



## Clinical trial results:

### A Phase 1b, Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Single Ascending Dose Study to Assess the Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of DS-1040b when Added to Standard of Care Anticoagulation Therapy in Subjects with Acute Submassive Pulmonary Embolism

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2015-005211-32 |
| Trial protocol           | NL             |
| Global end of trial date | 05 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-B-U107 |
|-----------------------|---------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02923115 |
| 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, Inc., +1 908-992-6400, CTRinfo@dsi.com |
| Scientific contact           | Contact for Clinical Trial Information, Daiichi Sankyo, Inc., +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                       | 05 August 2019 |
| Is this the analysis of the primary completion data? | No             |
| Global end of trial reached?                         | Yes            |
| Global end of trial date                             | 05 August 2019 |
| Was the trial ended prematurely?                     | No             |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study is to assess the safety and tolerability of ascending doses of DS-1040b given as a single IV infusion over 12, 24, 48 and 72 hours, respectively, when added to standard of care (SOC) anticoagulation therapy, compared to placebo by evaluating the rate of clinically relevant bleeding (International Society of Thrombosis and Haemostasis (ISTH) major or clinically relevant non-major bleeding [CRNM]).

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 (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 23 June 2016 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | Yes          |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Netherlands: 25   |
| Country: Number of subjects enrolled | Spain: 2          |
| Country: Number of subjects enrolled | Austria: 2        |
| Country: Number of subjects enrolled | Belgium: 12       |
| Country: Number of subjects enrolled | France: 47        |
| Country: Number of subjects enrolled | Germany: 10       |
| Country: Number of subjects enrolled | United States: 25 |
| Country: Number of subjects enrolled | Italy: 11         |
| Worldwide total number of subjects   | 134               |
| EEA total number of subjects         | 109               |

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)                     | 86 |
| From 65 to 84 years                      | 48 |
| 85 years and over                        | 0  |

## Subject disposition

### Recruitment

Recruitment details:

A total of 134 subjects who met all inclusion and no exclusion criteria were enrolled in the study at 47 clinic sites (15 in the United States and 32 in Europe). Of the 134 subjects randomized to treatment, 125 received treatment.

### Pre-assignment

Screening details:

This study enrolled up to 5 sequential, ascending-dose, continuous infusion cohorts (starting DS1040b dose 20 mg). In Cohorts 1 and 2, eligible subjects were randomized in a 2:1 ratio to either DS-1040b or placebo. Starting with Cohort 3, the ratio changed to 3:1. All participants received standard of care enoxaparin during study drug infusion.

### 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 20 mg |

Arm description:

Subjects who received an intravenous infusion of 20 mg DS-1040b in addition to standard of care anticoagulation therapy.

|  |                       |
|--|-----------------------|
| 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:

Single, continuous intravenous infusion over 12 to 24 hours (depending on cohort)

|  |  |
|--|--|
| Investigational medicinal product name | Enoxaparin                                   |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe |
| Routes of administration               | Subcutaneous use                             |

Dosage and administration details:

Subcutaneous injection 1 mg/kg twice daily

|                  |                          |
|------------------|--------------------------|
| <b>Arm title</b> | Cohort 2: DS-1040b 40 mg |
|------------------|--------------------------|

Arm description:

Subjects who received an intravenous infusion of 40 mg DS-1040b in addition to standard of care anticoagulation therapy.

|  |                       |
|--|-----------------------|
| 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:   |  |
| Single, continuous intravenous infusion over 12 to 24 hours (depending on cohort)  |  |
| Investigational medicinal product name   | Enoxaparin                                   |
| Investigational medicinal product code   |  |
| Other name   |  |
| Pharmaceutical forms   | Solution for injection in pre-filled syringe |
| Routes of administration   | Subcutaneous use                             |
| Dosage and administration details:   |  |
| Subcutaneous injection 1 mg/kg twice daily   |  |
| <b>Arm title</b>   | Cohort 3: DS-1040b 60 mg                     |
| Arm description:   |  |
| Subjects who received an intravenous infusion of 60 mg DS-1040b in addition to standard of care anticoagulation therapy. |  |
| 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:   |  |
| Single, continuous intravenous infusion over 12 to 24 hours (depending on cohort)  |  |
| Investigational medicinal product name   | Enoxaparin                                   |
| Investigational medicinal product code   |  |
| Other name   |  |
| Pharmaceutical forms   | Solution for injection in pre-filled syringe |
| Routes of administration   | Subcutaneous use                             |
| Dosage and administration details:   |  |
| Subcutaneous injection 1 mg/kg twice daily   |  |
| <b>Arm title</b>   | Cohort 4: DS-1040 80 mg                      |
| Arm description:   |  |
| Subjects who received an intravenous infusion of 80 mg DS-1040b in addition to standard of care anticoagulation therapy. |  |
| 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:   |  |
| Single, continuous intravenous infusion over 12 to 24 hours (depending on cohort)  |  |
| Investigational medicinal product name   | Enoxaparin                                   |
| Investigational medicinal product code   |  |
| Other name   |  |
| Pharmaceutical forms   | Solution for injection in pre-filled syringe |
| Routes of administration   | Subcutaneous use                             |
| Dosage and administration details:   |  |
| Subcutaneous injection 1 mg/kg twice daily   |  |
| <b>Arm title</b>   | Cohort 5: DS-1040b 40 mg                     |
| Arm description:   |  |
| Subjects who received an intravenous infusion of 40 mg DS-1040b in addition to standard of care anticoagulation therapy. |  |
| 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:  |  |
| Single, continuous intravenous infusion over 12 to 24 hours (depending on cohort) |  |
| Investigational medicinal product name  | Enoxaparin                                   |
| Investigational medicinal product code  |  |
| Other name  |  |
| Pharmaceutical forms  | Solution for injection in pre-filled syringe |
| Routes of administration  | Subcutaneous use                             |
| Dosage and administration details:  |  |
| Subcutaneous injection 1 mg/kg twice daily  |  |
| <b>Arm title</b>  | Placebo                                      |

Arm description:

Subjects who received an intravenous infusion of placebo in addition to standard of care anticoagulation therapy.

|  |                                |
|--|--------------------------------|
| Arm type                               | Placebo                        |
| Investigational medicinal product name | Placebo                        |
| Investigational medicinal product code |                                |
| Other name                             | 0.9% Sodium chloride injection |
| Pharmaceutical forms                   | Solution for infusion          |
| Routes of administration               | Intravenous use                |

Dosage and administration details:

Single, continuous intravenous infusion of 0.9% sodium chloride over 12 to 24 hours

|  |  |
|--|--|
| Investigational medicinal product name | Enoxaparin                                   |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe |
| Routes of administration               | Subcutaneous use                             |

Dosage and administration details:

Subcutaneous injection 1 mg/kg twice daily

| <b>Number of subjects in period 1</b> | Cohort 1: DS-1040b<br>20 mg | Cohort 2: DS-1040b<br>40 mg | Cohort 3: DS-1040b<br>60 mg |
|---------------------------------------|-----------------------------|-----------------------------|-----------------------------|
| Started                               | 12                          | 16                          | 23                          |
| Treated                               | 12                          | 16                          | 20                          |
| Completed                             | 12                          | 15                          | 20                          |
| Not completed                         | 0                           | 1                           | 3                           |
| Consent withdrawn by subject          | -                           | 1                           | -                           |
| Lost to follow-up                     | -                           | -                           | -                           |
| Randomized, but not dosed             | -                           | -                           | 3                           |

| <b>Number of subjects in period 1</b> | Cohort 4: DS-1040<br>80 mg | Cohort 5: DS-1040b<br>40 mg | Placebo |
|---------------------------------------|----------------------------|-----------------------------|---------|
| Started                               | 23                         | 22                          | 38      |
| Treated                               | 22                         | 17                          | 38      |

|                              |    |    |    |
|------------------------------|----|----|----|
| Completed                    | 21 | 17 | 38 |
| Not completed                | 2  | 5  | 0  |
| Consent withdrawn by subject | -  | -  | -  |
| Lost to follow-up            | 1  | -  | -  |
| Randomized, but not dosed    | 1  | 5  | -  |

## Baseline characteristics

### Reporting groups

|  |                          |
|--|--------------------------|
| Reporting group title  | Cohort 1: DS-1040b 20 mg |
| Reporting group description:<br>Subjects who received an intravenous infusion of 20 mg DS-1040b in addition to standard of care anticoagulation therapy. |                          |
| Reporting group title  | Cohort 2: DS-1040b 40 mg |
| Reporting group description:<br>Subjects who received an intravenous infusion of 40 mg DS-1040b in addition to standard of care anticoagulation therapy. |                          |
| Reporting group title  | Cohort 3: DS-1040b 60 mg |
| Reporting group description:<br>Subjects who received an intravenous infusion of 60 mg DS-1040b in addition to standard of care anticoagulation therapy. |                          |
| Reporting group title  | Cohort 4: DS-1040 80 mg  |
| Reporting group description:<br>Subjects who received an intravenous infusion of 80 mg DS-1040b in addition to standard of care anticoagulation therapy. |                          |
| Reporting group title  | Cohort 5: DS-1040b 40 mg |
| Reporting group description:<br>Subjects who received an intravenous infusion of 40 mg DS-1040b in addition to standard of care anticoagulation therapy. |                          |
| Reporting group title  | Placebo                  |
| Reporting group description:<br>Subjects who received an intravenous infusion of placebo in addition to standard of care anticoagulation therapy.        |                          |

| Reporting group values                                | Cohort 1: DS-1040b<br>20 mg | Cohort 2: DS-1040b<br>40 mg | Cohort 3: DS-1040b<br>60 mg |
|---|-----------------------------|-----------------------------|-----------------------------|
| Number of subjects                                    | 12                          | 16                          | 23                          |
| Age categorical<br>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                           | 7                           | 14                          |
| From 65-84 years                                      | 4                           | 9                           | 9                           |
| 85 years and over                                     | 0                           | 0                           | 0                           |
| Age continuous<br>Units: years                        |                             |                             |                             |
| arithmetic mean                                       | 56.1                        | 62.1                        | 55.1                        |
| standard deviation                                    | ± 16.3                      | ± 10.9                      | ± 17.5                      |
| Gender categorical<br>Units: Subjects                 |                             |                             |                             |
| Female  | 4                           | 8                           | 5                           |
| Male  | 8                           | 8                           | 18                          |



| Reporting group values                                | Cohort 4: DS-1040<br>80 mg | Cohort 5: DS-1040b<br>40 mg | Placebo |
|---|----------------------------|-----------------------------|---------|
| Number of subjects                                    | 23                         | 22                          | 38      |
| Age categorical<br>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)                                  | 16                         | 18                          | 23      |
| From 65-84 years                                      | 7                          | 4                           | 15      |
| 85 years and over                                     | 0                          | 0                           | 0       |
| Age continuous<br>Units: years                        |                            |                             |         |
| arithmetic mean                                       | 55.0                       | 56.5                        | 58.3    |
| standard deviation                                    | ± 13.5                     | ± 9.8                       | ± 10.7  |
| Gender categorical<br>Units: Subjects                 |                            |                             |         |
| Female  | 8                          | 7                           | 12      |
| Male  | 15                         | 15                          | 26      |

| Reporting group values                                | Total |  |  |
|---|-------|--|--|
| Number of subjects                                    | 134   |  |  |
| Age categorical<br>Units: Subjects                    |       |  |  |
| In utero  | 0     |  |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0     |  |  |
| Newborns (0-27 days)                                  | 0     |  |  |
| Infants and toddlers (28 days-23<br>months)           | 0     |  |  |
| Children (2-11 years)                                 | 0     |  |  |
| Adolescents (12-17 years)                             | 0     |  |  |
| Adults (18-64 years)                                  | 86    |  |  |
| From 65-84 years                                      | 48    |  |  |
| 85 years and over                                     | 0     |  |  |
| Age continuous<br>Units: years                        |       |  |  |
| arithmetic mean                                       | -     |  |  |
| standard deviation                                    | -     |  |  |
| Gender categorical<br>Units: Subjects                 |       |  |  |
| Female  | 44    |  |  |
| Male  | 90    |  |  |

## End points

### End points reporting groups

|  |                          |
|--|--------------------------|
| Reporting group title  | Cohort 1: DS-1040b 20 mg |
| Reporting group description:<br>Subjects who received an intravenous infusion of 20 mg DS-1040b in addition to standard of care anticoagulation therapy. |                          |
| Reporting group title  | Cohort 2: DS-1040b 40 mg |
| Reporting group description:<br>Subjects who received an intravenous infusion of 40 mg DS-1040b in addition to standard of care anticoagulation therapy. |                          |
| Reporting group title  | Cohort 3: DS-1040b 60 mg |
| Reporting group description:<br>Subjects who received an intravenous infusion of 60 mg DS-1040b in addition to standard of care anticoagulation therapy. |                          |
| Reporting group title  | Cohort 4: DS-1040 80 mg  |
| Reporting group description:<br>Subjects who received an intravenous infusion of 80 mg DS-1040b in addition to standard of care anticoagulation therapy. |                          |
| Reporting group title  | Cohort 5: DS-1040b 40 mg |
| Reporting group description:<br>Subjects who received an intravenous infusion of 40 mg DS-1040b in addition to standard of care anticoagulation therapy. |                          |
| Reporting group title  | Placebo                  |
| Reporting group description:<br>Subjects who received an intravenous infusion of placebo in addition to standard of care anticoagulation therapy.        |                          |

### **Primary: Number of Subjects Experiencing Adjudicated Clinically Relevant Bleeding Events Following Intravenous Infusion of DS-1040b or Placebo in Addition to Standard of Care Anti-coagulation Therapy in Subjects With Acute Submassive Pulmonary Embolism**

|  |  |
|--|--|
| End point title  | Number of Subjects Experiencing Adjudicated Clinically Relevant Bleeding Events Following Intravenous Infusion of DS-1040b or Placebo in Addition to Standard of Care Anti-coagulation Therapy in Subjects With Acute Submassive Pulmonary Embolism <sup>[1]</sup> |
| End point description:<br>Clinically relevant bleeding was defined as major or clinically relevant non-major (CRNM) bleeding adjudicated by the Clinical Events Committee (CEC) based on International Society of Thrombosis and Haemostasis (ISTH) definitions and the CEC charter. |  |
| End point type   | Primary  |
| End point timeframe:<br>Baseline up to Day 30 post infusion, up to approximately 3 years 2 months  |  |

#### Notes:

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

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

| End point values   | Cohort 1: DS-1040b 20 mg | Cohort 2: DS-1040b 40 mg | Cohort 3: DS-1040b 60 mg | Cohort 4: DS-1040 80 mg |
|--|--------------------------|--------------------------|--------------------------|-------------------------|
| Subject group type   | Reporting group          | Reporting group          | Reporting group          | Reporting group         |
| Number of subjects analysed  | 12                       | 16                       | 20                       | 22                      |
| Units: Subjects  |                          |                          |                          |                         |
| number (not applicable)  |                          |                          |                          |                         |
| At least 1 bleeding event  | 4                        | 3                        | 3                        | 4                       |
| Major bleeding event   | 0                        | 0                        | 0                        | 1                       |
| Non-major clinically relevant bleeding event                           | 0                        | 0                        | 0                        | 2                       |
| Minor or nuisance bleeding event                                       | 3                        | 2                        | 3                        | 2                       |
| Fatal bleeding event   | 0                        | 0                        | 0                        | 0                       |
| Bleeding with Hb drop $\geq 2\text{g/dL}$ , transfusion $\geq 2$ units | 0                        | 0                        | 0                        | 1                       |

| End point values   | Cohort 5: DS-1040b 40 mg | Placebo         |  |  |
|--|--------------------------|-----------------|--|--|
| Subject group type   | Reporting group          | Reporting group |  |  |
| Number of subjects analysed  | 17                       | 38              |  |  |
| Units: Subjects  |                          |                 |  |  |
| number (not applicable)  |                          |                 |  |  |
| At least 1 bleeding event  | 1                        | 10              |  |  |
| Major bleeding event   | 0                        | 00              |  |  |
| Non-major clinically relevant bleeding event                           | 1                        | 1               |  |  |
| Minor or nuisance bleeding event                                       | 0                        | 6               |  |  |
| Fatal bleeding event   | 0                        | 0               |  |  |
| Bleeding with Hb drop $\geq 2\text{g/dL}$ , transfusion $\geq 2$ units | 0                        | 0               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Mean Percent Change From Baseline in Total Thrombus Volume at 12-72 Hours Post Start of Infusion of DS-1040b Compared to Placebo When Added to Standard of Care Anticoagulation Therapy in Subjects With Acute Submassive Pulmonary Embolism

|                 |  |
|-----------------|--|
| End point title | Mean Percent Change From Baseline in Total Thrombus Volume at 12-72 Hours Post Start of Infusion of DS-1040b Compared to Placebo When Added to Standard of Care Anticoagulation Therapy in Subjects With Acute Submassive Pulmonary Embolism |
|-----------------|--|

End point description:

The change from baseline in total thrombus volume was assessed by computed tomography angiography in segmental or larger pulmonary arteries following intravenous infusion of DS-1040b or placebo in addition to standard of care anticoagulation therapy.

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

End point timeframe:

Baseline to 12-72 hours post start of infusion, up to approximately 3 years 2 months

| End point values                     | Cohort 1: DS-1040b 20 mg | Cohort 2: DS-1040b 40 mg | Cohort 3: DS-1040b 60 mg | Cohort 4: DS-1040 80 mg |
|--------------------------------------|--------------------------|--------------------------|--------------------------|-------------------------|
| Subject group type                   | Reporting group          | Reporting group          | Reporting group          | Reporting group         |
| Number of subjects analysed          | 11                       | 15                       | 20                       | 22                      |
| Units: Percent change                |                          |                          |                          |                         |
| arithmetic mean (standard deviation) |                          |                          |                          |                         |
| Mean percent change from baseline    | -23.78 (± 24.49)         | -38.67 (± 17.34)         | -33.50 (± 17.41)         | -37.36 (± 26.90)        |

| End point values                     | Cohort 5: DS-1040b 40 mg | Placebo          |  |  |
|--------------------------------------|--------------------------|------------------|--|--|
| Subject group type                   | Reporting group          | Reporting group  |  |  |
| Number of subjects analysed          | 16                       | 36               |  |  |
| Units: Percent change                |                          |                  |  |  |
| arithmetic mean (standard deviation) |                          |                  |  |  |
| Mean percent change from baseline    | -32.33 (± 19.03)         | -31.35 (± 17.74) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Subjects Achieving Reductions in Total Thrombus Volume at 12-72 Hours Post Infusion of DS-1040b Compared to Placebo When Added to Standard of Care Anticoagulation Therapy in Subjects With Acute Submassive Pulmonary Embolism

|                 |   |
|-----------------|---|
| End point title | Subjects Achieving Reductions in Total Thrombus Volume at 12-72 Hours Post Infusion of DS-1040b Compared to Placebo When Added to Standard of Care Anticoagulation Therapy in Subjects With Acute Submassive Pulmonary Embolism |
|-----------------|---|

End point description:

Change in total pulmonary thrombus burden (total thrombus volume) was assessed by computed tomography pulmonary angiography (CTPA). All CTPA scans were evaluated by a central imaging laboratory in a blinded manner by radiologists.

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

End point timeframe:

Baseline to 12-72 hours post start of infusion, up to approximately 3 years 2 months

| End point values            | Cohort 1: DS-1040b 20 mg | Cohort 2: DS-1040b 40 mg | Cohort 3: DS-1040b 60 mg | Cohort 4: DS-1040 80 mg |
|-----------------------------|--------------------------|--------------------------|--------------------------|-------------------------|
| Subject group type          | Reporting group          | Reporting group          | Reporting group          | Reporting group         |
| Number of subjects analysed | 12                       | 15                       | 20                       | 22                      |
| Units: Subjects             |                          |                          |                          |                         |
| number (not applicable)     |                          |                          |                          |                         |
| No change or increase       | 2                        | 0                        | 1                        | 0                       |
| <20% reduction              | 2                        | 3                        | 3                        | 5                       |
| ≥20% reduction              | 7                        | 12                       | 16                       | 17                      |
| Missing data                | 1                        | 0                        | 0                        | 0                       |

| End point values            | Cohort 5: DS-1040b 40 mg | Placebo         |  |  |
|-----------------------------|--------------------------|-----------------|--|--|
| Subject group type          | Reporting group          | Reporting group |  |  |
| Number of subjects analysed | 17                       | 38              |  |  |
| Units: Subjects             |                          |                 |  |  |
| number (not applicable)     |                          |                 |  |  |
| No change or increase       | 1                        | 3               |  |  |
| <20% reduction              | 3                        | 5               |  |  |
| ≥20% reduction              | 12                       | 28              |  |  |
| Missing data                | 1                        | 2               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Pharmacokinetic (PK) Parameter Maximum Concentration (Cmax) Following Intravenous Infusion of DS-1040b in Addition to Standard of Care Anti-coagulation Therapy in Subjects With Acute Submassive Pulmonary Embolism

|                 |   |
|-----------------|---|
| End point title | Pharmacokinetic (PK) Parameter Maximum Concentration (Cmax) Following Intravenous Infusion of DS-1040b in Addition to Standard of Care Anti-coagulation Therapy in Subjects With Acute Submassive Pulmonary Embolism <sup>[2]</sup> |
|-----------------|---|

End point description:

Plasma concentrations at each time point and PK parameter Cmax of DS 1040b was calculated using noncompartmental analysis.

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

End point timeframe:

Cohort 1: 0 up to 72 h post infusion; Cohorts 2 and 3: 0 up to 96 h post infusion; Cohort 4 and 5: 0 up to 120 h post infusion

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 20 mg | Cohort 2: DS-1040b 40 mg | Cohort 3: DS-1040b 60 mg | Cohort 4: DS-1040 80 mg |
|--------------------------------------|--------------------------|--------------------------|--------------------------|-------------------------|
| Subject group type                   | Reporting group          | Reporting group          | Reporting group          | Reporting group         |
| Number of subjects analysed          | 11                       | 15                       | 19                       | 22                      |
| Units: ng/mL                         |                          |                          |                          |                         |
| arithmetic mean (standard deviation) |                          |                          |                          |                         |
| Cmax                                 | 970.09 (± 1373.43)       | 421.73 (± 515.57)        | 608.84 (± 562.94)        | 1006.41 (± 1883.49)     |

| End point values                     | Cohort 5: DS-1040b 40 mg |  |  |  |
|--------------------------------------|--------------------------|--|--|--|
| Subject group type                   | Reporting group          |  |  |  |
| Number of subjects analysed          | 17                       |  |  |  |
| Units: ng/mL                         |                          |  |  |  |
| arithmetic mean (standard deviation) |                          |  |  |  |
| Cmax                                 | 526.12 (± 535.03)        |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacokinetic Parameter Area Under the Concentration Versus Time Curve (0 to Last) Following Intravenous Infusion of DS-1040b In Addition to Standard of Care Anti-coagulation Therapy in Participants With Acute Submassive Pulmonary Embolism

|                 |  |
|-----------------|--|
| End point title | Pharmacokinetic Parameter Area Under the Concentration Versus Time Curve (0 to Last) Following Intravenous Infusion of DS-1040b In Addition to Standard of Care Anti-coagulation Therapy in Participants With Acute Submassive Pulmonary Embolism <sup>[3]</sup> |
|-----------------|--|

End point description:

Plasma concentrations at each time point and PK parameter of Area Under the Concentration Versus Time Curve (0 to last) of DS 1040b was calculated using non-compartmental analysis.

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

End point timeframe:

Cohort 1: 0 up to 72 h post infusion; Cohorts 2 and 3: 0 up to 96 h post infusion; Cohort 4 and 5: 0 up to 120 h post infusion

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 20 mg | Cohort 2: DS-1040b 40 mg | Cohort 3: DS-1040b 60 mg | Cohort 4: DS-1040 80 mg |
|--------------------------------------|--------------------------|--------------------------|--------------------------|-------------------------|
| Subject group type                   | Reporting group          | Reporting group          | Reporting group          | Reporting group         |
| Number of subjects analysed          | 11                       | 15                       | 19                       | 22                      |
| Units: ng*h/mL                       |                          |                          |                          |                         |
| arithmetic mean (standard deviation) |                          |                          |                          |                         |
| AUC(0 to last)                       | 5532.92 (± 4090.34)      | 7819.53 (± 2870.13)      | 13403.15 (± 8047.13)     | 17147.27 (± 15024.61)   |

|                                      |                          |  |  |  |
|--------------------------------------|--------------------------|--|--|--|
| <b>End point values</b>              | Cohort 5: DS-1040b 40 mg |  |  |  |
| Subject group type                   | Reporting group          |  |  |  |
| Number of subjects analysed          | 17                       |  |  |  |
| Units: ng*h/mL                       |                          |  |  |  |
| arithmetic mean (standard deviation) |                          |  |  |  |
| AUC(0 to last)                       | 8014.73 ( $\pm$ 2870.19) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Pharmacokinetic Parameter Terminal Half-life Following Intravenous Infusion of DS-1040b Combined With Standard of Care Anti-coagulation Therapy in Subjects With Acute Submassive Pulmonary Embolism

|                 |   |
|-----------------|---|
| End point title | Pharmacokinetic Parameter Terminal Half-life Following Intravenous Infusion of DS-1040b Combined With Standard of Care Anti-coagulation Therapy in Subjects With Acute Submassive Pulmonary Embolism <sup>[4]</sup> |
|-----------------|---|

End point description:

Plasma concentrations at each time point and PK parameter Terminal Half-life of DS 1062b was calculated using noncompartmental analysis.

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

End point timeframe:

Cohort 1: 0 up to 72 h post infusion; Cohorts 2 and 3: 0 up to 96 h post infusion; Cohort 4 and 5: 0 up to 120 h post infusion

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.

|                                      |                          |                          |                          |                         |
|--------------------------------------|--------------------------|--------------------------|--------------------------|-------------------------|
| <b>End point values</b>              | Cohort 1: DS-1040b 20 mg | Cohort 2: DS-1040b 40 mg | Cohort 3: DS-1040b 60 mg | Cohort 4: DS-1040 80 mg |
| Subject group type                   | Reporting group          | Reporting group          | Reporting group          | Reporting group         |
| Number of subjects analysed          | 9                        | 13                       | 18                       | 5                       |
| Units: hours                         |                          |                          |                          |                         |
| arithmetic mean (standard deviation) |                          |                          |                          |                         |
| Terminal half-life                   | 22.81 ( $\pm$ 3.13)      | 28.44 ( $\pm$ 5.75)      | 29.06 ( $\pm$ 7.60)      | 36.39 ( $\pm$ 2.07)     |

|                                      |                          |  |  |  |
|--------------------------------------|--------------------------|--|--|--|
| <b>End point values</b>              | Cohort 5: DS-1040b 40 mg |  |  |  |
| Subject group type                   | Reporting group          |  |  |  |
| Number of subjects analysed          | 9                        |  |  |  |
| Units: hours                         |                          |  |  |  |
| arithmetic mean (standard deviation) |                          |  |  |  |

|                    |                     |  |  |  |
|--------------------|---------------------|--|--|--|
| Terminal half-life | 30.06 ( $\pm$ 3.45) |  |  |  |
|--------------------|---------------------|--|--|--|

## Statistical analyses

---

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events (TEAEs) were collected from baseline up to Day 30 post infusion, up to approximately 3 years 2 months.

Adverse event reporting additional description:

A TEAE is defined as an adverse event that emerges during treatment, having been absent pretreatment, or worsening relative to the pre-treatment state.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 19.1 |
|--------------------|------|

### Reporting groups

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Cohort 1: DS-1040b 20 mg |
|-----------------------|--------------------------|

Reporting group description:

Subjects who received an intravenous infusion of 20 mg DS-1040b in addition to standard of care anticoagulation therapy.

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Cohort 2: DS-1040b 40 mg |
|-----------------------|--------------------------|

Reporting group description:

Subjects who received an intravenous infusion of 40 mg DS-1040b in addition to standard of care anticoagulation therapy.

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Cohort 3: DS-1040b 60 mg |
|-----------------------|--------------------------|

Reporting group description:

Subjects who received an intravenous infusion of 60 mg DS-1040b in addition to standard of care anticoagulation therapy.

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Cohort 4: DS-1040 80 mg |
|-----------------------|-------------------------|

Reporting group description:

Subjects who received an intravenous infusion of 80 mg DS-1040b in addition to standard of care anticoagulation therapy.

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Cohort 5: DS-1040b 40 mg |
|-----------------------|--------------------------|

Reporting group description:

Subjects who received an intravenous infusion of 40 mg DS-1040b in addition to standard of care anticoagulation therapy.

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

Reporting group description:

Subjects who received an intravenous infusion of placebo in addition to standard of care anticoagulation therapy.

| Serious adverse events  | Cohort 1: DS-1040b<br>20 mg | Cohort 2: DS-1040b<br>40 mg | Cohort 3: DS-1040b<br>60 mg |
|---|-----------------------------|-----------------------------|-----------------------------|
| Total subjects affected by serious adverse events                                     |                             |                             |                             |
| subjects affected / exposed   | 3 / 12 (25.00%)             | 0 / 16 (0.00%)              | 2 / 20 (10.00%)             |
| number of deaths (all causes)   | 0                           | 0                           | 0                           |
| number of deaths resulting from adverse events  | 0                           | 0                           | 0                           |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps)<br>Colon neoplasm |                             |                             |                             |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (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          |
| Metastases to liver                             |                |                |                |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (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          |
| Metastases to nervous system                    |                |                |                |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 1 / 20 (5.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Metastases to peritoneum                        |                |                |                |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (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          |
| Testicular cancer metastatic                    |                |                |                |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 1 / 20 (5.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac disorders                               |                |                |                |
| Sinus tachycardia                               |                |                |                |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (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                        |                |                |                |
| Presyncope                                      |                |                |                |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 1 / 20 (5.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Reproductive system and breast disorders        |                |                |                |
| Endometrial hyperplasia                         |                |                |                |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (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                         |                |                |                |
| Hepatocellular injury                           |                |                |                |
| subjects affected / exposed                     | 1 / 12 (8.33%) | 0 / 16 (0.00%) | 0 / 20 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders |                |                |                |
| Pleural effusion                                |                |                |                |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (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          |
| Pulmonary embolism                              |                |                |                |
| subjects affected / exposed                     | 1 / 12 (8.33%) | 0 / 16 (0.00%) | 0 / 20 (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          |
| Pulmonary infarction                            |                |                |                |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (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                           |                |                |                |
| Depression                                      |                |                |                |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (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                     |                |                |                |
| Anal abscess                                    |                |                |                |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 1 / 20 (5.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infection                                       |                |                |                |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (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          |
| Lung infection                                  |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 12 (8.33%) | 0 / 16 (0.00%) | 0 / 20 (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          |
| Pneumonia                                       |                |                |                |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (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>                                       | Cohort 4: DS-1040<br>80 mg | Cohort 5: DS-1040b<br>40 mg | Placebo         |
|---|----------------------------|-----------------------------|-----------------|
| Total subjects affected by serious adverse events                   |                            |                             |                 |
| subjects affected / exposed   | 1 / 22 (4.55%)             | 3 / 17 (17.65%)             | 5 / 38 (13.16%) |
| number of deaths (all causes)                                       | 0                          | 0                           | 0               |
| number of deaths resulting from adverse events                      | 0                          | 0                           | 0               |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                            |                             |                 |
| Colon neoplasm  |                            |                             |                 |
| subjects affected / exposed   | 0 / 22 (0.00%)             | 0 / 17 (0.00%)              | 1 / 38 (2.63%)  |
| occurrences causally related to treatment / all                     | 0 / 0                      | 0 / 0                       | 0 / 1           |
| deaths causally related to treatment / all                          | 0 / 0                      | 0 / 0                       | 0 / 0           |
| Metastases to liver   |                            |                             |                 |
| subjects affected / exposed   | 0 / 22 (0.00%)             | 0 / 17 (0.00%)              | 1 / 38 (2.63%)  |
| occurrences causally related to treatment / all                     | 0 / 0                      | 0 / 0                       | 0 / 1           |
| deaths causally related to treatment / all                          | 0 / 0                      | 0 / 0                       | 0 / 0           |
| Metastases to nervous system  |                            |                             |                 |
| subjects affected / exposed   | 0 / 22 (0.00%)             | 0 / 17 (0.00%)              | 0 / 38 (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           |
| Metastases to peritoneum  |                            |                             |                 |
| subjects affected / exposed   | 0 / 22 (0.00%)             | 0 / 17 (0.00%)              | 1 / 38 (2.63%)  |
| occurrences causally related to treatment / all                     | 0 / 0                      | 0 / 0                       | 0 / 1           |
| deaths causally related to treatment / all                          | 0 / 0                      | 0 / 0                       | 0 / 0           |
| Testicular cancer metastatic  |                            |                             |                 |
| subjects affected / exposed   | 0 / 22 (0.00%)             | 0 / 17 (0.00%)              | 0 / 38 (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                               |                |                |                |
| Sinus tachycardia                               |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 17 (0.00%) | 1 / 38 (2.63%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nervous system disorders                        |                |                |                |
| Presyncope                                      |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 17 (0.00%) | 0 / 38 (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          |
| Reproductive system and breast disorders        |                |                |                |
| Endometrial hyperplasia                         |                |                |                |
| subjects affected / exposed                     | 1 / 22 (4.55%) | 0 / 17 (0.00%) | 0 / 38 (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          |
| Hepatobiliary disorders                         |                |                |                |
| Hepatocellular injury                           |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 17 (0.00%) | 0 / 38 (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 |                |                |                |
| Pleural effusion                                |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 1 / 17 (5.88%) | 0 / 38 (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          |
| Pulmonary embolism                              |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 17 (0.00%) | 0 / 38 (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          |
| Pulmonary infarction                            |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 17 (0.00%) | 1 / 38 (2.63%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Psychiatric disorders                           |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Depression                                      |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 1 / 17 (5.88%) | 1 / 38 (2.63%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                |                |                |
| Anal abscess                                    |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 17 (0.00%) | 0 / 38 (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          |
| Infection                                       |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 17 (0.00%) | 1 / 38 (2.63%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Lung infection                                  |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 17 (0.00%) | 1 / 38 (2.63%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pneumonia                                       |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 1 / 17 (5.88%) | 0 / 38 (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          |

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

| <b>Non-serious adverse events</b>                                   | Cohort 1: DS-1040b<br>20 mg | Cohort 2: DS-1040b<br>40 mg | Cohort 3: DS-1040b<br>60 mg |
|---|-----------------------------|-----------------------------|-----------------------------|
| Total subjects affected by non-serious adverse events               |                             |                             |                             |
| subjects affected / exposed   | 8 / 12 (66.67%)             | 6 / 16 (37.50%)             | 13 / 20 (65.00%)            |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                             |                             |                             |
| Metastases to nervous system  |                             |                             |                             |
| subjects affected / exposed   | 0 / 12 (0.00%)              | 0 / 16 (0.00%)              | 1 / 20 (5.00%)              |
| occurrences (all)   | 0                           | 0                           | 1                           |
| Testicular cancer metastatic  |                             |                             |                             |
| subjects affected / exposed   | 0 / 12 (0.00%)              | 0 / 16 (0.00%)              | 1 / 20 (5.00%)              |
| occurrences (all)   | 0                           | 0                           | 1                           |

|  |                 |                |                |
|--|-----------------|----------------|----------------|
| Vascular disorders                                   |                 |                |                |
| Circulatory collapse                                 |                 |                |                |
| subjects affected / exposed                          | 0 / 12 (0.00%)  | 0 / 16 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all)                                    | 0               | 0              | 0              |
| Deep vein thrombosis                                 |                 |                |                |
| subjects affected / exposed                          | 2 / 12 (16.67%) | 0 / 16 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all)                                    | 2               | 0              | 1              |
| Haemorrhage  |                 |                |                |
| subjects affected / exposed                          | 0 / 12 (0.00%)  | 0 / 16 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all)                                    | 0               | 0              | 0              |
| Hypertension   |                 |                |                |
| subjects affected / exposed                          | 0 / 12 (0.00%)  | 0 / 16 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all)                                    | 0               | 0              | 1              |
| Hypotension  |                 |                |                |
| subjects affected / exposed                          | 0 / 12 (0.00%)  | 1 / 16 (6.25%) | 0 / 20 (0.00%) |
| occurrences (all)                                    | 0               | 1              | 0              |
| Surgical and medical procedures                      |                 |                |                |
| Sinus operation                                      |                 |                |                |
| subjects affected / exposed                          | 0 / 12 (0.00%)  | 0 / 16 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all)                                    | 0               | 0              | 0              |
| General disorders and administration site conditions |                 |                |                |
| Chest pain   |                 |                |                |
| subjects affected / exposed                          | 0 / 12 (0.00%)  | 1 / 16 (6.25%) | 0 / 20 (0.00%) |
| occurrences (all)                                    | 0               | 1              | 0              |
| Feeling cold   |                 |                |                |
| subjects affected / exposed                          | 0 / 12 (0.00%)  | 0 / 16 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all)                                    | 0               | 0              | 0              |
| Feeling hot  |                 |                |                |
| subjects affected / exposed                          | 0 / 12 (0.00%)  | 0 / 16 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all)                                    | 0               | 0              | 0              |
| Infusion site extravasation                          |                 |                |                |
| subjects affected / exposed                          | 0 / 12 (0.00%)  | 0 / 16 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all)                                    | 0               | 0              | 0              |
| Infusion site phlebitis                              |                 |                |                |
| subjects affected / exposed                          | 1 / 12 (8.33%)  | 0 / 16 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all)                                    | 1               | 0              | 0              |

|   |                      |                      |                      |
|---|----------------------|----------------------|----------------------|
| Malaise<br>subjects affected / exposed<br>occurrences (all)   | 0 / 12 (0.00%)<br>0  | 0 / 16 (0.00%)<br>0  | 1 / 20 (5.00%)<br>1  |
| Non-cardiac chest pain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 12 (0.00%)<br>0  | 0 / 16 (0.00%)<br>0  | 0 / 20 (0.00%)<br>0  |
| Peripheral swelling<br>subjects affected / exposed<br>occurrences (all)   | 0 / 12 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1  | 0 / 20 (0.00%)<br>0  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 12 (0.00%)<br>0  | 0 / 16 (0.00%)<br>0  | 0 / 20 (0.00%)<br>0  |
| Vessel puncture site haematoma<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 12 (0.00%)<br>0  | 0 / 16 (0.00%)<br>0  | 0 / 20 (0.00%)<br>0  |
| Reproductive system and breast disorders<br>Endometrial hyperplasia<br>subjects affected / exposed<br>occurrences (all) | 0 / 12 (0.00%)<br>0  | 0 / 16 (0.00%)<br>0  | 0 / 20 (0.00%)<br>0  |
| Gynaecomastia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 12 (0.00%)<br>0  | 0 / 16 (0.00%)<br>0  | 0 / 20 (0.00%)<br>0  |
| Vaginal haemorrhage<br>subjects affected / exposed<br>occurrences (all)   | 1 / 12 (8.33%)<br>1  | 0 / 16 (0.00%)<br>0  | 0 / 20 (0.00%)<br>0  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)            | 1 / 12 (8.33%)<br>1  | 0 / 16 (0.00%)<br>0  | 0 / 20 (0.00%)<br>0  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)  | 0 / 12 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1  | 1 / 20 (5.00%)<br>1  |
| Epistaxis<br>subjects affected / exposed<br>occurrences (all)   | 2 / 12 (16.67%)<br>2 | 2 / 16 (12.50%)<br>2 | 2 / 20 (10.00%)<br>2 |
| Haemoptysis   |                      |                      |                      |



|                                      |                |                |                 |
|--------------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed          | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 1 / 20 (5.00%)  |
| occurrences (all)                    | 0              | 0              | 1               |
| Hyperventilation                     |                |                |                 |
| subjects affected / exposed          | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 1 / 20 (5.00%)  |
| occurrences (all)                    | 0              | 0              | 1               |
| Pleural effusion                     |                |                |                 |
| subjects affected / exposed          | 1 / 12 (8.33%) | 0 / 16 (0.00%) | 2 / 20 (10.00%) |
| occurrences (all)                    | 1              | 0              | 2               |
| Pleurisy                             |                |                |                 |
| subjects affected / exposed          | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (0.00%)  |
| occurrences (all)                    | 0              | 0              | 0               |
| Pulmonary embolism                   |                |                |                 |
| subjects affected / exposed          | 1 / 12 (8.33%) | 0 / 16 (0.00%) | 0 / 20 (0.00%)  |
| occurrences (all)                    | 1              | 0              | 0               |
| Pulmonary infarction                 |                |                |                 |
| subjects affected / exposed          | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (0.00%)  |
| occurrences (all)                    | 0              | 0              | 0               |
| Psychiatric disorders                |                |                |                 |
| Anxiety                              |                |                |                 |
| subjects affected / exposed          | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 2 / 20 (10.00%) |
| occurrences (all)                    | 0              | 0              | 2               |
| Delirium                             |                |                |                 |
| subjects affected / exposed          | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (0.00%)  |
| occurrences (all)                    | 0              | 0              | 0               |
| Depression                           |                |                |                 |
| subjects affected / exposed          | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (0.00%)  |
| occurrences (all)                    | 0              | 0              | 0               |
| Investigations                       |                |                |                 |
| Aspartate aminotransferase increased |                |                |                 |
| subjects affected / exposed          | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (0.00%)  |
| occurrences (all)                    | 0              | 0              | 0               |
| Blood pressure increased             |                |                |                 |
| subjects affected / exposed          | 1 / 12 (8.33%) | 0 / 16 (0.00%) | 0 / 20 (0.00%)  |
| occurrences (all)                    | 1              | 0              | 0               |
| Crystal urine present                |                |                |                 |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed                    | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all)                              | 0              | 0              | 0              |
| Electrocardiogram QT prolonged                 |                |                |                |
| subjects affected / exposed                    | 1 / 12 (8.33%) | 0 / 16 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all)                              | 1              | 0              | 0              |
| Electrocardiogram T wave inversion             |                |                |                |
| subjects affected / exposed                    | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all)                              | 0              | 0              | 0              |
| Electrocardiogram abnormal                     |                |                |                |
| subjects affected / exposed                    | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all)                              | 0              | 0              | 1              |
| Liver function test increased                  |                |                |                |
| subjects affected / exposed                    | 1 / 12 (8.33%) | 0 / 16 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all)                              | 1              | 0              | 0              |
| Mean cell volume increased                     |                |                |                |
| subjects affected / exposed                    | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all)                              | 0              | 0              | 0              |
| Occult blood positive                          |                |                |                |
| subjects affected / exposed                    | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all)                              | 0              | 0              | 0              |
| Urobilinogen urine increased                   |                |                |                |
| subjects affected / exposed                    | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all)                              | 0              | 0              | 0              |
| Injury, poisoning and procedural complications |                |                |                |
| Clavicle fracture                              |                |                |                |
| subjects affected / exposed                    | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all)                              | 0              | 0              | 0              |
| Skin abrasion                                  |                |                |                |
| subjects affected / exposed                    | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all)                              | 0              | 0              | 0              |
| Synovial rupture                               |                |                |                |
| subjects affected / exposed                    | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all)                              | 0              | 0              | 0              |
| Urinary retention postoperative                |                |                |                |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 12 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 1 / 20 (5.00%)<br>1 |
| Cardiac disorders                                |                     |                     |                     |
| Atrial fibrillation                              |                     |                     |                     |
| subjects affected / exposed                      | 0 / 12 (0.00%)      | 0 / 16 (0.00%)      | 0 / 20 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Bundle branch block right                        |                     |                     |                     |
| subjects affected / exposed                      | 0 / 12 (0.00%)      | 0 / 16 (0.00%)      | 0 / 20 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Right ventricular dysfunction                    |                     |                     |                     |
| subjects affected / exposed                      | 0 / 12 (0.00%)      | 0 / 16 (0.00%)      | 0 / 20 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Sinus tachycardia                                |                     |                     |                     |
| subjects affected / exposed                      | 0 / 12 (0.00%)      | 0 / 16 (0.00%)      | 0 / 20 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Nervous system disorders                         |                     |                     |                     |
| Dizziness  |                     |                     |                     |
| subjects affected / exposed                      | 0 / 12 (0.00%)      | 0 / 16 (0.00%)      | 1 / 20 (5.00%)      |
| occurrences (all)                                | 0                   | 0                   | 1                   |
| Haemorrhage intracranial                         |                     |                     |                     |
| subjects affected / exposed                      | 0 / 12 (0.00%)      | 0 / 16 (0.00%)      | 1 / 20 (5.00%)      |
| occurrences (all)                                | 0                   | 0                   | 1                   |
| Headache   |                     |                     |                     |
| subjects affected / exposed                      | 1 / 12 (8.33%)      | 0 / 16 (0.00%)      | 3 / 20 (15.00%)     |
| occurrences (all)                                | 1                   | 0                   | 3                   |
| Lethargy   |                     |                     |                     |
| subjects affected / exposed                      | 0 / 12 (0.00%)      | 0 / 16 (0.00%)      | 0 / 20 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Migraine   |                     |                     |                     |
| subjects affected / exposed                      | 1 / 12 (8.33%)      | 0 / 16 (0.00%)      | 1 / 20 (5.00%)      |
| occurrences (all)                                | 1                   | 0                   | 1                   |
| Muscle spasticity                                |                     |                     |                     |
| subjects affected / exposed                      | 0 / 12 (0.00%)      | 0 / 16 (0.00%)      | 0 / 20 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Presyncope                                       |                     |                     |                     |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)   | 0 / 12 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 1 / 20 (5.00%)<br>1 |
| Tremor<br>subjects affected / exposed<br>occurrences (all)   | 0 / 12 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 0 / 20 (0.00%)<br>0 |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)    | 0 / 12 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 1 / 20 (5.00%)<br>1 |
| Microcytic anaemia<br>subjects affected / exposed<br>occurrences (all)                                 | 1 / 12 (8.33%)<br>1 | 0 / 16 (0.00%)<br>0 | 0 / 20 (0.00%)<br>0 |
| Ear and labyrinth disorders<br>Tinnitus<br>subjects affected / exposed<br>occurrences (all)            | 0 / 12 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 1 / 20 (5.00%)<br>1 |
| Vertigo<br>subjects affected / exposed<br>occurrences (all)  | 0 / 12 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 0 / 20 (0.00%)<br>0 |
| Eye disorders<br>Vision blurred<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 12 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 1 / 20 (5.00%)<br>1 |
| Gastrointestinal disorders<br>Abdominal discomfort<br>subjects affected / exposed<br>occurrences (all) | 0 / 12 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1 | 1 / 20 (5.00%)<br>1 |
| Abdominal distension<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 12 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1 | 0 / 20 (0.00%)<br>0 |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 12 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1 | 0 / 20 (0.00%)<br>0 |
| Anal haemorrhage<br>subjects affected / exposed<br>occurrences (all)                                   | 1 / 12 (8.33%)<br>1 | 0 / 16 (0.00%)<br>0 | 0 / 20 (0.00%)<br>0 |
| Constipation   |                     |                     |                     |

|  |                 |                |                 |
|--|-----------------|----------------|-----------------|
| subjects affected / exposed            | 0 / 12 (0.00%)  | 0 / 16 (0.00%) | 2 / 20 (10.00%) |
| occurrences (all)                      | 0               | 0              | 2               |
| Diarrhoea                              |                 |                |                 |
| subjects affected / exposed            | 2 / 12 (16.67%) | 1 / 16 (6.25%) | 2 / 20 (10.00%) |
| occurrences (all)                      | 2               | 1              | 2               |
| Faeces discoloured                     |                 |                |                 |
| subjects affected / exposed            | 0 / 12 (0.00%)  | 1 / 16 (6.25%) | 0 / 20 (0.00%)  |
| occurrences (all)                      | 0               | 1              | 0               |
| Nausea                                 |                 |                |                 |
| subjects affected / exposed            | 0 / 12 (0.00%)  | 0 / 16 (0.00%) | 1 / 20 (5.00%)  |
| occurrences (all)                      | 0               | 0              | 1               |
| Paraesthesia oral                      |                 |                |                 |
| subjects affected / exposed            | 0 / 12 (0.00%)  | 0 / 16 (0.00%) | 1 / 20 (5.00%)  |
| occurrences (all)                      | 0               | 0              | 1               |
| Vomiting                               |                 |                |                 |
| subjects affected / exposed            | 0 / 12 (0.00%)  | 0 / 16 (0.00%) | 2 / 20 (10.00%) |
| occurrences (all)                      | 0               | 0              | 2               |
| Hepatobiliary disorders                |                 |                |                 |
| Hepatocellular injury                  |                 |                |                 |
| subjects affected / exposed            | 1 / 12 (8.33%)  | 1 / 16 (6.25%) | 0 / 20 (0.00%)  |
| occurrences (all)                      | 1               | 1              | 0               |
| Hypertransaminasaemia                  |                 |                |                 |
| subjects affected / exposed            | 0 / 12 (0.00%)  | 0 / 16 (0.00%) | 0 / 20 (0.00%)  |
| occurrences (all)                      | 0               | 0              | 0               |
| Skin and subcutaneous tissue disorders |                 |                |                 |
| Ecchymosis                             |                 |                |                 |
| subjects affected / exposed            | 1 / 12 (8.33%)  | 0 / 16 (0.00%) | 0 / 20 (0.00%)  |
| occurrences (all)                      | 1               | 0              | 0               |
| Night sweats                           |                 |                |                 |
| subjects affected / exposed            | 0 / 12 (0.00%)  | 0 / 16 (0.00%) | 0 / 20 (0.00%)  |
| occurrences (all)                      | 0               | 0              | 0               |
| Rash                                   |                 |                |                 |
| subjects affected / exposed            | 1 / 12 (8.33%)  | 0 / 16 (0.00%) | 0 / 20 (0.00%)  |
| occurrences (all)                      | 1               | 0              | 0               |
| Renal and urinary disorders            |                 |                |                 |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Dysuria   |                |                |                |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Haematuria                                      |                |                |                |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all)                               | 0              | 0              | 1              |
| Ketonuria                                       |                |                |                |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Proteinuria                                     |                |                |                |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Urine abnormality                               |                |                |                |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Musculoskeletal and connective tissue disorders |                |                |                |
| Arthralgia                                      |                |                |                |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Arthritis                                       |                |                |                |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 1 / 16 (6.25%) | 0 / 20 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0              |
| Back pain                                       |                |                |                |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Bursitis  |                |                |                |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Groin pain                                      |                |                |                |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Muscle contracture                              |                |                |                |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Musculoskeletal discomfort                      |                |                |                |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Pain in extremity           |                |                |                 |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Spinal pain                 |                |                |                 |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Infections and infestations |                |                |                 |
| Abscess limb                |                |                |                 |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Anal abscess                |                |                |                 |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 1 / 20 (5.00%)  |
| occurrences (all)           | 0              | 0              | 1               |
| Appendicitis                |                |                |                 |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 16 (6.25%) | 0 / 20 (0.00%)  |
| occurrences (all)           | 0              | 1              | 0               |
| Bacteriuria                 |                |                |                 |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Infection                   |                |                |                 |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Lung infection              |                |                |                 |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 16 (0.00%) | 2 / 20 (10.00%) |
| occurrences (all)           | 1              | 0              | 2               |
| Oral fungal infection       |                |                |                 |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Pneumonia                   |                |                |                 |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 0 / 20 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Respiratory tract infection |                |                |                 |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 16 (0.00%) | 2 / 20 (10.00%) |
| occurrences (all)           | 0              | 0              | 2               |

|   |                     |                     |                      |
|---|---------------------|---------------------|----------------------|
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all) | 0 / 12 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1 | 2 / 20 (10.00%)<br>2 |
| Metabolism and nutrition disorders  |                     |                     |                      |
| Folate deficiency<br>subjects affected / exposed<br>occurrences (all)       | 0 / 12 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 0 / 20 (0.00%)<br>0  |
| Hyperphosphataemia<br>subjects affected / exposed<br>occurrences (all)      | 1 / 12 (8.33%)<br>1 | 0 / 16 (0.00%)<br>0 | 0 / 20 (0.00%)<br>0  |
| Hypokalaemia<br>subjects affected / exposed<br>occurrences (all)            | 0 / 12 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 0 / 20 (0.00%)<br>0  |

| <b>Non-serious adverse events</b>   | Cohort 4: DS-1040<br>80 mg | Cohort 5: DS-1040b<br>40 mg | Placebo             |
|---|----------------------------|-----------------------------|---------------------|
| Total subjects affected by non-serious<br>adverse events<br>subjects affected / exposed | 10 / 22 (45.45%)           | 8 / 17 (47.06%)             | 25 / 38 (65.79%)    |
| Neoplasms benign, malignant and<br>unspecified (incl cysts and polyps)                  |                            |                             |                     |
| Metastases to nervous system<br>subjects affected / exposed<br>occurrences (all)        | 0 / 22 (0.00%)<br>0        | 0 / 17 (0.00%)<br>0         | 0 / 38 (0.00%)<br>0 |
| Testicular cancer metastatic<br>subjects affected / exposed<br>occurrences (all)        | 0 / 22 (0.00%)<br>0        | 0 / 17 (0.00%)<br>0         | 0 / 38 (0.00%)<br>0 |
| Vascular disorders  |                            |                             |                     |
| Circulatory collapse<br>subjects affected / exposed<br>occurrences (all)                | 0 / 22 (0.00%)<br>0        | 1 / 17 (5.88%)<br>1         | 0 / 38 (0.00%)<br>0 |
| Deep vein thrombosis<br>subjects affected / exposed<br>occurrences (all)                | 0 / 22 (0.00%)<br>0        | 0 / 17 (0.00%)<br>0         | 1 / 38 (2.63%)<br>1 |
| Haemorrhage<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 22 (0.00%)<br>0        | 0 / 17 (0.00%)<br>0         | 1 / 38 (2.63%)<br>1 |
| Hypertension  |                            |                             |                     |



|   |                     |                     |                     |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)  | 0 / 22 (0.00%)<br>0 | 0 / 17 (0.00%)<br>0 | 0 / 38 (0.00%)<br>0 |
| Hypotension<br>subjects affected / exposed<br>occurrences (all)   | 0 / 22 (0.00%)<br>0 | 0 / 17 (0.00%)<br>0 | 0 / 38 (0.00%)<br>0 |
| Surgical and medical procedures<br>Sinus operation<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 22 (0.00%)<br>0 | 0 / 17 (0.00%)<br>0 | 1 / 38 (2.63%)<br>1 |
| General disorders and administration<br>site conditions<br>Chest pain<br>subjects affected / exposed<br>occurrences (all) | 0 / 22 (0.00%)<br>0 | 0 / 17 (0.00%)<br>0 | 0 / 38 (0.00%)<br>0 |
| Feeling cold<br>subjects affected / exposed<br>occurrences (all)  | 1 / 22 (4.55%)<br>1 | 0 / 17 (0.00%)<br>0 | 0 / 38 (0.00%)<br>0 |
| Feeling hot<br>subjects affected / exposed<br>occurrences (all)   | 0 / 22 (0.00%)<br>0 | 0 / 17 (0.00%)<br>0 | 1 / 38 (2.63%)<br>1 |
| Infusion site extravasation<br>subjects affected / exposed<br>occurrences (all)   | 1 / 22 (4.55%)<br>1 | 0 / 17 (0.00%)<br>0 | 0 / 38 (0.00%)<br>0 |
| Infusion site phlebitis<br>subjects affected / exposed<br>occurrences (all)   | 0 / 22 (0.00%)<br>0 | 0 / 17 (0.00%)<br>0 | 0 / 38 (0.00%)<br>0 |
| Malaise<br>subjects affected / exposed<br>occurrences (all)   | 0 / 22 (0.00%)<br>0 | 0 / 17 (0.00%)<br>0 | 0 / 38 (0.00%)<br>0 |
| Non-cardiac chest pain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 22 (0.00%)<br>0 | 0 / 17 (0.00%)<br>0 | 2 / 38 (5.26%)<br>2 |
| Peripheral swelling<br>subjects affected / exposed<br>occurrences (all)   | 0 / 22 (0.00%)<br>0 | 0 / 17 (0.00%)<br>0 | 0 / 38 (0.00%)<br>0 |
| Pyrexia   |                     |                     |                     |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 22 (0.00%) | 1 / 17 (5.88%) | 0 / 38 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0              |
| Vessel puncture site haematoma                  |                |                |                |
| subjects affected / exposed                     | 1 / 22 (4.55%) | 0 / 17 (0.00%) | 0 / 38 (0.00%) |
| occurrences (all)                               | 1              | 0              | 0              |
| Reproductive system and breast disorders        |                |                |                |
| Endometrial hyperplasia                         |                |                |                |
| subjects affected / exposed                     | 1 / 22 (4.55%) | 0 / 17 (0.00%) | 0 / 38 (0.00%) |
| occurrences (all)                               | 1              | 0              | 0              |
| Gynaecomastia                                   |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 1 / 17 (5.88%) | 0 / 38 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0              |
| Vaginal haemorrhage                             |                |                |                |
| subjects affected / exposed                     | 1 / 22 (4.55%) | 0 / 17 (0.00%) | 0 / 38 (0.00%) |
| occurrences (all)                               | 1              | 0              | 0              |
| Respiratory, thoracic and mediastinal disorders |                |                |                |
| Cough   |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 17 (0.00%) | 0 / 38 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Dyspnoea  |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 17 (0.00%) | 0 / 38 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Epistaxis                                       |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 17 (0.00%) | 3 / 38 (7.89%) |
| occurrences (all)                               | 0              | 0              | 3              |
| Haemoptysis                                     |                |                |                |
| subjects affected / exposed                     | 1 / 22 (4.55%) | 1 / 17 (5.88%) | 3 / 38 (7.89%) |
| occurrences (all)                               | 1              | 1              | 3              |
| Hyperventilation                                |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 17 (0.00%) | 0 / 38 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Pleural effusion                                |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 1 / 17 (5.88%) | 2 / 38 (5.26%) |
| occurrences (all)                               | 0              | 1              | 2              |
| Pleurisy  |                |                |                |

|                                      |                |                |                |
|--------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed          | 0 / 22 (0.00%) | 1 / 17 (5.88%) | 0 / 38 (0.00%) |
| occurrences (all)                    | 0              | 1              | 0              |
| Pulmonary embolism                   |                |                |                |
| subjects affected / exposed          | 0 / 22 (0.00%) | 0 / 17 (0.00%) | 0 / 38 (0.00%) |
| occurrences (all)                    | 0              | 0              | 0              |
| Pulmonary infarction                 |                |                |                |
| subjects affected / exposed          | 1 / 22 (4.55%) | 1 / 17 (5.88%) | 1 / 38 (2.63%) |
| occurrences (all)                    | 1              | 1              | 1              |
| Psychiatric disorders                |                |                |                |
| Anxiety                              |                |                |                |
| subjects affected / exposed          | 0 / 22 (0.00%) | 0 / 17 (0.00%) | 0 / 38 (0.00%) |
| occurrences (all)                    | 0              | 0              | 0              |
| Delirium                             |                |                |                |
| subjects affected / exposed          | 0 / 22 (0.00%) | 0 / 17 (0.00%) | 1 / 38 (2.63%) |
| occurrences (all)                    | 0              | 0              | 1              |
| Depression                           |                |                |                |
| subjects affected / exposed          | 0 / 22 (0.00%) | 1 / 17 (5.88%) | 1 / 38 (2.63%) |
| occurrences (all)                    | 0              | 1              | 1              |
| Investigations                       |                |                |                |
| Aspartate aminotransferase increased |                |                |                |
| subjects affected / exposed          | 1 / 22 (4.55%) | 0 / 17 (0.00%) | 1 / 38 (2.63%) |
| occurrences (all)                    | 1              | 0              | 1              |
| Blood pressure increased             |                |                |                |
| subjects affected / exposed          | 0 / 22 (0.00%) | 0 / 17 (0.00%) | 0 / 38 (0.00%) |
| occurrences (all)                    | 0              | 0              | 0              |
| Crystal urine present                |                |                |                |
| subjects affected / exposed          | 1 / 22 (4.55%) | 0 / 17 (0.00%) | 0 / 38 (0.00%) |
| occurrences (all)                    | 1              | 0              | 0              |
| Electrocardiogram QT prolonged       |                |                |                |
| subjects affected / exposed          | 0 / 22 (0.00%) | 0 / 17 (0.00%) | 1 / 38 (2.63%) |
| occurrences (all)                    | 0              | 0              | 1              |
| Electrocardiogram T wave inversion   |                |                |                |
| subjects affected / exposed          | 1 / 22 (4.55%) | 0 / 17 (0.00%) | 0 / 38 (0.00%) |
| occurrences (all)                    | 1              | 0              | 0              |
| Electrocardiogram abnormal           |                |                |                |

|   |                     |                     |                     |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)                                    | 0 / 22 (0.00%)<br>0 | 0 / 17 (0.00%)<br>0 | 0 / 38 (0.00%)<br>0 |
| Liver function test increased<br>subjects affected / exposed<br>occurrences (all)   | 0 / 22 (0.00%)<br>0 | 0 / 17 (0.00%)<br>0 | 1 / 38 (2.63%)<br>1 |
| Mean cell volume increased<br>subjects affected / exposed<br>occurrences (all)      | 1 / 22 (4.55%)<br>1 | 0 / 17 (0.00%)<br>0 | 0 / 38 (0.00%)<br>0 |
| Occult blood positive<br>subjects affected / exposed<br>occurrences (all)           | 0 / 22 (0.00%)<br>0 | 0 / 17 (0.00%)<br>0 | 1 / 38 (2.63%)<br>1 |
| Urobilinogen urine increased<br>subjects affected / exposed<br>occurrences (all)    | 1 / 22 (4.55%)<br>1 | 0 / 17 (0.00%)<br>0 | 0 / 38 (0.00%)<br>0 |
| Injury, poisoning and procedural complications                                      |                     |                     |                     |
| Clavicle fracture<br>subjects affected / exposed<br>occurrences (all)               | 0 / 22 (0.00%)<br>0 | 0 / 17 (0.00%)<br>0 | 1 / 38 (2.63%)<br>1 |
| Skin abrasion<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 22 (0.00%)<br>0 | 0 / 17 (0.00%)<br>0 | 1 / 38 (2.63%)<br>1 |
| Synovial rupture<br>subjects affected / exposed<br>occurrences (all)                | 1 / 22 (4.55%)<br>1 | 0 / 17 (0.00%)<br>0 | 0 / 38 (0.00%)<br>0 |
| Urinary retention postoperative<br>subjects affected / exposed<br>occurrences (all) | 0 / 22 (0.00%)<br>0 | 0 / 17 (0.00%)<br>0 | 0 / 38 (0.00%)<br>0 |
| Cardiac disorders   |                     |                     |                     |
| Atrial fibrillation<br>subjects affected / exposed<br>occurrences (all)             | 0 / 22 (0.00%)<br>0 | 1 / 17 (5.88%)<br>1 | 0 / 38 (0.00%)<br>0 |
| Bundle branch block right<br>subjects affected / exposed<br>occurrences (all)       | 0 / 22 (0.00%)<br>0 | 1 / 17 (5.88%)<br>1 | 0 / 38 (0.00%)<br>0 |
| Right ventricular dysfunction   |                     |                     |                     |

|                                      |                |                |                |
|--------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed          | 1 / 22 (4.55%) | 0 / 17 (0.00%) | 0 / 38 (0.00%) |
| occurrences (all)                    | 1              | 0              | 0              |
| Sinus tachycardia                    |                |                |                |
| subjects affected / exposed          | 0 / 22 (0.00%) | 0 / 17 (0.00%) | 1 / 38 (2.63%) |
| occurrences (all)                    | 0              | 0              | 1              |
| Nervous system disorders             |                |                |                |
| Dizziness                            |                |                |                |
| subjects affected / exposed          | 0 / 22 (0.00%) | 0 / 17 (0.00%) | 1 / 38 (2.63%) |
| occurrences (all)                    | 0              | 0              | 1              |
| Haemorrhage intracranial             |                |                |                |
| subjects affected / exposed          | 0 / 22 (0.00%) | 0 / 17 (0.00%) | 0 / 38 (0.00%) |
| occurrences (all)                    | 0              | 0              | 0              |
| Headache                             |                |                |                |
| subjects affected / exposed          | 2 / 22 (9.09%) | 0 / 17 (0.00%) | 0 / 38 (0.00%) |
| occurrences (all)                    | 2              | 0              | 0              |
| Lethargy                             |                |                |                |
| subjects affected / exposed          | 0 / 22 (0.00%) | 0 / 17 (0.00%) | 1 / 38 (2.63%) |
| occurrences (all)                    | 0              | 0              | 1              |
| Migraine                             |                |                |                |
| subjects affected / exposed          | 0 / 22 (0.00%) | 0 / 17 (0.00%) | 0 / 38 (0.00%) |
| occurrences (all)                    | 0              | 0              | 0              |
| Muscle spasticity                    |                |                |                |
| subjects affected / exposed          | 0 / 22 (0.00%) | 0 / 17 (0.00%) | 1 / 38 (2.63%) |
| occurrences (all)                    | 0              | 0              | 1              |
| Presyncope                           |                |                |                |
| subjects affected / exposed          | 0 / 22 (0.00%) | 0 / 17 (0.00%) | 0 / 38 (0.00%) |
| occurrences (all)                    | 0              | 0              | 0              |
| Tremor                               |                |                |                |
| subjects affected / exposed          | 0 / 22 (0.00%) | 0 / 17 (0.00%) | 1 / 38 (2.63%) |
| occurrences (all)                    | 0              | 0              | 1              |
| Blood and lymphatic system disorders |                |                |                |
| Anaemia                              |                |                |                |
| subjects affected / exposed          | 0 / 22 (0.00%) | 0 / 17 (0.00%) | 1 / 38 (2.63%) |
| occurrences (all)                    | 0              | 0              | 1              |
| Microcytic anaemia                   |                |                |                |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 22 (0.00%)<br>0 | 0 / 17 (0.00%)<br>0 | 0 / 38 (0.00%)<br>0 |
| Ear and labyrinth disorders                      |                     |                     |                     |
| Tinnitus   |                     |                     |                     |
| subjects affected / exposed                      | 0 / 22 (0.00%)      | 0 / 17 (0.00%)      | 0 / 38 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Vertigo  |                     |                     |                     |
| subjects affected / exposed                      | 0 / 22 (0.00%)      | 0 / 17 (0.00%)      | 1 / 38 (2.63%)      |
| occurrences (all)                                | 0                   | 0                   | 1                   |
| Eye disorders                                    |                     |                     |                     |
| Vision blurred                                   |                     |                     |                     |
| subjects affected / exposed                      | 0 / 22 (0.00%)      | 0 / 17 (0.00%)      | 0 / 38 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Gastrointestinal disorders                       |                     |                     |                     |
| Abdominal discomfort                             |                     |                     |                     |
| subjects affected / exposed                      | 0 / 22 (0.00%)      | 0 / 17 (0.00%)      | 0 / 38 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Abdominal distension                             |                     |                     |                     |
| subjects affected / exposed                      | 0 / 22 (0.00%)      | 0 / 17 (0.00%)      | 0 / 38 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Abdominal pain                                   |                     |                     |                     |
| subjects affected / exposed                      | 0 / 22 (0.00%)      | 0 / 17 (0.00%)      | 0 / 38 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Anal haemorrhage                                 |                     |                     |                     |
| subjects affected / exposed                      | 0 / 22 (0.00%)      | 0 / 17 (0.00%)      | 0 / 38 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Constipation                                     |                     |                     |                     |
| subjects affected / exposed                      | 1 / 22 (4.55%)      | 0 / 17 (0.00%)      | 0 / 38 (0.00%)      |
| occurrences (all)                                | 1                   | 0                   | 0                   |
| Diarrhoea  |                     |                     |                     |
| subjects affected / exposed                      | 0 / 22 (0.00%)      | 0 / 17 (0.00%)      | 0 / 38 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Faeces discoloured                               |                     |                     |                     |
| subjects affected / exposed                      | 0 / 22 (0.00%)      | 0 / 17 (0.00%)      | 0 / 38 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Nausea   |                     |                     |                     |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)   | 0 / 22 (0.00%)<br>0 | 0 / 17 (0.00%)<br>0 | 1 / 38 (2.63%)<br>1 |
| Paraesthesia oral<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 22 (0.00%)<br>0 | 0 / 17 (0.00%)<br>0 | 0 / 38 (0.00%)<br>0 |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)   | 0 / 22 (0.00%)<br>0 | 0 / 17 (0.00%)<br>0 | 0 / 38 (0.00%)<br>0 |
| Hepatobiliary disorders<br>Hepatocellular injury<br>subjects affected / exposed<br>occurrences (all)     | 0 / 22 (0.00%)<br>0 | 0 / 17 (0.00%)<br>0 | 0 / 38 (0.00%)<br>0 |
| Hypertransaminasaemia<br>subjects affected / exposed<br>occurrences (all)                                | 1 / 22 (4.55%)<br>1 | 0 / 17 (0.00%)<br>0 | 1 / 38 (2.63%)<br>1 |
| Skin and subcutaneous tissue disorders<br>Ecchymosis<br>subjects affected / exposed<br>occurrences (all) | 0 / 22 (0.00%)<br>0 | 0 / 17 (0.00%)<br>0 | 0 / 38 (0.00%)<br>0 |
| Night sweats<br>subjects affected / exposed<br>occurrences (all)   | 1 / 22 (4.55%)<br>1 | 0 / 17 (0.00%)<br>0 | 0 / 38 (0.00%)<br>0 |
| Rash<br>subjects affected / exposed<br>occurrences (all)   | 0 / 22 (0.00%)<br>0 | 0 / 17 (0.00%)<br>0 | 1 / 38 (2.63%)<br>1 |
| Renal and urinary disorders<br>Dysuria<br>subjects affected / exposed<br>occurrences (all)               | 0 / 22 (0.00%)<br>0 | 0 / 17 (0.00%)<br>0 | 1 / 38 (2.63%)<br>1 |
| Haematuria<br>subjects affected / exposed<br>occurrences (all)   | 0 / 22 (0.00%)<br>0 | 0 / 17 (0.00%)<br>0 | 0 / 38 (0.00%)<br>0 |
| Ketonuria<br>subjects affected / exposed<br>occurrences (all)  | 1 / 22 (4.55%)<br>1 | 0 / 17 (0.00%)<br>0 | 0 / 38 (0.00%)<br>0 |
| Proteinuria  |                     |                     |                     |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 22 (4.55%) | 0 / 17 (0.00%) | 0 / 38 (0.00%) |
| occurrences (all)                               | 1              | 0              | 0              |
| Urine abnormality                               |                |                |                |
| subjects affected / exposed                     | 1 / 22 (4.55%) | 0 / 17 (0.00%) | 0 / 38 (0.00%) |
| occurrences (all)                               | 1              | 0              | 0              |
| Musculoskeletal and connective tissue disorders |                |                |                |
| Arthralgia                                      |                |                |                |
| subjects affected / exposed                     | 1 / 22 (4.55%) | 0 / 17 (0.00%) | 2 / 38 (5.26%) |
| occurrences (all)                               | 1              | 0              | 2              |
| Arthritis                                       |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 17 (0.00%) | 0 / 38 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Back pain                                       |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 17 (0.00%) | 1 / 38 (2.63%) |
| occurrences (all)                               | 0              | 0              | 1              |
| Bursitis  |                |                |                |
| subjects affected / exposed                     | 1 / 22 (4.55%) | 0 / 17 (0.00%) | 0 / 38 (0.00%) |
| occurrences (all)                               | 1              | 0              | 0              |
| Groin pain                                      |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 17 (0.00%) | 1 / 38 (2.63%) |
| occurrences (all)                               | 0              | 0              | 1              |
| Muscle contracture                              |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 1 / 17 (5.88%) | 0 / 38 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0              |
| Musculoskeletal discomfort                      |                |                |                |
| subjects affected / exposed                     | 1 / 22 (4.55%) | 0 / 17 (0.00%) | 0 / 38 (0.00%) |
| occurrences (all)                               | 1              | 0              | 0              |
| Pain in extremity                               |                |                |                |
| subjects affected / exposed                     | 1 / 22 (4.55%) | 0 / 17 (0.00%) | 2 / 38 (5.26%) |
| occurrences (all)                               | 1              | 0              | 2              |
| Spinal pain                                     |                |                |                |
| subjects affected / exposed                     | 0 / 22 (0.00%) | 0 / 17 (0.00%) | 1 / 38 (2.63%) |
| occurrences (all)                               | 0              | 0              | 1              |
| Infections and infestations                     |                |                |                |



|                                    |                |                 |                |
|------------------------------------|----------------|-----------------|----------------|
| Abscess limb                       |                |                 |                |
| subjects affected / exposed        | 1 / 22 (4.55%) | 0 / 17 (0.00%)  | 0 / 38 (0.00%) |
| occurrences (all)                  | 1              | 0               | 0              |
| Anal abscess                       |                |                 |                |
| subjects affected / exposed        | 0 / 22 (0.00%) | 0 / 17 (0.00%)  | 0 / 38 (0.00%) |
| occurrences (all)                  | 0              | 0               | 0              |
| Appendicitis                       |                |                 |                |
| subjects affected / exposed        | 0 / 22 (0.00%) | 0 / 17 (0.00%)  | 0 / 38 (0.00%) |
| occurrences (all)                  | 0              | 0               | 0              |
| Bacteriuria                        |                |                 |                |
| subjects affected / exposed        | 1 / 22 (4.55%) | 0 / 17 (0.00%)  | 0 / 38 (0.00%) |
| occurrences (all)                  | 1              | 0               | 0              |
| Infection                          |                |                 |                |
| subjects affected / exposed        | 0 / 22 (0.00%) | 0 / 17 (0.00%)  | 1 / 38 (2.63%) |
| occurrences (all)                  | 0              | 0               | 1              |
| Lung infection                     |                |                 |                |
| subjects affected / exposed        | 0 / 22 (0.00%) | 0 / 17 (0.00%)  | 2 / 38 (5.26%) |
| occurrences (all)                  | 0              | 0               | 2              |
| Oral fungal infection              |                |                 |                |
| subjects affected / exposed        | 0 / 22 (0.00%) | 1 / 17 (5.88%)  | 0 / 38 (0.00%) |
| occurrences (all)                  | 0              | 1               | 0              |
| Pneumonia                          |                |                 |                |
| subjects affected / exposed        | 0 / 22 (0.00%) | 2 / 17 (11.76%) | 0 / 38 (0.00%) |
| occurrences (all)                  | 0              | 2               | 0              |
| Respiratory tract infection        |                |                 |                |
| subjects affected / exposed        | 0 / 22 (0.00%) | 0 / 17 (0.00%)  | 0 / 38 (0.00%) |
| occurrences (all)                  | 0              | 0               | 0              |
| Urinary tract infection            |                |                 |                |
| subjects affected / exposed        | 0 / 22 (0.00%) | 0 / 17 (0.00%)  | 2 / 38 (5.26%) |
| occurrences (all)                  | 0              | 0               | 2              |
| Metabolism and nutrition disorders |                |                 |                |
| Folate deficiency                  |                |                 |                |
| subjects affected / exposed        | 0 / 22 (0.00%) | 1 / 17 (5.88%)  | 0 / 38 (0.00%) |
| occurrences (all)                  | 0              | 1               | 0              |
| Hyperphosphataemia                 |                |                 |                |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 17 (0.00%) | 0 / 38 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Hypokalaemia                |                |                |                |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 17 (5.88%) | 1 / 38 (2.63%) |
| occurrences (all)           | 0              | 1              | 1              |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment   |
|-----------------|---|
| 10 March 2016   | Included information on assessment of the cardiac biomarkers troponin and NT-proBNP, added information regarding stopping the study due to excessive mortality rates or incidence of major bleeding, and included instruction on recording RV/LV ratio at baseline  |
| 09 January 2017 | Updated details of administration of edoxaban; stated changes made for measuring total thrombus volume; clarified definitions for clinically relevant bleeding, highly effective contraception, and venous thromboembolism; updated procedures for subject enrollment; clarified inclusion and exclusion criteria, updated protocol for disposal of Investigational Product |
| 26 April 2017   | Updated inclusion and exclusion criteria, clarified the details for the supply of edoxaban, specified details of the administration of enoxaparin, and updated the documentation procedure for adverse events   |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported