    | 17                          | 16                           | 16                           |
| Not completed                                | 0                           | 2                            | 2                            |
| Randomized, but did not receive<br>treatment | -                           | -                            | 2                            |
| Death  | -                           | 2                            | -                            |

| <b>Number of subjects in period 1</b>        | Placebo |
|--|---------|
| Started                                      | 26      |
| Completed                                    | 24      |
| Not completed                                | 2       |
| Randomized, but did not receive<br>treatment | 2       |
| Death  | -       |

## Baseline characteristics

| Reporting groups  |                           |
|---|---------------------------|
| Reporting group title   | Cohort 1: DS-1040b 0.6 mg |
| Reporting group description:  |                           |
| Subjects who received a single intravenous infusion of DS-1040b 0.6 mg. |                           |
| Reporting group title   | Cohort 2: DS-1040b 1.2 mg |
| Reporting group description:  |                           |
| Subjects who received a single intravenous infusion of DS-1040b 1.2 mg. |                           |
| Reporting group title   | Cohort 3: DS-1040b 2.4 mg |
| Reporting group description:  |                           |
| Subjects who received a single intravenous infusion of DS-1040b 2.4 mg. |                           |
| Reporting group title   | Cohort 4: DS-1040 4.8 mg  |
| Reporting group description:  |                           |
| Subjects who received a single intravenous infusion of DS-1040b 4.8 mg. |                           |
| Reporting group title   | Cohort 5: DS-1040b 7.2 mg |
| Reporting group description:  |                           |
| Subjects who received a single intravenous infusion of DS-1040b 7.2 mg. |                           |
| Reporting group title   | Cohort 6: DS-1040b 9.6 mg |
| Reporting group description:  |                           |
| Subjects who received a single intravenous infusion of DS-1040b 9.6 mg. |                           |
| Reporting group title   | Placebo                   |
| Reporting group description:  |                           |
| Subjects who received a single intravenous infusion of placebo.         |                           |

| Reporting group values  | Cohort 1: DS-1040b<br>0.6 mg | Cohort 2: DS-1040b<br>1.2 mg | Cohort 3: DS-1040b<br>2.4 mg |
|---|------------------------------|------------------------------|------------------------------|
| Number of subjects  | 7                            | 7                            | 13                           |
| Age categorical   |                              |                              |                              |
| Based on Randomized Analysis Set  |                              |                              |                              |
| Units: Subjects   |                              |                              |                              |
| In utero  | 0                            | 0                            | 0                            |
| Preterm newborn infants<br>(gestational age < 37 wks)   | 0                            | 0                            | 0                            |
| Newborns (0-27 days)  | 0                            | 0                            | 0                            |
| Infants and toddlers (28 days-23<br>months)   | 0                            | 0                            | 0                            |
| Children (2-11 years)   | 0                            | 0                            | 0                            |
| Adolescents (12-17 years)   | 0                            | 0                            | 0                            |
| Adults (18-64 years)  | 2                            | 4                            | 8                            |
| From 65-84 years  | 5                            | 2                            | 5                            |
| 85 years and over   | 0                            | 1                            | 0                            |
| Age continuous  |                              |                              |                              |
| Based on Safety Analysis Set (N=101); age data were missing for participants in some cohorts. |                              |                              |                              |
| Units: years  |                              |                              |                              |
| arithmetic mean   | 68.2                         | 68.2                         | 62.7                         |
| standard deviation  | ± 7.8                        | ± 10.2                       | ± 9.7                        |
| Gender categorical  |                              |                              |                              |
| Based on the Randomized Analysis Set  |                              |                              |                              |
| Units: Subjects   |                              |                              |                              |

|        |   |   |   |
|--------|---|---|---|
| Female | 3 | 2 | 5 |
| Male   | 4 | 5 | 8 |

| Reporting group values  | Cohort 4: DS-1040<br>4.8 mg | Cohort 5: DS-1040b<br>7.2 mg | Cohort 6: DS-1040b<br>9.6 mg |
|---|-----------------------------|------------------------------|------------------------------|
| Number of subjects  | 17                          | 18                           | 18                           |
| Age categorical   |                             |                              |                              |
| Based on Randomized Analysis Set  |                             |                              |                              |
| Units: Subjects   |                             |                              |                              |
| In utero  | 0                           | 0                            | 0                            |
| Preterm newborn infants<br>(gestational age < 37 wks)   | 0                           | 0                            | 0                            |
| Newborns (0-27 days)  | 0                           | 0                            | 0                            |
| Infants and toddlers (28 days-23<br>months)   | 0                           | 0                            | 0                            |
| Children (2-11 years)   | 0                           | 0                            | 0                            |
| Adolescents (12-17 years)   | 0                           | 0                            | 0                            |
| Adults (18-64 years)  | 8                           | 9                            | 10                           |
| From 65-84 years  | 9                           | 9                            | 7                            |
| 85 years and over   | 0                           | 0                            | 1                            |
| Age continuous  |                             |                              |                              |
| Based on Safety Analysis Set (N=101); age data were missing for participants in some cohorts. |                             |                              |                              |
| Units: years  |                             |                              |                              |
| arithmetic mean   | 69.1                        | 65.8                         | 64.8                         |
| standard deviation  | ± 11.1                      | ± 11.7                       | ± 12.8                       |
| Gender categorical  |                             |                              |                              |
| Based on the Randomized Analysis Set  |                             |                              |                              |
| Units: Subjects   |                             |                              |                              |
| Female  | 6                           | 8                            | 7                            |
| Male  | 11                          | 10                           | 11                           |

| Reporting group values  | Placebo | Total |  |
|---|---------|-------|--|
| Number of subjects  | 26      | 106   |  |
| Age categorical   |         |       |  |
| Based on Randomized Analysis Set  |         |       |  |
| Units: Subjects   |         |       |  |
| In utero  | 0       | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks)   | 0       | 0     |  |
| Newborns (0-27 days)  | 0       | 0     |  |
| Infants and toddlers (28 days-23<br>months)   | 0       | 0     |  |
| Children (2-11 years)   | 0       | 0     |  |
| Adolescents (12-17 years)   | 0       | 0     |  |
| Adults (18-64 years)  | 14      | 55    |  |
| From 65-84 years  | 12      | 49    |  |
| 85 years and over   | 0       | 2     |  |
| Age continuous  |         |       |  |
| Based on Safety Analysis Set (N=101); age data were missing for participants in some cohorts. |         |       |  |
| Units: years  |         |       |  |
| arithmetic mean   | 62.2    |       |  |
| standard deviation  | ± 12.3  | -     |  |



|                                      |    |    |  |
|--------------------------------------|----|----|--|
| Gender categorical                   |    |    |  |
| Based on the Randomized Analysis Set |    |    |  |
| Units: Subjects                      |    |    |  |
| Female                               | 11 | 42 |  |
| Male                                 | 15 | 64 |  |

## End points

### End points reporting groups

|   |                           |
|---|---------------------------|
| Reporting group title   | Cohort 1: DS-1040b 0.6 mg |
| Reporting group description:<br>Subjects who received a single intravenous infusion of DS-1040b 0.6 mg.   |                           |
| Reporting group title   | Cohort 2: DS-1040b 1.2 mg |
| Reporting group description:<br>Subjects who received a single intravenous infusion of DS-1040b 1.2 mg.   |                           |
| Reporting group title   | Cohort 3: DS-1040b 2.4 mg |
| Reporting group description:<br>Subjects who received a single intravenous infusion of DS-1040b 2.4 mg.   |                           |
| Reporting group title   | Cohort 4: DS-1040 4.8 mg  |
| Reporting group description:<br>Subjects who received a single intravenous infusion of DS-1040b 4.8 mg.   |                           |
| Reporting group title   | Cohort 5: DS-1040b 7.2 mg |
| Reporting group description:<br>Subjects who received a single intravenous infusion of DS-1040b 7.2 mg.   |                           |
| Reporting group title   | Cohort 6: DS-1040b 9.6 mg |
| Reporting group description:<br>Subjects who received a single intravenous infusion of DS-1040b 9.6 mg.   |                           |
| Reporting group title   | Placebo                   |
| Reporting group description:<br>Subjects who received a single intravenous infusion of placebo.           |                           |
| Subject analysis set title  | All DS-1040b              |
| Subject analysis set type   | Safety analysis           |
| Subject analysis set description:<br>All subjects who received a single intravenous infusion of DS-1040b. |                           |

### Primary: Treatment-emergent Adverse Event Reported by >10% of Participants Following Ascending Doses of DS-1040b and a Placebo in Subjects With Acute Ischemic Stroke

|  |   |
|--|---|
| End point title  | Treatment-emergent Adverse Event Reported by >10% of Participants Following Ascending Doses of DS-1040b and a Placebo in Subjects With Acute Ischemic Stroke <sup>[1]</sup> |
| End point description:<br>Treatment-emergent adverse event (TEAE) is defined as an adverse event that emerges during the treatment period (from first dose date until 30 days after the last dosing date), having been absent at predose; or reemerges during treatment, having been present at baseline but stopped prior to treatment; or worsens in severity after starting treatment relative to the pre-dose state, when the adverse event is continuous. |   |
| End point type   | Primary   |
| End point timeframe:<br>Baseline up to 90 days post last dose, up to 3 years 11 months   |   |
| Notes:<br>[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.<br>Justification: Descriptive analyses were performed based on the study groups and study drugs administered for this outcome.   |   |

| End point values            | Cohort 1: DS-1040b 0.6 mg | Cohort 2: DS-1040b 1.2 mg | Cohort 3: DS-1040b 2.4 mg | Cohort 4: DS-1040 4.8 mg |
|-----------------------------|---------------------------|---------------------------|---------------------------|--------------------------|
| Subject group type          | Reporting group           | Reporting group           | Reporting group           | Reporting group          |
| Number of subjects analysed | 7                         | 6                         | 13                        | 17                       |
| Units: Subjects             |                           |                           |                           |                          |
| number (not applicable)     |                           |                           |                           |                          |
| Any TEAE                    | 5                         | 5                         | 10                        | 15                       |
| Hypokalaemia                | 1                         | 2                         | 2                         | 0                        |
| Constipation                | 1                         | 2                         | 3                         | 1                        |
| Insomnia                    | 0                         | 0                         | 1                         | 0                        |
| Hypertension                | 0                         | 0                         | 1                         | 3                        |
| Anxiety                     | 0                         | 1                         | 0                         | 0                        |
| Hyperglycaemia              | 0                         | 0                         | 0                         | 1                        |
| Dyslipidaemia               | 0                         | 0                         | 0                         | 0                        |
| Thrombocytopenia            | 0                         | 1                         | 0                         | 0                        |
| Vomiting                    | 0                         | 1                         | 0                         | 0                        |
| Pyrexia                     | 0                         | 0                         | 0                         | 1                        |
| Vitamin B12 deficiency      | 0                         | 0                         | 0                         | 0                        |
| Headache                    | 3                         | 1                         | 2                         | 2                        |

| End point values            | Cohort 5: DS-1040b 7.2 mg | Cohort 6: DS-1040b 9.6 mg | Placebo         | All DS-1040b         |
|-----------------------------|---------------------------|---------------------------|-----------------|----------------------|
| Subject group type          | Reporting group           | Reporting group           | Reporting group | Subject analysis set |
| Number of subjects analysed | 18                        | 16                        | 24              | 77                   |
| Units: Subjects             |                           |                           |                 |                      |
| number (not applicable)     |                           |                           |                 |                      |
| Any TEAE                    | 14                        | 14                        | 18              | 63                   |
| Hypokalaemia                | 2                         | 2                         | 6               | 9                    |
| Constipation                | 5                         | 2                         | 5               | 14                   |
| Insomnia                    | 1                         | 3                         | 5               | 5                    |
| Hypertension                | 1                         | 0                         | 3               | 5                    |
| Anxiety                     | 0                         | 2                         | 3               | 3                    |
| Hyperglycaemia              | 1                         | 0                         | 3               | 2                    |
| Dyslipidaemia               | 1                         | 1                         | 3               | 2                    |
| Thrombocytopenia            | 0                         | 0                         | 3               | 1                    |
| Vomiting                    | 0                         | 0                         | 3               | 1                    |
| Pyrexia                     | 0                         | 0                         | 3               | 1                    |
| Vitamin B12 deficiency      | 0                         | 0                         | 3               | 0                    |
| Headache                    | 1                         | 4                         | 2               | 13                   |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Pharmacokinetic Parameter Maximum (Peak) Observed Plasma Concentration (C<sub>max</sub>) of DS-1040b Following Ascending Doses in Subjects With Acute Ischemic Stroke

|                 |  |
|-----------------|--|
| End point title | Pharmacokinetic Parameter Maximum (Peak) Observed Plasma |
|-----------------|--|

## End point description:

The PK parameter of Maximum (Peak) Observed Plasma Concentration (Cmax) of DS-1040b was calculated from the plasma concentrations of DS-1040b using non-compartmental analysis.

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

## End point timeframe:

Predose, 0.5, 3, 6, 9, 12, 24, 48, 72, and 96 hours postdose

## Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Descriptive analyses were performed based on the study groups and study drugs administered for this outcome.

| End point values                     | Cohort 1: DS-1040b 0.6 mg | Cohort 2: DS-1040b 1.2 mg | Cohort 3: DS-1040b 2.4 mg | Cohort 4: DS-1040b 4.8 mg |
|--------------------------------------|---------------------------|---------------------------|---------------------------|---------------------------|
| Subject group type                   | Reporting group           | Reporting group           | Reporting group           | Reporting group           |
| Number of subjects analysed          | 5                         | 6                         | 13                        | 16                        |
| Units: ng/mL                         |                           |                           |                           |                           |
| arithmetic mean (standard deviation) |                           |                           |                           |                           |
| Cmax                                 | 10.09 (± 3.26)            | 26.95 (± 9.39)            | 61.28 (± 35.67)           | 729.76 (± 1661.06)        |

| End point values                     | Cohort 5: DS-1040b 7.2 mg | Cohort 6: DS-1040b 9.6 mg |  |  |
|--------------------------------------|---------------------------|---------------------------|--|--|
| Subject group type                   | Reporting group           | Reporting group           |  |  |
| Number of subjects analysed          | 17                        | 10                        |  |  |
| Units: ng/mL                         |                           |                           |  |  |
| arithmetic mean (standard deviation) |                           |                           |  |  |
| Cmax                                 | 191.06 (± 59.60)          | 203.70 (± 41.49)          |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacokinetic Parameter Area Under the Concentration Versus Time Curve From Zero to Last Quantifiable Concentration Sampling Point (AUClast) of DS-1040b Following Ascending Doses in Subjects With Acute Ischemic Stroke

|                 |  |
|-----------------|--|
| End point title | Pharmacokinetic Parameter Area Under the Concentration Versus Time Curve From Zero to Last Quantifiable Concentration Sampling Point (AUClast) of DS-1040b Following Ascending Doses in Subjects With Acute Ischemic Stroke <sup>[3]</sup> |
|-----------------|--|

## End point description:

The PK parameter of Area Under the Concentration Versus Time Curve from Zero to Last Quantifiable Concentration Sampling Point of DS-1040b was calculated from the plasma concentrations of DS-1040b using non-compartmental analysis.

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

## End point timeframe:

Pre-dose, 0.5, 3, 6, 9, 12, 24, 48, 72, and 96 hours post-dose

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.  
Justification: Descriptive analyses were performed based on the study groups and study drugs administered for this outcome.

| End point values                     | Cohort 1: DS-1040b 0.6 mg | Cohort 2: DS-1040b 1.2 mg | Cohort 3: DS-1040b 2.4 mg | Cohort 4: DS-1040b 4.8 mg |
|--------------------------------------|---------------------------|---------------------------|---------------------------|---------------------------|
| Subject group type                   | Reporting group           | Reporting group           | Reporting group           | Reporting group           |
| Number of subjects analysed          | 5                         | 6                         | 13                        | 16                        |
| Units: ng*h/mL                       |                           |                           |                           |                           |
| arithmetic mean (standard deviation) |                           |                           |                           |                           |
| AUClast                              | 69.74 (± 16.19)           | 219.83 (± 95.16)          | 447.75 (± 199.97)         | 2611.87 (± 4471.65)       |

| End point values                     | Cohort 5: DS-1040b 7.2 mg | Cohort 6: DS-1040b 9.6 mg |  |  |
|--------------------------------------|---------------------------|---------------------------|--|--|
| Subject group type                   | Reporting group           | Reporting group           |  |  |
| Number of subjects analysed          | 17                        | 10                        |  |  |
| Units: ng*h/mL                       |                           |                           |  |  |
| arithmetic mean (standard deviation) |                           |                           |  |  |
| AUClast                              | 1489.21 (± 460.78)        | 1700.24 (± 346.43)        |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Pharmacokinetic Parameter Terminal Half-life (t<sub>1/2</sub>) of DS-1040b Following Ascending Doses in Subjects With Acute Ischemic Stroke

|                 |  |
|-----------------|--|
| End point title | Pharmacokinetic Parameter Terminal Half-life (t <sub>1/2</sub> ) of DS-1040b Following Ascending Doses in Subjects With Acute Ischemic Stroke <sup>[4]</sup> |
|-----------------|--|

End point description:

The PK parameter of Terminal Half-life of DS-1040b was calculated from the plasma concentrations of DS-1040b using non-compartmental analysis in patients with available sample for the analysis.

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

End point timeframe:

Pre-dose, 0.5, 3, 6, 9, 12, 24, 48, 72, and 96 hours post-dose

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.  
Justification: Descriptive analyses were performed based on the study groups and study drugs administered for this outcome.

| End point values                     | Cohort 1: DS-1040b 0.6 mg | Cohort 2: DS-1040b 1.2 mg | Cohort 3: DS-1040b 2.4 mg | Cohort 4: DS-1040 4.8 mg |
|--------------------------------------|---------------------------|---------------------------|---------------------------|--------------------------|
| Subject group type                   | Reporting group           | Reporting group           | Reporting group           | Reporting group          |
| Number of subjects analysed          | 4                         | 2                         | 7                         | 8                        |
| Units: hours                         |                           |                           |                           |                          |
| arithmetic mean (standard deviation) |                           |                           |                           |                          |
| Terminal half-life                   | 2.59 ( $\pm$ 0.46)        | 4.14 ( $\pm$ 0.17)        | 10.50 ( $\pm$ 15.02)      | 36.68 ( $\pm$ 25.94)     |

| End point values                     | Cohort 5: DS-1040b 7.2 mg | Cohort 6: DS-1040b 9.6 mg |  |  |
|--------------------------------------|---------------------------|---------------------------|--|--|
| Subject group type                   | Reporting group           | Reporting group           |  |  |
| Number of subjects analysed          | 14                        | 8                         |  |  |
| Units: hours                         |                           |                           |  |  |
| arithmetic mean (standard deviation) |                           |                           |  |  |
| Terminal half-life                   | 33.37 ( $\pm$ 14.71)      | 35.86 ( $\pm$ 10.98)      |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Activated Form of Thrombin-activatable Fibrinolysis Inhibitor (TAFIa) Following Ascending Doses of DS-1040b and a Placebo in Subjects With Acute Ischemic Stroke

|                 |  |
|-----------------|--|
| End point title | Activated Form of Thrombin-activatable Fibrinolysis Inhibitor (TAFIa) Following Ascending Doses of DS-1040b and a Placebo in Subjects With Acute Ischemic Stroke |
|-----------------|--|

End point description:

The enzymatic activity of thrombin-activatable fibrinolysis inhibitor was assessed using the Stago Coagulation Analyzer.

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

End point timeframe:

Baseline and 6 hours postdose

| End point values                         | Cohort 1: DS-1040b 0.6 mg | Cohort 2: DS-1040b 1.2 mg | Cohort 3: DS-1040b 2.4 mg | Cohort 4: DS-1040 4.8 mg |
|--|---------------------------|---------------------------|---------------------------|--------------------------|
| Subject group type                       | Reporting group           | Reporting group           | Reporting group           | Reporting group          |
| Number of subjects analysed              | 7                         | 6                         | 13                        | 17                       |
| Units: Mean percentage of TAFIa activity |                           |                           |                           |                          |
| arithmetic mean (standard deviation)     |                           |                           |                           |                          |
| Baseline                                 | 96.7 ( $\pm$ 23.7)        | 97.8 ( $\pm$ 17.5)        | 100.4 ( $\pm$ 21.6)       | 105.1 ( $\pm$ 23.4)      |
| 6 hours postdose                         | 93.5 ( $\pm$ 26.6)        | 98.8 ( $\pm$ 27.2)        | 86.7 ( $\pm$ 16.7)        | 75.9 ( $\pm$ 20.9)       |

| End point values                         | Cohort 5: DS-1040b 7.2 mg | Cohort 6: DS-1040b 9.6 mg | Placebo         |  |
|--|---------------------------|---------------------------|-----------------|--|
| Subject group type                       | Reporting group           | Reporting group           | Reporting group |  |
| Number of subjects analysed              | 18                        | 10                        | 24              |  |
| Units: Mean percentage of TAFIa activity |                           |                           |                 |  |
| arithmetic mean (standard deviation)     |                           |                           |                 |  |
| Baseline                                 | 108.1 (± 30.5)            | 112.6 (± 27.2)            | 100.9 (± 20.8)  |  |
| 6 hours postdose                         | 72.9 (± 22.6)             | 73.9 (± 14.4)             | 104.1 (± 24.7)  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline at Day 30 in National Institute of Health Stroke Scale (NIHSS) Score Following Ascending Doses of DS-1040b and a Placebo in Subjects With Acute Ischemic Stroke

|                 |  |
|-----------------|--|
| End point title | Change From Baseline at Day 30 in National Institute of Health Stroke Scale (NIHSS) Score Following Ascending Doses of DS-1040b and a Placebo in Subjects With Acute Ischemic Stroke |
|-----------------|--|

End point description:

The National Institute of Health Stroke Scale (NIHSS) quantifies stroke severity based on weighted evaluation findings. The score for each ability is a number between 0 and 4, with 0 being normal functioning and 4 being completely impaired. The patient's NIHSS score is calculated by adding the number for each element of the scale; 42 is the highest score possible. In the NIHSS, the higher the score indicates more impairment (worse outcome) in a stroke patient.

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

End point timeframe:

30 days postdose

| End point values                     | Cohort 1: DS-1040b 0.6 mg | Cohort 2: DS-1040b 1.2 mg | Cohort 3: DS-1040b 2.4 mg | Cohort 4: DS-1040b 4.8 mg |
|--------------------------------------|---------------------------|---------------------------|---------------------------|---------------------------|
| Subject group type                   | Reporting group           | Reporting group           | Reporting group           | Reporting group           |
| Number of subjects analysed          | 7                         | 6                         | 13                        | 17                        |
| Units: Units on a scale              |                           |                           |                           |                           |
| arithmetic mean (standard deviation) |                           |                           |                           |                           |
| Change from baseline in NIHSS score  | -3.7 (± 2.21)             | -3.0 (± 2.00)             | -3.5 (± 1.71)             | -2.06 (± 1.06)            |

| End point values                     | Cohort 5: DS-1040b 7.2 mg | Cohort 6: DS-1040b 9.6 mg | Placebo         | All DS-1040b         |
|--------------------------------------|---------------------------|---------------------------|-----------------|----------------------|
| Subject group type                   | Reporting group           | Reporting group           | Reporting group | Subject analysis set |
| Number of subjects analysed          | 18                        | 16                        | 24              | 77                   |
| Units: Units on a scale              |                           |                           |                 |                      |
| arithmetic mean (standard deviation) |                           |                           |                 |                      |
| Change from baseline in NIHSS score  | -3.4 (± 2.70)             | -6.2 (± 3.08)             | -3.6 (± 4.27)   | -3.9 (± 2.56)        |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants With a Modified Rankin Scale (mRS) Score of 0 to 2 Following Ascending Doses of DS-1040b and a Placebo in Subjects With Acute Ischemic Stroke

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants With a Modified Rankin Scale (mRS) Score of 0 to 2 Following Ascending Doses of DS-1040b and a Placebo in Subjects With Acute Ischemic Stroke |
|-----------------|--|

End point description:

The modified Rankin scale (mRS) is a commonly used disability scale derived from the Rankin scale that is used to measure the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. The level of disability following a stroke is assessed via a scale from 0 to 6, where 0 is no symptoms at all and 6 indicates death. Higher scores indicate worse outcome. The proportion (%) of participants with an mRS score of 0 to 2 at Day 5 (baseline) and Day 90 is being reported.

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

End point timeframe:

Day 5 (baseline) and Day 90 post dose

| End point values              | Cohort 1: DS-1040b 0.6 mg | Cohort 2: DS-1040b 1.2 mg | Cohort 3: DS-1040b 2.4 mg | Cohort 4: DS-1040b 4.8 mg |
|-------------------------------|---------------------------|---------------------------|---------------------------|---------------------------|
| Subject group type            | Reporting group           | Reporting group           | Reporting group           | Reporting group           |
| Number of subjects analysed   | 7                         | 6                         | 13                        | 17                        |
| Units: Percentage of subjects |                           |                           |                           |                           |
| number (not applicable)       |                           |                           |                           |                           |
| Day 5 (baseline)              | 66.7                      | 40.0                      | 76.9                      | 82.4                      |
| Day 90 postdose               | 85.7                      | 60.0                      | 76.9                      | 82.4                      |

| End point values              | Cohort 5: DS-1040b 7.2 mg | Cohort 6: DS-1040b 9.6 mg | Placebo         | All DS-1040b         |
|-------------------------------|---------------------------|---------------------------|-----------------|----------------------|
| Subject group type            | Reporting group           | Reporting group           | Reporting group | Subject analysis set |
| Number of subjects analysed   | 18                        | 16                        | 24              | 77                   |
| Units: Percentage of subjects |                           |                           |                 |                      |
| number (not applicable)       |                           |                           |                 |                      |
| Day 5 (baseline)              | 72.2                      | 53.3                      | 54.2            | 68.9                 |
| Day 90 postdose               | 93.8                      | 68.8                      | 75.0            | 79.7                 |

## Statistical analyses





## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events (TEAEs) were collected from baseline up to 30 days post last dose, up to 3 years 11 months.

Adverse event reporting additional description:

A TEAE is defined as an adverse event (AE) that emerges from first dose date until 30 days after the last dose, having been absent at predose; or reemerges during treatment, having been present at baseline but stopped prior to treatment; or worsens in severity after starting treatment relative to the pre-dose state, when the AE is continuous.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 17.1   |

### Reporting groups

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | Cohort 1: DS-1040b 0.6 mg |
|-----------------------|---------------------------|

Reporting group description:

Subjects who received a single intravenous infusion of DS-1040b 0.6 mg.

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | Cohort 2: DS-1040b 1.2 mg |
|-----------------------|---------------------------|

Reporting group description:

Subjects who received a single intravenous infusion of DS-1040b 1.2 mg.

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | Cohort 3: DS-1040b 2.4 mg |
|-----------------------|---------------------------|

Reporting group description:

Subjects who received a single intravenous infusion of DS-1040b 2.4 mg.

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Cohort 4: DS-1040 4.8 mg |
|-----------------------|--------------------------|

Reporting group description:

Subjects who received a single intravenous infusion of DS-1040b 4.8 mg.

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | Cohort 5: DS-1040b 7.2 mg |
|-----------------------|---------------------------|

Reporting group description:

Subjects who received a single intravenous infusion of DS-1040b 7.2 mg.

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | Cohort 6: DS-1040b 9.6 mg |
|-----------------------|---------------------------|

Reporting group description:

Subjects who received a single intravenous infusion of DS-1040b 9.6 mg.

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects who received a single intravenous infusion of placebo.

|                       |              |
|-----------------------|--------------|
| Reporting group title | All DS-1040b |
|-----------------------|--------------|

Reporting group description:

All subjects who received a single intravenous infusion of DS-1040b.

| Serious adverse events                            | Cohort 1: DS-1040b<br>0.6 mg | Cohort 2: DS-1040b<br>1.2 mg | Cohort 3: DS-1040b<br>2.4 mg |
|---|------------------------------|------------------------------|------------------------------|
| Total subjects affected by serious adverse events |                              |                              |                              |
| subjects affected / exposed                       | 1 / 7 (14.29%)               | 4 / 6 (66.67%)               | 0 / 13 (0.00%)               |
| number of deaths (all causes)                     | 0                            | 1                            | 0                            |
| number of deaths resulting from adverse events    | 0                            | 0                            | 0                            |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Vascular disorders                              |                |                |                |
| Haematoma                                       |                |                |                |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac disorders                               |                |                |                |
| Cardiac arrest                                  |                |                |                |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 6 (16.67%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| Nervous system disorders                        |                |                |                |
| Carotid arteriosclerosis                        |                |                |                |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Carotid artery stenosis                         |                |                |                |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cerebrovascular accident                        |                |                |                |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Haemorrhage intracranial                        |                |                |                |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Simple partial seizures                         |                |                |                |
| subjects affected / exposed                     | 1 / 7 (14.29%) | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Spinal cord infarction                          |                |                |                |

|   |               |                |                |
|---|---------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 7 (0.00%) | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Hepatobiliary disorders                         |               |                |                |
| Cholestasis                                     |               |                |                |
| subjects affected / exposed                     | 0 / 7 (0.00%) | 1 / 6 (16.67%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Hepatocellular injury                           |               |                |                |
| subjects affected / exposed                     | 0 / 7 (0.00%) | 1 / 6 (16.67%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders |               |                |                |
| Pulmonary embolism                              |               |                |                |
| subjects affected / exposed                     | 0 / 7 (0.00%) | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Psychiatric disorders                           |               |                |                |
| Agitation                                       |               |                |                |
| subjects affected / exposed                     | 0 / 7 (0.00%) | 1 / 6 (16.67%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Renal and urinary disorders                     |               |                |                |
| Renal failure acute                             |               |                |                |
| subjects affected / exposed                     | 0 / 7 (0.00%) | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Infections and infestations                     |               |                |                |
| Escherichia urinary tract infection             |               |                |                |
| subjects affected / exposed                     | 0 / 7 (0.00%) | 1 / 6 (16.67%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Pneumonia                                       |               |                |                |

|   |               |                |                |
|---|---------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 7 (0.00%) | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |
| Urosepsis                                       |               |                |                |
| subjects affected / exposed                     | 0 / 7 (0.00%) | 1 / 6 (16.67%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          | 0 / 0          |

| Serious adverse events                            | Cohort 4: DS-1040<br>4.8 mg | Cohort 5: DS-1040b<br>7.2 mg | Cohort 6: DS-1040b<br>9.6 mg |
|---|-----------------------------|------------------------------|------------------------------|
| Total subjects affected by serious adverse events |                             |                              |                              |
| subjects affected / exposed                       | 1 / 17 (5.88%)              | 2 / 18 (11.11%)              | 2 / 16 (12.50%)              |
| number of deaths (all causes)                     | 0                           | 2                            | 0                            |
| number of deaths resulting from adverse events    | 0                           | 0                            | 0                            |
| Vascular disorders                                |                             |                              |                              |
| Haematoma   |                             |                              |                              |
| subjects affected / exposed                       | 1 / 17 (5.88%)              | 0 / 18 (0.00%)               | 0 / 16 (0.00%)               |
| occurrences causally related to treatment / all   | 0 / 1                       | 0 / 0                        | 0 / 0                        |
| deaths causally related to treatment / all        | 0 / 0                       | 0 / 0                        | 0 / 0                        |
| Cardiac disorders                                 |                             |                              |                              |
| Cardiac arrest                                    |                             |                              |                              |
| subjects affected / exposed                       | 0 / 17 (0.00%)              | 0 / 18 (0.00%)               | 0 / 16 (0.00%)               |
| occurrences causally related to treatment / all   | 0 / 0                       | 0 / 0                        | 0 / 0                        |
| deaths causally related to treatment / all        | 0 / 0                       | 0 / 0                        | 0 / 0                        |
| Nervous system disorders                          |                             |                              |                              |
| Carotid arteriosclerosis                          |                             |                              |                              |
| subjects affected / exposed                       | 0 / 17 (0.00%)              | 1 / 18 (5.56%)               | 0 / 16 (0.00%)               |
| occurrences causally related to treatment / all   | 0 / 0                       | 0 / 1                        | 0 / 0                        |
| deaths causally related to treatment / all        | 0 / 0                       | 0 / 0                        | 0 / 0                        |
| Carotid artery stenosis                           |                             |                              |                              |
| subjects affected / exposed                       | 0 / 17 (0.00%)              | 1 / 18 (5.56%)               | 0 / 16 (0.00%)               |
| occurrences causally related to treatment / all   | 0 / 0                       | 0 / 1                        | 0 / 0                        |
| deaths causally related to treatment / all        | 0 / 0                       | 0 / 0                        | 0 / 0                        |
| Cerebrovascular accident                          |                             |                              |                              |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 18 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Haemorrhage intracranial                        |                |                |                |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 18 (0.00%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Simple partial seizures                         |                |                |                |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 18 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Spinal cord infarction                          |                |                |                |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 18 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hepatobiliary disorders                         |                |                |                |
| Cholestasis                                     |                |                |                |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 18 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hepatocellular injury                           |                |                |                |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 18 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders |                |                |                |
| Pulmonary embolism                              |                |                |                |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 18 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Psychiatric disorders                           |                |                |                |
| Agitation                                       |                |                |                |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 18 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Renal and urinary disorders                     |                |                |                |
| Renal failure acute                             |                |                |                |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 18 (0.00%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                |                |                |
| Escherichia urinary tract infection             |                |                |                |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 18 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pneumonia                                       |                |                |                |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 18 (0.00%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Urosepsis                                       |                |                |                |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 18 (0.00%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

| <b>Serious adverse events</b>                     | Placebo         | All DS-1040b     |  |
|---|-----------------|------------------|--|
| Total subjects affected by serious adverse events |                 |                  |  |
| subjects affected / exposed                       | 4 / 24 (16.67%) | 10 / 77 (12.99%) |  |
| number of deaths (all causes)                     | 0               | 3                |  |
| number of deaths resulting from adverse events    | 0               | 0                |  |
| Vascular disorders                                |                 |                  |  |
| Haematoma   |                 |                  |  |
| subjects affected / exposed                       | 0 / 24 (0.00%)  | 1 / 77 (1.30%)   |  |
| occurrences causally related to treatment / all   | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0            |  |
| Cardiac disorders                                 |                 |                  |  |
| Cardiac arrest                                    |                 |                  |  |
| subjects affected / exposed                       | 1 / 24 (4.17%)  | 1 / 77 (1.30%)   |  |
| occurrences causally related to treatment / all   | 0 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 1            |  |
| Nervous system disorders                          |                 |                  |  |
| Carotid arteriosclerosis                          |                 |                  |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Carotid artery stenosis                         |                |                |  |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cerebrovascular accident                        |                |                |  |
| subjects affected / exposed                     | 1 / 24 (4.17%) | 0 / 77 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Haemorrhage intracranial                        |                |                |  |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Simple partial seizures                         |                |                |  |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Spinal cord infarction                          |                |                |  |
| subjects affected / exposed                     | 1 / 24 (4.17%) | 0 / 77 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hepatobiliary disorders                         |                |                |  |
| Cholestasis                                     |                |                |  |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hepatocellular injury                           |                |                |  |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders |                |                |  |



|   |                |                |  |
|---|----------------|----------------|--|
| Pulmonary embolism                              |                |                |  |
| subjects affected / exposed                     | 1 / 24 (4.17%) | 0 / 77 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Psychiatric disorders                           |                |                |  |
| Agitation                                       |                |                |  |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Renal and urinary disorders                     |                |                |  |
| Renal failure acute                             |                |                |  |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Infections and infestations                     |                |                |  |
| Escherichia urinary tract infection             |                |                |  |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pneumonia                                       |                |                |  |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Urosepsis                                       |                |                |  |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

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

| Non-serious adverse events                            | Cohort 1: DS-1040b<br>0.6 mg | Cohort 2: DS-1040b<br>1.2 mg | Cohort 3: DS-1040b<br>2.4 mg |
|---|------------------------------|------------------------------|------------------------------|
| Total subjects affected by non-serious adverse events |                              |                              |                              |
| subjects affected / exposed                           | 5 / 7 (71.43%)               | 5 / 6 (83.33%)               | 10 / 13 (76.92%)             |
| Vascular disorders                                    |                              |                              |                              |

|  |                |                |                |
|--|----------------|----------------|----------------|
| Arteriosclerosis                                     |                |                |                |
| subjects affected / exposed                          | 1 / 7 (14.29%) | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)                                    | 1              | 0              | 0              |
| Haematoma  |                |                |                |
| subjects affected / exposed                          | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)                                    | 0              | 0              | 0              |
| Hypertension   |                |                |                |
| subjects affected / exposed                          | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 1 / 13 (7.69%) |
| occurrences (all)                                    | 0              | 0              | 1              |
| Hypotension  |                |                |                |
| subjects affected / exposed                          | 0 / 7 (0.00%)  | 1 / 6 (16.67%) | 0 / 13 (0.00%) |
| occurrences (all)                                    | 0              | 1              | 0              |
| General disorders and administration site conditions |                |                |                |
| Asthenia   |                |                |                |
| subjects affected / exposed                          | 0 / 7 (0.00%)  | 1 / 6 (16.67%) | 0 / 13 (0.00%) |
| occurrences (all)                                    | 0              | 1              | 0              |
| Chest discomfort                                     |                |                |                |
| subjects affected / exposed                          | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)                                    | 0              | 0              | 0              |
| Chest pain   |                |                |                |
| subjects affected / exposed                          | 0 / 7 (0.00%)  | 1 / 6 (16.67%) | 1 / 13 (7.69%) |
| occurrences (all)                                    | 0              | 1              | 1              |
| Fatigue  |                |                |                |
| subjects affected / exposed                          | 1 / 7 (14.29%) | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)                                    | 1              | 0              | 0              |
| Inflammation   |                |                |                |
| subjects affected / exposed                          | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 1 / 13 (7.69%) |
| occurrences (all)                                    | 0              | 0              | 1              |
| Influenza like illness                               |                |                |                |
| subjects affected / exposed                          | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)                                    | 0              | 0              | 0              |
| Infusion site phlebitis                              |                |                |                |
| subjects affected / exposed                          | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)                                    | 0              | 0              | 0              |
| Pain   |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 6 (16.67%) | 0 / 13 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0              |
| Peripheral swelling                             |                |                |                |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Pyrexia   |                |                |                |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Vessel puncture site pain                       |                |                |                |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Respiratory, thoracic and mediastinal disorders |                |                |                |
| Bronchiectasis                                  |                |                |                |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Cough   |                |                |                |
| subjects affected / exposed                     | 1 / 7 (14.29%) | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)                               | 1              | 0              | 0              |
| Dyspnoea  |                |                |                |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 1 / 13 (7.69%) |
| occurrences (all)                               | 0              | 0              | 1              |
| Hypoxia   |                |                |                |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 6 (16.67%) | 0 / 13 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0              |
| Nasal obstruction                               |                |                |                |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Oropharyngeal pain                              |                |                |                |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Productive cough                                |                |                |                |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Pulmonary mass                                  |                |                |                |

|                             |               |                |                |
|-----------------------------|---------------|----------------|----------------|
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)           | 0             | 0              | 0              |
| Pulmonary oedema            |               |                |                |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)           | 0             | 0              | 0              |
| Respiratory failure         |               |                |                |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)           | 0             | 0              | 0              |
| Rhinorrhoea                 |               |                |                |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)           | 0             | 0              | 0              |
| Psychiatric disorders       |               |                |                |
| Affective disorder          |               |                |                |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)           | 0             | 0              | 0              |
| Agitation                   |               |                |                |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 6 (16.67%) | 0 / 13 (0.00%) |
| occurrences (all)           | 0             | 1              | 0              |
| Anxiety                     |               |                |                |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 6 (16.67%) | 0 / 13 (0.00%) |
| occurrences (all)           | 0             | 1              | 0              |
| Confusional state           |               |                |                |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)           | 0             | 0              | 0              |
| Delirium                    |               |                |                |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)           | 0             | 0              | 0              |
| Depressed mood              |               |                |                |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%)  | 1 / 13 (7.69%) |
| occurrences (all)           | 0             | 0              | 1              |
| Depression                  |               |                |                |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%)  | 1 / 13 (7.69%) |
| occurrences (all)           | 0             | 0              | 1              |
| Hallucination               |               |                |                |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)           | 0             | 0              | 0              |

|   |                |               |                |
|---|----------------|---------------|----------------|
| Insomnia  |                |               |                |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 0 / 6 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all)                               | 0              | 0             | 1              |
| Mood altered                                    |                |               |                |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 0 / 6 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all)                               | 0              | 0             | 0              |
| Sleep disorder                                  |                |               |                |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 0 / 6 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all)                               | 0              | 0             | 0              |
| Investigations                                  |                |               |                |
| Activated partial thromboplastin time prolonged |                |               |                |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 0 / 6 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all)                               | 0              | 0             | 0              |
| Biopsy bone                                     |                |               |                |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 0 / 6 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all)                               | 0              | 0             | 1              |
| Blood albumin decreased                         |                |               |                |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 0 / 6 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all)                               | 0              | 0             | 0              |
| Blood bicarbonate decreased                     |                |               |                |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 0 / 6 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all)                               | 0              | 0             | 0              |
| Blood creatinine increased                      |                |               |                |
| subjects affected / exposed                     | 1 / 7 (14.29%) | 0 / 6 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all)                               | 1              | 0             | 0              |
| Blood fibrinogen increased                      |                |               |                |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 0 / 6 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all)                               | 0              | 0             | 0              |
| Blood glucose increased                         |                |               |                |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 0 / 6 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all)                               | 0              | 0             | 0              |
| Body temperature increased                      |                |               |                |
| subjects affected / exposed                     | 1 / 7 (14.29%) | 0 / 6 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all)                               | 1              | 0             | 0              |
| Ejection fraction decreased                     |                |               |                |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed                    | 1 / 7 (14.29%) | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)                              | 1              | 0              | 0              |
| Electrocardiogram QT prolonged                 |                |                |                |
| subjects affected / exposed                    | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)                              | 0              | 0              | 0              |
| Red blood cell sedimentation rate increased    |                |                |                |
| subjects affected / exposed                    | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)                              | 0              | 0              | 0              |
| Vitamin D decreased                            |                |                |                |
| subjects affected / exposed                    | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)                              | 0              | 0              | 0              |
| Injury, poisoning and procedural complications |                |                |                |
| Fall   |                |                |                |
| subjects affected / exposed                    | 1 / 7 (14.29%) | 0 / 6 (0.00%)  | 1 / 13 (7.69%) |
| occurrences (all)                              | 1              | 0              | 1              |
| Joint injury                                   |                |                |                |
| subjects affected / exposed                    | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)                              | 0              | 0              | 0              |
| Post procedural haematuria                     |                |                |                |
| subjects affected / exposed                    | 0 / 7 (0.00%)  | 1 / 6 (16.67%) | 0 / 13 (0.00%) |
| occurrences (all)                              | 0              | 1              | 0              |
| Wound  |                |                |                |
| subjects affected / exposed                    | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)                              | 0              | 0              | 0              |
| Cardiac disorders                              |                |                |                |
| Atrial fibrillation                            |                |                |                |
| subjects affected / exposed                    | 1 / 7 (14.29%) | 0 / 6 (0.00%)  | 1 / 13 (7.69%) |
| occurrences (all)                              | 1              | 0              | 1              |
| Bradycardia                                    |                |                |                |
| subjects affected / exposed                    | 0 / 7 (0.00%)  | 1 / 6 (16.67%) | 0 / 13 (0.00%) |
| occurrences (all)                              | 0              | 1              | 0              |
| Cardiac arrest                                 |                |                |                |
| subjects affected / exposed                    | 0 / 7 (0.00%)  | 1 / 6 (16.67%) | 0 / 13 (0.00%) |
| occurrences (all)                              | 0              | 1              | 0              |
| Left ventricular dysfunction                   |                |                |                |

|                                 |                |                |                |
|---------------------------------|----------------|----------------|----------------|
| subjects affected / exposed     | 1 / 7 (14.29%) | 0 / 6 (0.00%)  | 1 / 13 (7.69%) |
| occurrences (all)               | 1              | 0              | 1              |
| Sinus tachycardia               |                |                |                |
| subjects affected / exposed     | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)               | 0              | 0              | 0              |
| Tachycardia                     |                |                |                |
| subjects affected / exposed     | 0 / 7 (0.00%)  | 1 / 6 (16.67%) | 0 / 13 (0.00%) |
| occurrences (all)               | 0              | 1              | 0              |
| Ventricular extrasystoles       |                |                |                |
| subjects affected / exposed     | 1 / 7 (14.29%) | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)               | 1              | 0              | 0              |
| Nervous system disorders        |                |                |                |
| Burning sensation               |                |                |                |
| subjects affected / exposed     | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)               | 0              | 0              | 0              |
| Carotid arteriosclerosis        |                |                |                |
| subjects affected / exposed     | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)               | 0              | 0              | 0              |
| Carotid artery stenosis         |                |                |                |
| subjects affected / exposed     | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)               | 0              | 0              | 0              |
| Carpal tunnel syndrome          |                |                |                |
| subjects affected / exposed     | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 1 / 13 (7.69%) |
| occurrences (all)               | 0              | 0              | 1              |
| Cerebral haemorrhage            |                |                |                |
| subjects affected / exposed     | 1 / 7 (14.29%) | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)               | 1              | 0              | 0              |
| Cerebrovascular accident        |                |                |                |
| subjects affected / exposed     | 1 / 7 (14.29%) | 0 / 6 (0.00%)  | 1 / 13 (7.69%) |
| occurrences (all)               | 1              | 0              | 1              |
| Circadian rhythm sleep disorder |                |                |                |
| subjects affected / exposed     | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)               | 0              | 0              | 0              |
| Dizziness                       |                |                |                |
| subjects affected / exposed     | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)               | 0              | 0              | 0              |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| Dysaesthesia                |                |                |                 |
| subjects affected / exposed | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Haemorrhage intracranial    |                |                |                 |
| subjects affected / exposed | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Haemorrhagic stroke         |                |                |                 |
| subjects affected / exposed | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Headache                    |                |                |                 |
| subjects affected / exposed | 3 / 7 (42.86%) | 1 / 6 (16.67%) | 2 / 13 (15.38%) |
| occurrences (all)           | 3              | 1              | 2               |
| Memory impairment           |                |                |                 |
| subjects affected / exposed | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Partial seizures            |                |                |                 |
| subjects affected / exposed | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Psychomotor hyperactivity   |                |                |                 |
| subjects affected / exposed | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 1 / 13 (7.69%)  |
| occurrences (all)           | 0              | 0              | 1               |
| Sedation                    |                |                |                 |
| subjects affected / exposed | 0 / 7 (0.00%)  | 1 / 6 (16.67%) | 0 / 13 (0.00%)  |
| occurrences (all)           | 0              | 1              | 0               |
| Simple partial seizures     |                |                |                 |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 6 (0.00%)  | 0 / 13 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0               |
| Somnolence                  |                |                |                 |
| subjects affected / exposed | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Stroke in evolution         |                |                |                 |
| subjects affected / exposed | 0 / 7 (0.00%)  | 1 / 6 (16.67%) | 0 / 13 (0.00%)  |
| occurrences (all)           | 0              | 1              | 0               |
| Syncope                     |                |                |                 |
| subjects affected / exposed | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |



|                                      |                |                |                 |
|--------------------------------------|----------------|----------------|-----------------|
| Blood and lymphatic system disorders |                |                |                 |
| Anaemia                              |                |                |                 |
| subjects affected / exposed          | 0 / 7 (0.00%)  | 1 / 6 (16.67%) | 2 / 13 (15.38%) |
| occurrences (all)                    | 0              | 1              | 2               |
| Hyperfibrinogenaemia                 |                |                |                 |
| subjects affected / exposed          | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%)  |
| occurrences (all)                    | 0              | 0              | 0               |
| Leukocytosis                         |                |                |                 |
| subjects affected / exposed          | 1 / 7 (14.29%) | 1 / 6 (16.67%) | 1 / 13 (7.69%)  |
| occurrences (all)                    | 1              | 1              | 1               |
| Thrombocytopenia                     |                |                |                 |
| subjects affected / exposed          | 0 / 7 (0.00%)  | 1 / 6 (16.67%) | 0 / 13 (0.00%)  |
| occurrences (all)                    | 0              | 1              | 0               |
| Eye disorders                        |                |                |                 |
| Conjunctival haemorrhage             |                |                |                 |
| subjects affected / exposed          | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 1 / 13 (7.69%)  |
| occurrences (all)                    | 0              | 0              | 1               |
| Dry eye                              |                |                |                 |
| subjects affected / exposed          | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 1 / 13 (7.69%)  |
| occurrences (all)                    | 0              | 0              | 1               |
| Vision blurred                       |                |                |                 |
| subjects affected / exposed          | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%)  |
| occurrences (all)                    | 0              | 0              | 0               |
| Gastrointestinal disorders           |                |                |                 |
| Abdominal pain upper                 |                |                |                 |
| subjects affected / exposed          | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%)  |
| occurrences (all)                    | 0              | 0              | 0               |
| Constipation                         |                |                |                 |
| subjects affected / exposed          | 1 / 7 (14.29%) | 2 / 6 (33.33%) | 3 / 13 (23.08%) |
| occurrences (all)                    | 1              | 2              | 3               |
| Diarrhoea                            |                |                |                 |
| subjects affected / exposed          | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%)  |
| occurrences (all)                    | 0              | 0              | 0               |
| Dyspepsia                            |                |                |                 |
| subjects affected / exposed          | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 1 / 13 (7.69%)  |
| occurrences (all)                    | 0              | 0              | 1               |
| Dysphagia                            |                |                |                 |

|  |                |                |                 |
|--|----------------|----------------|-----------------|
| subjects affected / exposed            | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 1 / 13 (7.69%)  |
| occurrences (all)                      | 0              | 0              | 1               |
| Nausea                                 |                |                |                 |
| subjects affected / exposed            | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 2 / 13 (15.38%) |
| occurrences (all)                      | 0              | 0              | 2               |
| Toothache                              |                |                |                 |
| subjects affected / exposed            | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%)  |
| occurrences (all)                      | 0              | 0              | 0               |
| Vomiting                               |                |                |                 |
| subjects affected / exposed            | 0 / 7 (0.00%)  | 1 / 6 (16.67%) | 0 / 13 (0.00%)  |
| occurrences (all)                      | 0              | 1              | 0               |
| Hepatobiliary disorders                |                |                |                 |
| Cholestasis                            |                |                |                 |
| subjects affected / exposed            | 0 / 7 (0.00%)  | 1 / 6 (16.67%) | 0 / 13 (0.00%)  |
| occurrences (all)                      | 0              | 1              | 0               |
| Hepatocellular injury                  |                |                |                 |
| subjects affected / exposed            | 0 / 7 (0.00%)  | 1 / 6 (16.67%) | 0 / 13 (0.00%)  |
| occurrences (all)                      | 0              | 1              | 0               |
| Skin and subcutaneous tissue disorders |                |                |                 |
| Angioedema                             |                |                |                 |
| subjects affected / exposed            | 1 / 7 (14.29%) | 0 / 6 (0.00%)  | 0 / 13 (0.00%)  |
| occurrences (all)                      | 1              | 0              | 0               |
| Decubitis ulcer                        |                |                |                 |
| subjects affected / exposed            | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%)  |
| occurrences (all)                      | 0              | 0              | 0               |
| Erythema                               |                |                |                 |
| subjects affected / exposed            | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 1 / 13 (7.69%)  |
| occurrences (all)                      | 0              | 0              | 1               |
| Petechiae                              |                |                |                 |
| subjects affected / exposed            | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%)  |
| occurrences (all)                      | 0              | 0              | 0               |
| Psoriasis                              |                |                |                 |
| subjects affected / exposed            | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%)  |
| occurrences (all)                      | 0              | 0              | 0               |
| Swelling face                          |                |                |                 |

|  |                    |                    |                     |
|--|--------------------|--------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 7 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 | 0 / 13 (0.00%)<br>0 |
| Renal and urinary disorders                      |                    |                    |                     |
| Dysuria  |                    |                    |                     |
| subjects affected / exposed                      | 0 / 7 (0.00%)      | 0 / 6 (0.00%)      | 0 / 13 (0.00%)      |
| occurrences (all)                                | 0                  | 0                  | 0                   |
| Glycosuria                                       |                    |                    |                     |
| subjects affected / exposed                      | 0 / 7 (0.00%)      | 0 / 6 (0.00%)      | 0 / 13 (0.00%)      |
| occurrences (all)                                | 0                  | 0                  | 0                   |
| Haematuria                                       |                    |                    |                     |
| subjects affected / exposed                      | 0 / 7 (0.00%)      | 1 / 6 (16.67%)     | 1 / 13 (7.69%)      |
| occurrences (all)                                | 0                  | 1                  | 1                   |
| Neurogenic bladder                               |                    |                    |                     |
| subjects affected / exposed                      | 0 / 7 (0.00%)      | 0 / 6 (0.00%)      | 0 / 13 (0.00%)      |
| occurrences (all)                                | 0                  | 0                  | 0                   |
| Renal failure acute                              |                    |                    |                     |
| subjects affected / exposed                      | 0 / 7 (0.00%)      | 0 / 6 (0.00%)      | 0 / 13 (0.00%)      |
| occurrences (all)                                | 0                  | 0                  | 0                   |
| Urethral pain                                    |                    |                    |                     |
| subjects affected / exposed                      | 0 / 7 (0.00%)      | 0 / 6 (0.00%)      | 0 / 13 (0.00%)      |
| occurrences (all)                                | 0                  | 0                  | 0                   |
| Urinary incontinence                             |                    |                    |                     |
| subjects affected / exposed                      | 0 / 7 (0.00%)      | 0 / 6 (0.00%)      | 0 / 13 (0.00%)      |
| occurrences (all)                                | 0                  | 0                  | 0                   |
| Urinary retention                                |                    |                    |                     |
| subjects affected / exposed                      | 0 / 7 (0.00%)      | 0 / 6 (0.00%)      | 0 / 13 (0.00%)      |
| occurrences (all)                                | 0                  | 0                  | 0                   |
| Musculoskeletal and connective tissue disorders  |                    |                    |                     |
| Arthralgia                                       |                    |                    |                     |
| subjects affected / exposed                      | 0 / 7 (0.00%)      | 0 / 6 (0.00%)      | 2 / 13 (15.38%)     |
| occurrences (all)                                | 0                  | 0                  | 2                   |
| Arthritis  |                    |                    |                     |
| subjects affected / exposed                      | 0 / 7 (0.00%)      | 0 / 6 (0.00%)      | 1 / 13 (7.69%)      |
| occurrences (all)                                | 0                  | 0                  | 1                   |
| Back pain  |                    |                    |                     |

|                             |               |                |                |
|-----------------------------|---------------|----------------|----------------|
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 6 (16.67%) | 0 / 13 (0.00%) |
| occurrences (all)           | 0             | 1              | 0              |
| Muscle spasms               |               |                |                |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%)  | 1 / 13 (7.69%) |
| occurrences (all)           | 0             | 0              | 1              |
| Muscle spasticity           |               |                |                |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%)  | 1 / 13 (7.69%) |
| occurrences (all)           | 0             | 0              | 1              |
| Muscular weakness           |               |                |                |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)           | 0             | 0              | 0              |
| Musculoskeletal pain        |               |                |                |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)           | 0             | 0              | 0              |
| Neurological decompensation |               |                |                |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 6 (16.67%) | 0 / 13 (0.00%) |
| occurrences (all)           | 0             | 1              | 0              |
| Neurological symptom        |               |                |                |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)           | 0             | 0              | 0              |
| Osteoarthritis              |               |                |                |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)           | 0             | 0              | 0              |
| Paraesthesia                |               |                |                |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)           | 0             | 0              | 0              |
| Tendonitis                  |               |                |                |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)           | 0             | 0              | 0              |
| Tenosynovitis               |               |                |                |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%)  | 1 / 13 (7.69%) |
| occurrences (all)           | 0             | 0              | 1              |
| Infections and infestations |               |                |                |
| Bacterial disease carrier   |               |                |                |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)           | 0             | 0              | 0              |

|                                     |                |                |                |
|-------------------------------------|----------------|----------------|----------------|
| Bronchitis                          |                |                |                |
| subjects affected / exposed         | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)                   | 0              | 0              | 0              |
| Clostridium difficile colitis       |                |                |                |
| subjects affected / exposed         | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)                   | 0              | 0              | 0              |
| Conjunctivitis bacterial            |                |                |                |
| subjects affected / exposed         | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)                   | 0              | 0              | 0              |
| Escherichia urinary tract infection |                |                |                |
| subjects affected / exposed         | 0 / 7 (0.00%)  | 1 / 6 (16.67%) | 0 / 13 (0.00%) |
| occurrences (all)                   | 0              | 1              | 0              |
| Hepatitis B                         |                |                |                |
| subjects affected / exposed         | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)                   | 0              | 0              | 0              |
| Nasopharyngitis                     |                |                |                |
| subjects affected / exposed         | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)                   | 0              | 0              | 0              |
| Pneumonia                           |                |                |                |
| subjects affected / exposed         | 1 / 7 (14.29%) | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)                   | 1              | 0              | 0              |
| Postoperative wound infection       |                |                |                |
| subjects affected / exposed         | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 1 / 13 (7.69%) |
| occurrences (all)                   | 0              | 0              | 1              |
| Pyuria                              |                |                |                |
| subjects affected / exposed         | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 1 / 13 (7.69%) |
| occurrences (all)                   | 0              | 0              | 1              |
| Respiratory tract infection         |                |                |                |
| subjects affected / exposed         | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 1 / 13 (7.69%) |
| occurrences (all)                   | 0              | 0              | 1              |
| Upper respiratory tract infection   |                |                |                |
| subjects affected / exposed         | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)                   | 0              | 0              | 0              |
| Urinary tract infection             |                |                |                |
| subjects affected / exposed         | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%) |
| occurrences (all)                   | 0              | 0              | 0              |

|   |                    |                     |                      |
|---|--------------------|---------------------|----------------------|
| Urosepsis<br>subjects affected / exposed<br>occurrences (all)             | 0 / 7 (0.00%)<br>0 | 1 / 6 (16.67%)<br>1 | 0 / 13 (0.00%)<br>0  |
| Metabolism and nutrition disorders  |                    |                     |                      |
| Diabetes mellitus<br>subjects affected / exposed<br>occurrences (all)     | 0 / 7 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 0 / 13 (0.00%)<br>0  |
| Dyslipidaemia<br>subjects affected / exposed<br>occurrences (all)         | 0 / 7 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 0 / 13 (0.00%)<br>0  |
| Electrolyte imbalance<br>subjects affected / exposed<br>occurrences (all) | 0 / 7 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 1 / 13 (7.69%)<br>1  |
| Fluid imbalance<br>subjects affected / exposed<br>occurrences (all)       | 0 / 7 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 0 / 13 (0.00%)<br>0  |
| Hyperchloraemia<br>subjects affected / exposed<br>occurrences (all)       | 0 / 7 (0.00%)<br>0 | 1 / 6 (16.67%)<br>1 | 4 / 13 (30.77%)<br>4 |
| Hypercholesterolaemia<br>subjects affected / exposed<br>occurrences (all) | 0 / 7 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 0 / 13 (0.00%)<br>0  |
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)        | 0 / 7 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 0 / 13 (0.00%)<br>0  |
| Hyperlipidaemia<br>subjects affected / exposed<br>occurrences (all)       | 0 / 7 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 0 / 13 (0.00%)<br>0  |
| Hyperuricaemia<br>subjects affected / exposed<br>occurrences (all)        | 0 / 7 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 0 / 13 (0.00%)<br>0  |
| Hypoalbuminaemia<br>subjects affected / exposed<br>occurrences (all)      | 0 / 7 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 0 / 13 (0.00%)<br>0  |
| Hypocalcaemia   |                    |                     |                      |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 7 (14.29%) | 1 / 6 (16.67%) | 2 / 13 (15.38%) |
| occurrences (all)           | 1              | 1              | 2               |
| Hypoglycaemia               |                |                |                 |
| subjects affected / exposed | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Hypokalaemia                |                |                |                 |
| subjects affected / exposed | 1 / 7 (14.29%) | 2 / 6 (33.33%) | 2 / 13 (15.38%) |
| occurrences (all)           | 1              | 2              | 2               |
| Hypomagnesaemia             |                |                |                 |
| subjects affected / exposed | 0 / 7 (0.00%)  | 1 / 6 (16.67%) | 0 / 13 (0.00%)  |
| occurrences (all)           | 0              | 1              | 0               |
| Hyponatraemia               |                |                |                 |
| subjects affected / exposed | 1 / 7 (14.29%) | 1 / 6 (16.67%) | 0 / 13 (0.00%)  |
| occurrences (all)           | 1              | 1              | 0               |
| Malnutrition                |                |                |                 |
| subjects affected / exposed | 0 / 7 (0.00%)  | 1 / 6 (16.67%) | 1 / 13 (7.69%)  |
| occurrences (all)           | 0              | 1              | 1               |
| Vitamin B12 deficiency      |                |                |                 |
| subjects affected / exposed | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 0 / 13 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Vitamin D deficiency        |                |                |                 |
| subjects affected / exposed | 0 / 7 (0.00%)  | 0 / 6 (0.00%)  | 1 / 13 (7.69%)  |
| occurrences (all)           | 0              | 0              | 1               |

| <b>Non-serious adverse events</b>                     | Cohort 4: DS-1040<br>4.8 mg | Cohort 5: DS-1040b<br>7.2 mg | Cohort 6: DS-1040b<br>9.6 mg |
|---|-----------------------------|------------------------------|------------------------------|
| Total subjects affected by non-serious adverse events |                             |                              |                              |
| subjects affected / exposed                           | 15 / 17 (88.24%)            | 14 / 18 (77.78%)             | 14 / 16 (87.50%)             |
| Vascular disorders                                    |                             |                              |                              |
| Arteriosclerosis                                      |                             |                              |                              |
| subjects affected / exposed                           | 0 / 17 (0.00%)              | 0 / 18 (0.00%)               | 0 / 16 (0.00%)               |
| occurrences (all)                                     | 0                           | 0                            | 0                            |
| Haematoma   |                             |                              |                              |
| subjects affected / exposed                           | 1 / 17 (5.88%)              | 0 / 18 (0.00%)               | 1 / 16 (6.25%)               |
| occurrences (all)                                     | 1                           | 0                            | 1                            |
| Hypertension  |                             |                              |                              |

|  |                 |                |                |
|--|-----------------|----------------|----------------|
| subjects affected / exposed                          | 3 / 17 (17.65%) | 1 / 18 (5.56%) | 0 / 16 (0.00%) |
| occurrences (all)                                    | 3               | 1              | 0              |
| Hypotension  |                 |                |                |
| subjects affected / exposed                          | 0 / 17 (0.00%)  | 0 / 18 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                                    | 0               | 0              | 0              |
| General disorders and administration site conditions |                 |                |                |
| Asthenia   |                 |                |                |
| subjects affected / exposed                          | 0 / 17 (0.00%)  | 0 / 18 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                                    | 0               | 0              | 0              |
| Chest discomfort                                     |                 |                |                |
| subjects affected / exposed                          | 1 / 17 (5.88%)  | 0 / 18 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                                    | 1               | 0              | 0              |
| Chest pain   |                 |                |                |
| subjects affected / exposed                          | 0 / 17 (0.00%)  | 0 / 18 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                                    | 0               | 0              | 0              |
| Fatigue  |                 |                |                |
| subjects affected / exposed                          | 1 / 17 (5.88%)  | 1 / 18 (5.56%) | 1 / 16 (6.25%) |
| occurrences (all)                                    | 1               | 1              | 1              |
| Inflammation   |                 |                |                |
| subjects affected / exposed                          | 0 / 17 (0.00%)  | 0 / 18 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                                    | 0               | 0              | 0              |
| Influenza like illness                               |                 |                |                |
| subjects affected / exposed                          | 0 / 17 (0.00%)  | 0 / 18 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)                                    | 0               | 0              | 1              |
| Infusion site phlebitis                              |                 |                |                |
| subjects affected / exposed                          | 0 / 17 (0.00%)  | 0 / 18 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)                                    | 0               | 0              | 1              |
| Pain   |                 |                |                |
| subjects affected / exposed                          | 1 / 17 (5.88%)  | 0 / 18 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                                    | 1               | 0              | 0              |
| Peripheral swelling                                  |                 |                |                |
| subjects affected / exposed                          | 1 / 17 (5.88%)  | 0 / 18 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                                    | 1               | 0              | 0              |
| Pyrexia  |                 |                |                |



|   |                |                 |                |
|---|----------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 17 (5.88%) | 0 / 18 (0.00%)  | 0 / 16 (0.00%) |
| occurrences (all)                               | 1              | 0               | 0              |
| Vessel puncture site pain                       |                |                 |                |
| subjects affected / exposed                     | 1 / 17 (5.88%) | 0 / 18 (0.00%)  | 0 / 16 (0.00%) |
| occurrences (all)                               | 1              | 0               | 0              |
| Respiratory, thoracic and mediastinal disorders |                |                 |                |
| Bronchiectasis                                  |                |                 |                |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 18 (5.56%)  | 0 / 16 (0.00%) |
| occurrences (all)                               | 0              | 1               | 0              |
| Cough   |                |                 |                |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 2 / 18 (11.11%) | 0 / 16 (0.00%) |
| occurrences (all)                               | 0              | 2               | 0              |
| Dyspnoea  |                |                 |                |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 18 (0.00%)  | 0 / 16 (0.00%) |
| occurrences (all)                               | 0              | 0               | 0              |
| Hypoxia   |                |                 |                |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 18 (0.00%)  | 0 / 16 (0.00%) |
| occurrences (all)                               | 0              | 0               | 0              |
| Nasal obstruction                               |                |                 |                |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 18 (0.00%)  | 1 / 16 (6.25%) |
| occurrences (all)                               | 0              | 0               | 1              |
| Oropharyngeal pain                              |                |                 |                |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 18 (0.00%)  | 1 / 16 (6.25%) |
| occurrences (all)                               | 0              | 0               | 1              |
| Productive cough                                |                |                 |                |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 18 (5.56%)  | 0 / 16 (0.00%) |
| occurrences (all)                               | 0              | 1               | 0              |
| Pulmonary mass                                  |                |                 |                |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 18 (0.00%)  | 1 / 16 (6.25%) |
| occurrences (all)                               | 0              | 0               | 1              |
| Pulmonary oedema                                |                |                 |                |
| subjects affected / exposed                     | 1 / 17 (5.88%) | 0 / 18 (0.00%)  | 0 / 16 (0.00%) |
| occurrences (all)                               | 1              | 0               | 0              |
| Respiratory failure                             |                |                 |                |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 18 (5.56%) | 1 / 16 (6.25%)  |
| occurrences (all)           | 0              | 1              | 1               |
| Rhinorrhoea                 |                |                |                 |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 18 (0.00%) | 0 / 16 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Psychiatric disorders       |                |                |                 |
| Affective disorder          |                |                |                 |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 18 (0.00%) | 0 / 16 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0               |
| Agitation                   |                |                |                 |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 18 (5.56%) | 1 / 16 (6.25%)  |
| occurrences (all)           | 0              | 1              | 1               |
| Anxiety                     |                |                |                 |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 18 (0.00%) | 2 / 16 (12.50%) |
| occurrences (all)           | 0              | 0              | 2               |
| Confusional state           |                |                |                 |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 18 (0.00%) | 1 / 16 (6.25%)  |
| occurrences (all)           | 1              | 0              | 1               |
| Delirium                    |                |                |                 |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 18 (0.00%) | 0 / 16 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Depressed mood              |                |                |                 |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 18 (0.00%) | 0 / 16 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0               |
| Depression                  |                |                |                 |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 18 (0.00%) | 0 / 16 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0               |
| Hallucination               |                |                |                 |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 18 (0.00%) | 1 / 16 (6.25%)  |
| occurrences (all)           | 0              | 0              | 1               |
| Insomnia                    |                |                |                 |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 18 (5.56%) | 3 / 16 (18.75%) |
| occurrences (all)           | 0              | 1              | 3               |
| Mood altered                |                |                |                 |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 18 (0.00%) | 0 / 16 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0               |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| Sleep disorder<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 17 (0.00%)<br>0 | 1 / 18 (5.56%)<br>1 | 0 / 16 (0.00%)<br>0 |
| Investigations   |                     |                     |                     |
| Activated partial thromboplastin time<br>prolonged<br>subjects affected / exposed<br>occurrences (all) | 0 / 17 (0.00%)<br>0 | 0 / 18 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 |
| Biopsy bone<br>subjects affected / exposed<br>occurrences (all)  | 0 / 17 (0.00%)<br>0 | 0 / 18 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 |
| Blood albumin decreased<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 17 (0.00%)<br>0 | 1 / 18 (5.56%)<br>1 | 0 / 16 (0.00%)<br>0 |
| Blood bicarbonate decreased<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 17 (0.00%)<br>0 | 0 / 18 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 |
| Blood creatinine increased<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 17 (0.00%)<br>0 | 0 / 18 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 |
| Blood fibrinogen increased<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 17 (5.88%)<br>1 | 0 / 18 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 |
| Blood glucose increased<br>subjects affected / exposed<br>occurrences (all)                            | 1 / 17 (5.88%)<br>1 | 0 / 18 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 |
| Body temperature increased<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 17 (0.00%)<br>0 | 0 / 18 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 |
| Ejection fraction decreased<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 17 (0.00%)<br>0 | 0 / 18 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 |
| Electrocardiogram QT prolonged<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 17 (0.00%)<br>0 | 1 / 18 (5.56%)<br>1 | 0 / 16 (0.00%)<br>0 |
| Red blood cell sedimentation rate<br>increased   |                     |                     |                     |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed                    | 1 / 17 (5.88%) | 0 / 18 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                              | 1              | 0              | 0              |
| Vitamin D decreased                            |                |                |                |
| subjects affected / exposed                    | 1 / 17 (5.88%) | 0 / 18 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                              | 1              | 0              | 0              |
| Injury, poisoning and procedural complications |                |                |                |
| Fall   |                |                |                |
| subjects affected / exposed                    | 1 / 17 (5.88%) | 0 / 18 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)                              | 1              | 0              | 1              |
| Joint injury                                   |                |                |                |
| subjects affected / exposed                    | 0 / 17 (0.00%) | 1 / 18 (5.56%) | 0 / 16 (0.00%) |
| occurrences (all)                              | 0              | 1              | 0              |
| Post procedural haematuria                     |                |                |                |
| subjects affected / exposed                    | 0 / 17 (0.00%) | 0 / 18 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                              | 0              | 0              | 0              |
| Wound  |                |                |                |
| subjects affected / exposed                    | 0 / 17 (0.00%) | 1 / 18 (5.56%) | 0 / 16 (0.00%) |
| occurrences (all)                              | 0              | 1              | 0              |
| Cardiac disorders                              |                |                |                |
| Atrial fibrillation                            |                |                |                |
| subjects affected / exposed                    | 0 / 17 (0.00%) | 1 / 18 (5.56%) | 1 / 16 (6.25%) |
| occurrences (all)                              | 0              | 1              | 1              |
| Bradycardia                                    |                |                |                |
| subjects affected / exposed                    | 0 / 17 (0.00%) | 0 / 18 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)                              | 0              | 0              | 1              |
| Cardiac arrest                                 |                |                |                |
| subjects affected / exposed                    | 0 / 17 (0.00%) | 0 / 18 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                              | 0              | 0              | 0              |
| Left ventricular dysfunction                   |                |                |                |
| subjects affected / exposed                    | 0 / 17 (0.00%) | 0 / 18 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                              | 0              | 0              | 0              |
| Sinus tachycardia                              |                |                |                |
| subjects affected / exposed                    | 0 / 17 (0.00%) | 1 / 18 (5.56%) | 0 / 16 (0.00%) |
| occurrences (all)                              | 0              | 1              | 0              |
| Tachycardia                                    |                |                |                |

|                                 |                |                |                |
|---------------------------------|----------------|----------------|----------------|
| subjects affected / exposed     | 0 / 17 (0.00%) | 0 / 18 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)               | 0              | 0              | 0              |
| Ventricular extrasystoles       |                |                |                |
| subjects affected / exposed     | 0 / 17 (0.00%) | 0 / 18 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)               | 0              | 0              | 0              |
| Nervous system disorders        |                |                |                |
| Burning sensation               |                |                |                |
| subjects affected / exposed     | 0 / 17 (0.00%) | 0 / 18 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)               | 0              | 0              | 1              |
| Carotid arteriosclerosis        |                |                |                |
| subjects affected / exposed     | 0 / 17 (0.00%) | 1 / 18 (5.56%) | 0 / 16 (0.00%) |
| occurrences (all)               | 0              | 1              | 0              |
| Carotid artery stenosis         |                |                |                |
| subjects affected / exposed     | 0 / 17 (0.00%) | 1 / 18 (5.56%) | 0 / 16 (0.00%) |
| occurrences (all)               | 0              | 1              | 0              |
| Carpal tunnel syndrome          |                |                |                |
| subjects affected / exposed     | 0 / 17 (0.00%) | 0 / 18 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)               | 0              | 0              | 0              |
| Cerebral haemorrhage            |                |                |                |
| subjects affected / exposed     | 0 / 17 (0.00%) | 0 / 18 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)               | 0              | 0              | 0              |
| Cerebrovascular accident        |                |                |                |
| subjects affected / exposed     | 0 / 17 (0.00%) | 0 / 18 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)               | 0              | 0              | 0              |
| Circadian rhythm sleep disorder |                |                |                |
| subjects affected / exposed     | 0 / 17 (0.00%) | 1 / 18 (5.56%) | 0 / 16 (0.00%) |
| occurrences (all)               | 0              | 1              | 0              |
| Dizziness                       |                |                |                |
| subjects affected / exposed     | 0 / 17 (0.00%) | 0 / 18 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)               | 0              | 0              | 1              |
| Dysaesthesia                    |                |                |                |
| subjects affected / exposed     | 1 / 17 (5.88%) | 0 / 18 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)               | 1              | 0              | 0              |
| Haemorrhage intracranial        |                |                |                |
| subjects affected / exposed     | 0 / 17 (0.00%) | 0 / 18 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)               | 0              | 0              | 1              |

|                                      |                 |                |                 |
|--------------------------------------|-----------------|----------------|-----------------|
| Haemorrhagic stroke                  |                 |                |                 |
| subjects affected / exposed          | 0 / 17 (0.00%)  | 0 / 18 (0.00%) | 1 / 16 (6.25%)  |
| occurrences (all)                    | 0               | 0              | 1               |
| Headache                             |                 |                |                 |
| subjects affected / exposed          | 2 / 17 (11.76%) | 1 / 18 (5.56%) | 4 / 16 (25.00%) |
| occurrences (all)                    | 2               | 1              | 4               |
| Memory impairment                    |                 |                |                 |
| subjects affected / exposed          | 1 / 17 (5.88%)  | 1 / 18 (5.56%) | 0 / 16 (0.00%)  |
| occurrences (all)                    | 1               | 1              | 0               |
| Partial seizures                     |                 |                |                 |
| subjects affected / exposed          | 1 / 17 (5.88%)  | 0 / 18 (0.00%) | 0 / 16 (0.00%)  |
| occurrences (all)                    | 1               | 0              | 0               |
| Psychomotor hyperactivity            |                 |                |                 |
| subjects affected / exposed          | 1 / 17 (5.88%)  | 0 / 18 (0.00%) | 1 / 16 (6.25%)  |
| occurrences (all)                    | 1               | 0              | 1               |
| Sedation                             |                 |                |                 |
| subjects affected / exposed          | 0 / 17 (0.00%)  | 0 / 18 (0.00%) | 0 / 16 (0.00%)  |
| occurrences (all)                    | 0               | 0              | 0               |
| Simple partial seizures              |                 |                |                 |
| subjects affected / exposed          | 0 / 17 (0.00%)  | 0 / 18 (0.00%) | 0 / 16 (0.00%)  |
| occurrences (all)                    | 0               | 0              | 0               |
| Somnolence                           |                 |                |                 |
| subjects affected / exposed          | 0 / 17 (0.00%)  | 0 / 18 (0.00%) | 1 / 16 (6.25%)  |
| occurrences (all)                    | 0               | 0              | 1               |
| Stroke in evolution                  |                 |                |                 |
| subjects affected / exposed          | 0 / 17 (0.00%)  | 0 / 18 (0.00%) | 0 / 16 (0.00%)  |
| occurrences (all)                    | 0               | 0              | 0               |
| Syncope                              |                 |                |                 |
| subjects affected / exposed          | 0 / 17 (0.00%)  | 0 / 18 (0.00%) | 1 / 16 (6.25%)  |
| occurrences (all)                    | 0               | 0              | 1               |
| Blood and lymphatic system disorders |                 |                |                 |
| Anaemia                              |                 |                |                 |
| subjects affected / exposed          | 0 / 17 (0.00%)  | 1 / 18 (5.56%) | 0 / 16 (0.00%)  |
| occurrences (all)                    | 0               | 1              | 0               |
| Hyperfibrinogenaemia                 |                 |                |                 |

|                             |                |                 |                 |
|-----------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 18 (5.56%)  | 0 / 16 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0               |
| Leukocytosis                |                |                 |                 |
| subjects affected / exposed | 1 / 17 (5.88%) | 2 / 18 (11.11%) | 0 / 16 (0.00%)  |
| occurrences (all)           | 1              | 2               | 0               |
| Thrombocytopenia            |                |                 |                 |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 18 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0               |
| Eye disorders               |                |                 |                 |
| Conjunctival haemorrhage    |                |                 |                 |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 18 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0               |
| Dry eye                     |                |                 |                 |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 18 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0               |
| Vision blurred              |                |                 |                 |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 18 (0.00%)  | 1 / 16 (6.25%)  |
| occurrences (all)           | 0              | 0               | 1               |
| Gastrointestinal disorders  |                |                 |                 |
| Abdominal pain upper        |                |                 |                 |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 18 (5.56%)  | 0 / 16 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0               |
| Constipation                |                |                 |                 |
| subjects affected / exposed | 1 / 17 (5.88%) | 5 / 18 (27.78%) | 2 / 16 (12.50%) |
| occurrences (all)           | 1              | 5               | 2               |
| Diarrhoea                   |                |                 |                 |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 18 (0.00%)  | 2 / 16 (12.50%) |
| occurrences (all)           | 0              | 0               | 2               |
| Dyspepsia                   |                |                 |                 |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 18 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0               |
| Dysphagia                   |                |                 |                 |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 18 (0.00%)  | 1 / 16 (6.25%)  |
| occurrences (all)           | 0              | 0               | 1               |
| Nausea                      |                |                 |                 |

|  |                      |                     |                      |
|--|----------------------|---------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)   | 2 / 17 (11.76%)<br>2 | 0 / 18 (0.00%)<br>0 | 2 / 16 (12.50%)<br>2 |
| Toothache<br>subjects affected / exposed<br>occurrences (all)  | 0 / 17 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1 | 0 / 16 (0.00%)<br>0  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)   | 0 / 17 (0.00%)<br>0  | 0 / 18 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0  |
| Hepatobiliary disorders<br>Cholestasis<br>subjects affected / exposed<br>occurrences (all)               | 0 / 17 (0.00%)<br>0  | 0 / 18 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0  |
| Hepatocellular injury<br>subjects affected / exposed<br>occurrences (all)                                | 0 / 17 (0.00%)<br>0  | 0 / 18 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0  |
| Skin and subcutaneous tissue disorders<br>Angioedema<br>subjects affected / exposed<br>occurrences (all) | 0 / 17 (0.00%)<br>0  | 0 / 18 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0  |
| Decubitis ulcer<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 17 (0.00%)<br>0  | 0 / 18 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0  |
| Erythema<br>subjects affected / exposed<br>occurrences (all)   | 1 / 17 (5.88%)<br>1  | 0 / 18 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0  |
| Petechiae<br>subjects affected / exposed<br>occurrences (all)  | 1 / 17 (5.88%)<br>1  | 1 / 18 (5.56%)<br>1 | 0 / 16 (0.00%)<br>0  |
| Psoriasis<br>subjects affected / exposed<br>occurrences (all)  | 1 / 17 (5.88%)<br>1  | 0 / 18 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0  |
| Swelling face<br>subjects affected / exposed<br>occurrences (all)  | 1 / 17 (5.88%)<br>1  | 0 / 18 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0  |
| Renal and urinary disorders  |                      |                     |                      |



|   |                |                |                 |
|---|----------------|----------------|-----------------|
| Dysuria   |                |                |                 |
| subjects affected / exposed                     | 1 / 17 (5.88%) | 0 / 18 (0.00%) | 0 / 16 (0.00%)  |
| occurrences (all)                               | 1              | 0              | 0               |
| Glycosuria                                      |                |                |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 18 (5.56%) | 0 / 16 (0.00%)  |
| occurrences (all)                               | 0              | 1              | 0               |
| Haematuria                                      |                |                |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 18 (0.00%) | 0 / 16 (0.00%)  |
| occurrences (all)                               | 0              | 0              | 0               |
| Neurogenic bladder                              |                |                |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 18 (5.56%) | 0 / 16 (0.00%)  |
| occurrences (all)                               | 0              | 1              | 0               |
| Renal failure acute                             |                |                |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 18 (0.00%) | 2 / 16 (12.50%) |
| occurrences (all)                               | 0              | 0              | 2               |
| Urethral pain                                   |                |                |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 18 (0.00%) | 1 / 16 (6.25%)  |
| occurrences (all)                               | 0              | 0              | 1               |
| Urinary incontinence                            |                |                |                 |
| subjects affected / exposed                     | 1 / 17 (5.88%) | 0 / 18 (0.00%) | 0 / 16 (0.00%)  |
| occurrences (all)                               | 1              | 0              | 0               |
| Urinary retention                               |                |                |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 18 (5.56%) | 1 / 16 (6.25%)  |
| occurrences (all)                               | 0              | 1              | 1               |
| Musculoskeletal and connective tissue disorders |                |                |                 |
| Arthralgia                                      |                |                |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 1 / 18 (5.56%) | 0 / 16 (0.00%)  |
| occurrences (all)                               | 0              | 1              | 0               |
| Arthritis                                       |                |                |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 18 (0.00%) | 0 / 16 (0.00%)  |
| occurrences (all)                               | 0              | 0              | 0               |
| Back pain                                       |                |                |                 |
| subjects affected / exposed                     | 0 / 17 (0.00%) | 0 / 18 (0.00%) | 1 / 16 (6.25%)  |
| occurrences (all)                               | 0              | 0              | 1               |
| Muscle spasms                                   |                |                |                 |

|                             |                 |                |                |
|-----------------------------|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 17 (0.00%)  | 0 / 18 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)           | 0               | 0              | 0              |
| Muscle spasticity           |                 |                |                |
| subjects affected / exposed | 0 / 17 (0.00%)  | 0 / 18 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)           | 0               | 0              | 0              |
| Muscular weakness           |                 |                |                |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 18 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)           | 2               | 0              | 0              |
| Musculoskeletal pain        |                 |                |                |
| subjects affected / exposed | 1 / 17 (5.88%)  | 0 / 18 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)           | 1               | 0              | 0              |
| Neurological decompensation |                 |                |                |
| subjects affected / exposed | 0 / 17 (0.00%)  | 0 / 18 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)           | 0               | 0              | 0              |
| Neurological symptom        |                 |                |                |
| subjects affected / exposed | 0 / 17 (0.00%)  | 0 / 18 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)           | 0               | 0              | 1              |
| Osteoarthritis              |                 |                |                |
| subjects affected / exposed | 1 / 17 (5.88%)  | 0 / 18 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)           | 1               | 0              | 0              |
| Paraesthesia                |                 |                |                |
| subjects affected / exposed | 0 / 17 (0.00%)  | 0 / 18 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)           | 0               | 0              | 1              |
| Tendonitis                  |                 |                |                |
| subjects affected / exposed | 0 / 17 (0.00%)  | 0 / 18 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)           | 0               | 0              | 1              |
| Tenosynovitis               |                 |                |                |
| subjects affected / exposed | 0 / 17 (0.00%)  | 0 / 18 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)           | 0               | 0              | 0              |
| Infections and infestations |                 |                |                |
| Bacterial disease carrier   |                 |                |                |
| subjects affected / exposed | 0 / 17 (0.00%)  | 1 / 18 (5.56%) | 0 / 16 (0.00%) |
| occurrences (all)           | 0               | 1              | 0              |
| Bronchitis                  |                 |                |                |
| subjects affected / exposed | 1 / 17 (5.88%)  | 0 / 18 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)           | 1               | 0              | 0              |

|   |                      |                      |                     |
|---|----------------------|----------------------|---------------------|
| Clostridium difficile colitis<br>subjects affected / exposed<br>occurrences (all)       | 0 / 17 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  | 0 / 16 (0.00%)<br>0 |
| Conjunctivitis bacterial<br>subjects affected / exposed<br>occurrences (all)            | 1 / 17 (5.88%)<br>1  | 0 / 18 (0.00%)<br>0  | 0 / 16 (0.00%)<br>0 |
| Escherichia urinary tract infection<br>subjects affected / exposed<br>occurrences (all) | 0 / 17 (0.00%)<br>0  | 0 / 18 (0.00%)<br>0  | 0 / 16 (0.00%)<br>0 |
| Hepatitis B<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 17 (0.00%)<br>0  | 0 / 18 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1 |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 17 (5.88%)<br>1  | 1 / 18 (5.56%)<br>1  | 0 / 16 (0.00%)<br>0 |
| Pneumonia<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 17 (0.00%)<br>0  | 2 / 18 (11.11%)<br>2 | 1 / 16 (6.25%)<br>1 |
| Postoperative wound infection<br>subjects affected / exposed<br>occurrences (all)       | 0 / 17 (0.00%)<br>0  | 0 / 18 (0.00%)<br>0  | 0 / 16 (0.00%)<br>0 |
| Pyuria<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 17 (0.00%)<br>0  | 0 / 18 (0.00%)<br>0  | 0 / 16 (0.00%)<br>0 |
| Respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)         | 0 / 17 (0.00%)<br>0  | 0 / 18 (0.00%)<br>0  | 0 / 16 (0.00%)<br>0 |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)   | 0 / 17 (0.00%)<br>0  | 2 / 18 (11.11%)<br>2 | 0 / 16 (0.00%)<br>0 |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)             | 2 / 17 (11.76%)<br>2 | 3 / 18 (16.67%)<br>3 | 1 / 16 (6.25%)<br>1 |
| Urosepsis<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 17 (0.00%)<br>0  | 0 / 18 (0.00%)<br>0  | 0 / 16 (0.00%)<br>0 |

|                                    |                |                |                 |
|------------------------------------|----------------|----------------|-----------------|
| Metabolism and nutrition disorders |                |                |                 |
| Diabetes mellitus                  |                |                |                 |
| subjects affected / exposed        | 1 / 17 (5.88%) | 0 / 18 (0.00%) | 0 / 16 (0.00%)  |
| occurrences (all)                  | 1              | 0              | 0               |
| Dyslipidaemia                      |                |                |                 |
| subjects affected / exposed        | 0 / 17 (0.00%) | 1 / 18 (5.56%) | 1 / 16 (6.25%)  |
| occurrences (all)                  | 0              | 1              | 1               |
| Electrolyte imbalance              |                |                |                 |
| subjects affected / exposed        | 0 / 17 (0.00%) | 0 / 18 (0.00%) | 0 / 16 (0.00%)  |
| occurrences (all)                  | 0              | 0              | 0               |
| Fluid imbalance                    |                |                |                 |
| subjects affected / exposed        | 0 / 17 (0.00%) | 1 / 18 (5.56%) | 0 / 16 (0.00%)  |
| occurrences (all)                  | 0              | 1              | 0               |
| Hyperchloraemia                    |                |                |                 |
| subjects affected / exposed        | 0 / 17 (0.00%) | 0 / 18 (0.00%) | 0 / 16 (0.00%)  |
| occurrences (all)                  | 0              | 0              | 0               |
| Hypercholesterolaemia              |                |                |                 |
| subjects affected / exposed        | 1 / 17 (5.88%) | 0 / 18 (0.00%) | 2 / 16 (12.50%) |
| occurrences (all)                  | 1              | 0              | 2               |
| Hyperglycaemia                     |                |                |                 |
| subjects affected / exposed        | 1 / 17 (5.88%) | 1 / 18 (5.56%) | 0 / 16 (0.00%)  |
| occurrences (all)                  | 1              | 1              | 0               |
| Hyperlipidaemia                    |                |                |                 |
| subjects affected / exposed        | 0 / 17 (0.00%) | 0 / 18 (0.00%) | 1 / 16 (6.25%)  |
| occurrences (all)                  | 0              | 0              | 1               |
| Hyperuricaemia                     |                |                |                 |
| subjects affected / exposed        | 1 / 17 (5.88%) | 0 / 18 (0.00%) | 0 / 16 (0.00%)  |
| occurrences (all)                  | 1              | 0              | 0               |
| Hypoalbuminaemia                   |                |                |                 |
| subjects affected / exposed        | 0 / 17 (0.00%) | 0 / 18 (0.00%) | 1 / 16 (6.25%)  |
| occurrences (all)                  | 0              | 0              | 1               |
| Hypocalcaemia                      |                |                |                 |
| subjects affected / exposed        | 0 / 17 (0.00%) | 0 / 18 (0.00%) | 0 / 16 (0.00%)  |
| occurrences (all)                  | 0              | 0              | 0               |
| Hypoglycaemia                      |                |                |                 |

|                             |                |                 |                 |
|-----------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 18 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)           | 1              | 0               | 0               |
| Hypokalaemia                |                |                 |                 |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 18 (11.11%) | 2 / 16 (12.50%) |
| occurrences (all)           | 0              | 2               | 2               |
| Hypomagnesaemia             |                |                 |                 |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 18 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0               |
| Hyponatraemia               |                |                 |                 |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 18 (0.00%)  | 1 / 16 (6.25%)  |
| occurrences (all)           | 0              | 0               | 1               |
| Malnutrition                |                |                 |                 |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 18 (0.00%)  | 1 / 16 (6.25%)  |
| occurrences (all)           | 0              | 0               | 1               |
| Vitamin B12 deficiency      |                |                 |                 |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 18 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0               |
| Vitamin D deficiency        |                |                 |                 |
| subjects affected / exposed | 0 / 17 (0.00%) | 0 / 18 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0               |

| <b>Non-serious adverse events</b>                     | Placebo          | All DS-1040b     |  |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events |                  |                  |  |
| subjects affected / exposed                           | 18 / 24 (75.00%) | 63 / 77 (81.82%) |  |
| Vascular disorders                                    |                  |                  |  |
| Arteriosclerosis                                      |                  |                  |  |
| subjects affected / exposed                           | 0 / 24 (0.00%)   | 1 / 77 (1.30%)   |  |
| occurrences (all)                                     | 0                | 1                |  |
| Haematoma   |                  |                  |  |
| subjects affected / exposed                           | 0 / 24 (0.00%)   | 2 / 77 (2.60%)   |  |
| occurrences (all)                                     | 0                | 2                |  |
| Hypertension  |                  |                  |  |
| subjects affected / exposed                           | 3 / 24 (12.50%)  | 5 / 77 (6.49%)   |  |
| occurrences (all)                                     | 3                | 5                |  |
| Hypotension   |                  |                  |  |

|  |                 |                |  |
|--|-----------------|----------------|--|
| subjects affected / exposed                          | 1 / 24 (4.17%)  | 1 / 77 (1.30%) |  |
| occurrences (all)                                    | 1               | 1              |  |
| General disorders and administration site conditions |                 |                |  |
| Asthenia   |                 |                |  |
| subjects affected / exposed                          | 0 / 24 (0.00%)  | 1 / 77 (1.30%) |  |
| occurrences (all)                                    | 0               | 1              |  |
| Chest discomfort                                     |                 |                |  |
| subjects affected / exposed                          | 0 / 24 (0.00%)  | 1 / 77 (1.30%) |  |
| occurrences (all)                                    | 0               | 1              |  |
| Chest pain   |                 |                |  |
| subjects affected / exposed                          | 0 / 24 (0.00%)  | 2 / 77 (2.60%) |  |
| occurrences (all)                                    | 0               | 2              |  |
| Fatigue  |                 |                |  |
| subjects affected / exposed                          | 0 / 24 (0.00%)  | 4 / 77 (5.19%) |  |
| occurrences (all)                                    | 0               | 4              |  |
| Inflammation   |                 |                |  |
| subjects affected / exposed                          | 0 / 24 (0.00%)  | 1 / 77 (1.30%) |  |
| occurrences (all)                                    | 0               | 1              |  |
| Influenza like illness                               |                 |                |  |
| subjects affected / exposed                          | 0 / 24 (0.00%)  | 1 / 77 (1.30%) |  |
| occurrences (all)                                    | 0               | 1              |  |
| Infusion site phlebitis                              |                 |                |  |
| subjects affected / exposed                          | 0 / 24 (0.00%)  | 1 / 77 (1.30%) |  |
| occurrences (all)                                    | 0               | 1              |  |
| Pain   |                 |                |  |
| subjects affected / exposed                          | 0 / 24 (0.00%)  | 2 / 77 (2.60%) |  |
| occurrences (all)                                    | 0               | 2              |  |
| Peripheral swelling                                  |                 |                |  |
| subjects affected / exposed                          | 0 / 24 (0.00%)  | 1 / 77 (1.30%) |  |
| occurrences (all)                                    | 0               | 1              |  |
| Pyrexia  |                 |                |  |
| subjects affected / exposed                          | 3 / 24 (12.50%) | 1 / 77 (1.30%) |  |
| occurrences (all)                                    | 3               | 1              |  |
| Vessel puncture site pain                            |                 |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Respiratory, thoracic and mediastinal disorders |                |                |  |
| Bronchiectasis                                  |                |                |  |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Cough   |                |                |  |
| subjects affected / exposed                     | 1 / 24 (4.17%) | 3 / 77 (3.90%) |  |
| occurrences (all)                               | 1              | 3              |  |
| Dyspnoea  |                |                |  |
| subjects affected / exposed                     | 1 / 24 (4.17%) | 1 / 77 (1.30%) |  |
| occurrences (all)                               | 1              | 1              |  |
| Hypoxia   |                |                |  |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Nasal obstruction                               |                |                |  |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Oropharyngeal pain                              |                |                |  |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Productive cough                                |                |                |  |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Pulmonary mass                                  |                |                |  |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Pulmonary oedema                                |                |                |  |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Respiratory failure                             |                |                |  |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 2 / 77 (2.60%) |  |
| occurrences (all)                               | 0              | 2              |  |
| Rhinorrhoea                                     |                |                |  |

|                             |                 |                |  |
|-----------------------------|-----------------|----------------|--|
| subjects affected / exposed | 2 / 24 (8.33%)  | 0 / 77 (0.00%) |  |
| occurrences (all)           | 2               | 0              |  |
| Psychiatric disorders       |                 |                |  |
| Affective disorder          |                 |                |  |
| subjects affected / exposed | 0 / 24 (0.00%)  | 1 / 77 (1.30%) |  |
| occurrences (all)           | 0               | 1              |  |
| Agitation                   |                 |                |  |
| subjects affected / exposed | 0 / 24 (0.00%)  | 3 / 77 (3.90%) |  |
| occurrences (all)           | 0               | 3              |  |
| Anxiety                     |                 |                |  |
| subjects affected / exposed | 3 / 24 (12.50%) | 3 / 77 (3.90%) |  |
| occurrences (all)           | 3               | 3              |  |
| Confusional state           |                 |                |  |
| subjects affected / exposed | 0 / 24 (0.00%)  | 2 / 77 (2.60%) |  |
| occurrences (all)           | 0               | 2              |  |
| Delirium                    |                 |                |  |
| subjects affected / exposed | 2 / 24 (8.33%)  | 0 / 77 (0.00%) |  |
| occurrences (all)           | 2               | 0              |  |
| Depressed mood              |                 |                |  |
| subjects affected / exposed | 0 / 24 (0.00%)  | 2 / 77 (2.60%) |  |
| occurrences (all)           | 0               | 2              |  |
| Depression                  |                 |                |  |
| subjects affected / exposed | 2 / 24 (8.33%)  | 2 / 77 (2.60%) |  |
| occurrences (all)           | 2               | 2              |  |
| Hallucination               |                 |                |  |
| subjects affected / exposed | 0 / 24 (0.00%)  | 1 / 77 (1.30%) |  |
| occurrences (all)           | 0               | 1              |  |
| Insomnia                    |                 |                |  |
| subjects affected / exposed | 5 / 24 (20.83%) | 5 / 77 (6.49%) |  |
| occurrences (all)           | 5               | 5              |  |
| Mood altered                |                 |                |  |
| subjects affected / exposed | 0 / 24 (0.00%)  | 1 / 77 (1.30%) |  |
| occurrences (all)           | 0               | 1              |  |
| Sleep disorder              |                 |                |  |
| subjects affected / exposed | 1 / 24 (4.17%)  | 1 / 77 (1.30%) |  |
| occurrences (all)           | 1               | 1              |  |



|   |                |                |  |
|---|----------------|----------------|--|
| Investigations                                  |                |                |  |
| Activated partial thromboplastin time prolonged |                |                |  |
| subjects affected / exposed                     | 2 / 24 (8.33%) | 0 / 77 (0.00%) |  |
| occurrences (all)                               | 2              | 0              |  |
| Biopsy bone                                     |                |                |  |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Blood albumin decreased                         |                |                |  |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Blood bicarbonate decreased                     |                |                |  |
| subjects affected / exposed                     | 2 / 24 (8.33%) | 0 / 77 (0.00%) |  |
| occurrences (all)                               | 2              | 0              |  |
| Blood creatinine increased                      |                |                |  |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Blood fibrinogen increased                      |                |                |  |
| subjects affected / exposed                     | 2 / 24 (8.33%) | 1 / 77 (1.30%) |  |
| occurrences (all)                               | 2              | 1              |  |
| Blood glucose increased                         |                |                |  |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Body temperature increased                      |                |                |  |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Ejection fraction decreased                     |                |                |  |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Electrocardiogram QT prolonged                  |                |                |  |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Red blood cell sedimentation rate increased     |                |                |  |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Vitamin D decreased                             |                |                |  |

|  |                     |                     |  |
|--|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all) | 0 / 24 (0.00%)<br>0 | 1 / 77 (1.30%)<br>1 |  |
| Injury, poisoning and procedural complications   |                     |                     |  |
| Fall   |                     |                     |  |
| subjects affected / exposed                      | 1 / 24 (4.17%)      | 4 / 77 (5.19%)      |  |
| occurrences (all)                                | 1                   | 4                   |  |
| Joint injury                                     |                     |                     |  |
| subjects affected / exposed                      | 0 / 24 (0.00%)      | 1 / 77 (1.30%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| Post procedural haematuria                       |                     |                     |  |
| subjects affected / exposed                      | 0 / 24 (0.00%)      | 1 / 77 (1.30%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| Wound  |                     |                     |  |
| subjects affected / exposed                      | 0 / 24 (0.00%)      | 1 / 77 (1.30%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| Cardiac disorders                                |                     |                     |  |
| Atrial fibrillation                              |                     |                     |  |
| subjects affected / exposed                      | 1 / 24 (4.17%)      | 4 / 77 (5.19%)      |  |
| occurrences (all)                                | 1                   | 4                   |  |
| Bradycardia                                      |                     |                     |  |
| subjects affected / exposed                      | 0 / 24 (0.00%)      | 2 / 77 (2.60%)      |  |
| occurrences (all)                                | 0                   | 2                   |  |
| Cardiac arrest                                   |                     |                     |  |
| subjects affected / exposed                      | 1 / 24 (4.17%)      | 1 / 77 (1.30%)      |  |
| occurrences (all)                                | 1                   | 1                   |  |
| Left ventricular dysfunction                     |                     |                     |  |
| subjects affected / exposed                      | 0 / 24 (0.00%)      | 2 / 77 (2.60%)      |  |
| occurrences (all)                                | 0                   | 2                   |  |
| Sinus tachycardia                                |                     |                     |  |
| subjects affected / exposed                      | 0 / 24 (0.00%)      | 1 / 77 (1.30%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| Tachycardia                                      |                     |                     |  |
| subjects affected / exposed                      | 0 / 24 (0.00%)      | 1 / 77 (1.30%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| Ventricular extrasystoles                        |                     |                     |  |

|                                 |                |                |  |
|---------------------------------|----------------|----------------|--|
| subjects affected / exposed     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)               | 0              | 1              |  |
| Nervous system disorders        |                |                |  |
| Burning sensation               |                |                |  |
| subjects affected / exposed     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)               | 0              | 1              |  |
| Carotid arteriosclerosis        |                |                |  |
| subjects affected / exposed     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)               | 0              | 1              |  |
| Carotid artery stenosis         |                |                |  |
| subjects affected / exposed     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)               | 0              | 1              |  |
| Carpal tunnel syndrome          |                |                |  |
| subjects affected / exposed     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)               | 0              | 1              |  |
| Cerebral haemorrhage            |                |                |  |
| subjects affected / exposed     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)               | 0              | 1              |  |
| Cerebrovascular accident        |                |                |  |
| subjects affected / exposed     | 1 / 24 (4.17%) | 2 / 77 (2.60%) |  |
| occurrences (all)               | 1              | 2              |  |
| Circadian rhythm sleep disorder |                |                |  |
| subjects affected / exposed     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)               | 0              | 1              |  |
| Dizziness                       |                |                |  |
| subjects affected / exposed     | 1 / 24 (4.17%) | 1 / 77 (1.30%) |  |
| occurrences (all)               | 1              | 1              |  |
| Dysaesthesia                    |                |                |  |
| subjects affected / exposed     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)               | 0              | 1              |  |
| Haemorrhage intracranial        |                |                |  |
| subjects affected / exposed     | 1 / 24 (4.17%) | 1 / 77 (1.30%) |  |
| occurrences (all)               | 1              | 1              |  |
| Haemorrhagic stroke             |                |                |  |
| subjects affected / exposed     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)               | 0              | 1              |  |

|                                      |                |                  |  |
|--------------------------------------|----------------|------------------|--|
| Headache                             |                |                  |  |
| subjects affected / exposed          | 2 / 24 (8.33%) | 13 / 77 (16.88%) |  |
| occurrences (all)                    | 2              | 13               |  |
| Memory impairment                    |                |                  |  |
| subjects affected / exposed          | 0 / 24 (0.00%) | 2 / 77 (2.60%)   |  |
| occurrences (all)                    | 0              | 2                |  |
| Partial seizures                     |                |                  |  |
| subjects affected / exposed          | 0 / 24 (0.00%) | 1 / 77 (1.30%)   |  |
| occurrences (all)                    | 0              | 1                |  |
| Psychomotor hyperactivity            |                |                  |  |
| subjects affected / exposed          | 0 / 24 (0.00%) | 3 / 77 (3.90%)   |  |
| occurrences (all)                    | 0              | 3                |  |
| Sedation                             |                |                  |  |
| subjects affected / exposed          | 0 / 24 (0.00%) | 1 / 77 (1.30%)   |  |
| occurrences (all)                    | 0              | 1                |  |
| Simple partial seizures              |                |                  |  |
| subjects affected / exposed          | 0 / 24 (0.00%) | 1 / 77 (1.30%)   |  |
| occurrences (all)                    | 0              | 1                |  |
| Somnolence                           |                |                  |  |
| subjects affected / exposed          | 0 / 24 (0.00%) | 1 / 77 (1.30%)   |  |
| occurrences (all)                    | 0              | 1                |  |
| Stroke in evolution                  |                |                  |  |
| subjects affected / exposed          | 0 / 24 (0.00%) | 1 / 77 (1.30%)   |  |
| occurrences (all)                    | 0              | 1                |  |
| Syncope                              |                |                  |  |
| subjects affected / exposed          | 0 / 24 (0.00%) | 1 / 77 (1.30%)   |  |
| occurrences (all)                    | 0              | 1                |  |
| Blood and lymphatic system disorders |                |                  |  |
| Anaemia                              |                |                  |  |
| subjects affected / exposed          | 2 / 24 (8.33%) | 4 / 77 (5.19%)   |  |
| occurrences (all)                    | 2              | 4                |  |
| Hyperfibrinogenaemia                 |                |                  |  |
| subjects affected / exposed          | 0 / 24 (0.00%) | 1 / 77 (1.30%)   |  |
| occurrences (all)                    | 0              | 1                |  |
| Leukocytosis                         |                |                  |  |

|  |                      |                        |  |
|--|----------------------|------------------------|--|
| subjects affected / exposed<br>occurrences (all)                             | 2 / 24 (8.33%)<br>2  | 6 / 77 (7.79%)<br>6    |  |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)         | 3 / 24 (12.50%)<br>3 | 1 / 77 (1.30%)<br>1    |  |
| Eye disorders  |                      |                        |  |
| Conjunctival haemorrhage<br>subjects affected / exposed<br>occurrences (all) | 0 / 24 (0.00%)<br>0  | 1 / 77 (1.30%)<br>1    |  |
| Dry eye<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 24 (0.00%)<br>0  | 1 / 77 (1.30%)<br>1    |  |
| Vision blurred<br>subjects affected / exposed<br>occurrences (all)           | 0 / 24 (0.00%)<br>0  | 1 / 77 (1.30%)<br>1    |  |
| Gastrointestinal disorders   |                      |                        |  |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)     | 1 / 24 (4.17%)<br>1  | 1 / 77 (1.30%)<br>1    |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)             | 5 / 24 (20.83%)<br>5 | 14 / 77 (18.18%)<br>14 |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                | 1 / 24 (4.17%)<br>1  | 2 / 77 (2.60%)<br>2    |  |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)                | 0 / 24 (0.00%)<br>0  | 1 / 77 (1.30%)<br>1    |  |
| Dysphagia<br>subjects affected / exposed<br>occurrences (all)                | 1 / 24 (4.17%)<br>1  | 2 / 77 (2.60%)<br>2    |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                   | 2 / 24 (8.33%)<br>2  | 6 / 77 (7.79%)<br>6    |  |
| Toothache  |                      |                        |  |

|  |                      |                     |  |
|--|----------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 0 / 24 (0.00%)<br>0  | 1 / 77 (1.30%)<br>1 |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)   | 3 / 24 (12.50%)<br>3 | 1 / 77 (1.30%)<br>1 |  |
| Hepatobiliary disorders<br>Cholestasis<br>subjects affected / exposed<br>occurrences (all)               | 0 / 24 (0.00%)<br>0  | 1 / 77 (1.30%)<br>1 |  |
| Hepatocellular injury<br>subjects affected / exposed<br>occurrences (all)                                | 0 / 24 (0.00%)<br>0  | 1 / 77 (1.30%)<br>1 |  |
| Skin and subcutaneous tissue disorders<br>Angioedema<br>subjects affected / exposed<br>occurrences (all) | 0 / 24 (0.00%)<br>0  | 1 / 77 (1.30%)<br>1 |  |
| Decubitis ulcer<br>subjects affected / exposed<br>occurrences (all)                                      | 2 / 24 (8.33%)<br>2  | 0 / 77 (0.00%)<br>0 |  |
| Erythema<br>subjects affected / exposed<br>occurrences (all)   | 0 / 24 (0.00%)<br>0  | 2 / 77 (2.60%)<br>2 |  |
| Petechiae<br>subjects affected / exposed<br>occurrences (all)  | 0 / 24 (0.00%)<br>0  | 2 / 77 (2.60%)<br>2 |  |
| Psoriasis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 24 (0.00%)<br>0  | 1 / 77 (1.30%)<br>1 |  |
| Swelling face<br>subjects affected / exposed<br>occurrences (all)  | 0 / 24 (0.00%)<br>0  | 1 / 77 (1.30%)<br>1 |  |
| Renal and urinary disorders<br>Dysuria<br>subjects affected / exposed<br>occurrences (all)               | 0 / 24 (0.00%)<br>0  | 1 / 77 (1.30%)<br>1 |  |
| Glycosuria   |                      |                     |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Haematuria                                      |                |                |  |
| subjects affected / exposed                     | 2 / 24 (8.33%) | 2 / 77 (2.60%) |  |
| occurrences (all)                               | 2              | 2              |  |
| Neurogenic bladder                              |                |                |  |
| subjects affected / exposed                     | 1 / 24 (4.17%) | 1 / 77 (1.30%) |  |
| occurrences (all)                               | 1              | 1              |  |
| Renal failure acute                             |                |                |  |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 2 / 77 (2.60%) |  |
| occurrences (all)                               | 0              | 2              |  |
| Urethral pain                                   |                |                |  |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Urinary incontinence                            |                |                |  |
| subjects affected / exposed                     | 1 / 24 (4.17%) | 1 / 77 (1.30%) |  |
| occurrences (all)                               | 1              | 1              |  |
| Urinary retention                               |                |                |  |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 2 / 77 (2.60%) |  |
| occurrences (all)                               | 0              | 2              |  |
| Musculoskeletal and connective tissue disorders |                |                |  |
| Arthralgia                                      |                |                |  |
| subjects affected / exposed                     | 2 / 24 (8.33%) | 3 / 77 (3.90%) |  |
| occurrences (all)                               | 2              | 3              |  |
| Arthritis                                       |                |                |  |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Back pain                                       |                |                |  |
| subjects affected / exposed                     | 1 / 24 (4.17%) | 2 / 77 (2.60%) |  |
| occurrences (all)                               | 1              | 2              |  |
| Muscle spasms                                   |                |                |  |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Muscle spasticity                               |                |                |  |

|                               |                |                |  |
|-------------------------------|----------------|----------------|--|
| subjects affected / exposed   | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)             | 0              | 1              |  |
| Muscular weakness             |                |                |  |
| subjects affected / exposed   | 1 / 24 (4.17%) | 2 / 77 (2.60%) |  |
| occurrences (all)             | 1              | 2              |  |
| Musculoskeletal pain          |                |                |  |
| subjects affected / exposed   | 2 / 24 (8.33%) | 1 / 77 (1.30%) |  |
| occurrences (all)             | 2              | 1              |  |
| Neurological decompensation   |                |                |  |
| subjects affected / exposed   | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)             | 0              | 1              |  |
| Neurological symptom          |                |                |  |
| subjects affected / exposed   | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)             | 0              | 1              |  |
| Osteoarthritis                |                |                |  |
| subjects affected / exposed   | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)             | 0              | 1              |  |
| Paraesthesia                  |                |                |  |
| subjects affected / exposed   | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)             | 0              | 1              |  |
| Tendonitis                    |                |                |  |
| subjects affected / exposed   | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)             | 0              | 1              |  |
| Tenosynovitis                 |                |                |  |
| subjects affected / exposed   | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)             | 0              | 1              |  |
| Infections and infestations   |                |                |  |
| Bacterial disease carrier     |                |                |  |
| subjects affected / exposed   | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)             | 0              | 1              |  |
| Bronchitis                    |                |                |  |
| subjects affected / exposed   | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)             | 0              | 1              |  |
| Clostridium difficile colitis |                |                |  |
| subjects affected / exposed   | 0 / 24 (0.00%) | 1 / 77 (1.30%) |  |
| occurrences (all)             | 0              | 1              |  |



|   |                     |                     |  |
|---|---------------------|---------------------|--|
| Conjunctivitis bacterial<br>subjects affected / exposed<br>occurrences (all)            | 0 / 24 (0.00%)<br>0 | 1 / 77 (1.30%)<br>1 |  |
| Escherichia urinary tract infection<br>subjects affected / exposed<br>occurrences (all) | 0 / 24 (0.00%)<br>0 | 1 / 77 (1.30%)<br>1 |  |
| Hepatitis B<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 24 (0.00%)<br>0 | 1 / 77 (1.30%)<br>1 |  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 24 (0.00%)<br>0 | 2 / 77 (2.60%)<br>2 |  |
| Pneumonia<br>subjects affected / exposed<br>occurrences (all)                           | 1 / 24 (4.17%)<br>1 | 4 / 77 (5.19%)<br>4 |  |
| Postoperative wound infection<br>subjects affected / exposed<br>occurrences (all)       | 0 / 24 (0.00%)<br>0 | 1 / 77 (1.30%)<br>1 |  |
| Pyuria<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 24 (0.00%)<br>0 | 1 / 77 (1.30%)<br>1 |  |
| Respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)         | 0 / 24 (0.00%)<br>0 | 1 / 77 (1.30%)<br>1 |  |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)   | 0 / 24 (0.00%)<br>0 | 2 / 77 (2.60%)<br>2 |  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)             | 1 / 24 (4.17%)<br>1 | 6 / 77 (7.79%)<br>6 |  |
| Urosepsis<br>subjects affected / exposed<br>occurrences (all)                           | 1 / 24 (4.17%)<br>1 | 1 / 77 (1.30%)<br>1 |  |
| Metabolism and nutrition disorders<br>Diabetes mellitus                                 |                     |                     |  |

|                             |                 |                |
|-----------------------------|-----------------|----------------|
| subjects affected / exposed | 0 / 24 (0.00%)  | 1 / 77 (1.30%) |
| occurrences (all)           | 0               | 1              |
| Dyslipidaemia               |                 |                |
| subjects affected / exposed | 3 / 24 (12.50%) | 2 / 77 (2.60%) |
| occurrences (all)           | 3               | 2              |
| Electrolyte imbalance       |                 |                |
| subjects affected / exposed | 0 / 24 (0.00%)  | 1 / 77 (1.30%) |
| occurrences (all)           | 0               | 1              |
| Fluid imbalance             |                 |                |
| subjects affected / exposed | 0 / 24 (0.00%)  | 1 / 77 (1.30%) |
| occurrences (all)           | 0               | 1              |
| Hyperchloraemia             |                 |                |
| subjects affected / exposed | 2 / 24 (8.33%)  | 5 / 77 (6.49%) |
| occurrences (all)           | 2               | 5              |
| Hypercholesterolaemia       |                 |                |
| subjects affected / exposed | 0 / 24 (0.00%)  | 3 / 77 (3.90%) |
| occurrences (all)           | 0               | 3              |
| Hyperglycaemia              |                 |                |
| subjects affected / exposed | 3 / 24 (12.50%) | 2 / 77 (2.60%) |
| occurrences (all)           | 3               | 2              |
| Hyperlipidaemia             |                 |                |
| subjects affected / exposed | 1 / 24 (4.17%)  | 1 / 77 (1.30%) |
| occurrences (all)           | 1               | 1              |
| Hyperuricaemia              |                 |                |
| subjects affected / exposed | 0 / 24 (0.00%)  | 1 / 77 (1.30%) |
| occurrences (all)           | 0               | 1              |
| Hypoalbuminaemia            |                 |                |
| subjects affected / exposed | 2 / 24 (8.33%)  | 1 / 77 (1.30%) |
| occurrences (all)           | 2               | 1              |
| Hypocalcaemia               |                 |                |
| subjects affected / exposed | 2 / 24 (8.33%)  | 4 / 77 (5.19%) |
| occurrences (all)           | 2               | 4              |
| Hypoglycaemia               |                 |                |
| subjects affected / exposed | 1 / 24 (4.17%)  | 1 / 77 (1.30%) |
| occurrences (all)           | 1               | 1              |
| Hypokalaemia                |                 |                |

|                             |                 |                 |  |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 6 / 24 (25.00%) | 9 / 77 (11.69%) |  |
| occurrences (all)           | 6               | 9               |  |
| Hypomagnesaemia             |                 |                 |  |
| subjects affected / exposed | 0 / 24 (0.00%)  | 1 / 77 (1.30%)  |  |
| occurrences (all)           | 0               | 1               |  |
| Hyponatraemia               |                 |                 |  |
| subjects affected / exposed | 2 / 24 (8.33%)  | 3 / 77 (3.90%)  |  |
| occurrences (all)           | 2               | 3               |  |
| Malnutrition                |                 |                 |  |
| subjects affected / exposed | 0 / 24 (0.00%)  | 3 / 77 (3.90%)  |  |
| occurrences (all)           | 0               | 3               |  |
| Vitamin B12 deficiency      |                 |                 |  |
| subjects affected / exposed | 3 / 24 (12.50%) | 0 / 77 (0.00%)  |  |
| occurrences (all)           | 3               | 0               |  |
| Vitamin D deficiency        |                 |                 |  |
| subjects affected / exposed | 0 / 24 (0.00%)  | 1 / 77 (1.30%)  |  |
| occurrences (all)           | 0               | 1               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment   |
|-----------------|---|
| 11 May 2015     | Included an intermediate dose, updated number of sites, revised exclusion criteria, updated pharmacokinetics protocol, clarified dose escalation procedure, updated treatment details, and clarified purpose of assessments and details/timing of sample collection                                       |
| 01 October 2015 | Updated secondary objectives, study duration, pharmacokinetic parameters, updated inclusion and exclusion criteria, and clarified rationale for assessments and details/timing of sample collection   |
| 12 July 2016    | Revised inclusion and exclusion criteria, updated enrollment section and study duration, included exploratory assessments, updated primary objective, and clarified adverse event assessment  |
| 04 May 2018     | Updated study rationale and number of subjects, revised cohort enrollment description, updated eligibility criteria, updated pharmacokinetic parameters, added exploratory assessments, extended study duration, clarified concomitant medications and procedures, and provided details of ECG assessment |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported