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
Arm title	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

Arm title	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	
Arm title	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	
Arm title	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	
Arm title	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

Arm title	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

Number of subjects in period 1	Cohort 1: DS-1040b 20 mg	Cohort 2: DS-1040b 40 mg	Cohort 3: DS-1040b 60 mg
Started	12	16	23
Treated	12	16	20
Completed	12	15	20
Not completed	0	1	3

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:	
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.	

Reporting group values	Cohort 1: DS-1040b 20 mg	Cohort 2: DS-1040b 40 mg	Cohort 3: DS-1040b 60 mg
Number of subjects	12	16	23
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 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 Units: years			
arithmetic mean	56.1	62.1	55.1
standard deviation	± 16.3	± 10.9	± 17.5
Gender categorical Units: Subjects			
Female	4	8	5
Male	8	8	18

Reporting group values	Cohort 4: DS-1040 80 mg	Cohort 5: DS-1040b 40 mg	Placebo
Number of subjects	23	22	38
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 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 Units: years			
arithmetic mean	55.0	56.5	58.3
standard deviation	± 13.5	± 9.8	± 10.7
Gender categorical Units: Subjects			
Female	8	7	12
Male	15	15	26

Reporting group values	Total		
Number of subjects	134		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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 65-84 years	48		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	44		
Male	90		

End points 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.	

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[1]
End point description:	
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:	
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 ≥2g/dL, transfusion ≥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 ≥2g/dL, transfusion ≥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[2]

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[3]

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)

End point values	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 (± 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[4]

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.

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	9	13	18	5
Units: hours				
arithmetic mean (standard deviation)				
Terminal half-life	22.81 (± 3.13)	28.44 (± 5.75)	29.06 (± 7.60)	36.39 (± 2.07)

End point values	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 (± 3.45)			

Statistical analyses

No statistical analyses for this end point

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 20 mg	Cohort 2: DS-1040b 40 mg	Cohort 3: DS-1040b 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)			
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 / 20 (0.00%)

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

Serious adverse events	Cohort 4: DS-1040 80 mg	Cohort 5: DS-1040b 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 %

Non-serious adverse events	Cohort 1: DS-1040b 20 mg	Cohort 2: DS-1040b 40 mg	Cohort 3: DS-1040b 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			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Non-cardiac chest pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Peripheral swelling			
subjects affected / exposed	0 / 12 (0.00%)	1 / 16 (6.25%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Vessel puncture site haematoma			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	0 / 20 (0.00%)
occurrences (all)	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 (all)	0	0	0
Gynaecomastia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Vaginal haemorrhage			
subjects affected / exposed	1 / 12 (8.33%)	0 / 16 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 12 (8.33%)	0 / 16 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Dyspnoea			
subjects affected / exposed	0 / 12 (0.00%)	1 / 16 (6.25%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Epistaxis			
subjects affected / exposed	2 / 12 (16.67%)	2 / 16 (12.50%)	2 / 20 (10.00%)
occurrences (all)	2	2	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	0 / 12 (0.00%)	0 / 16 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	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	0 / 12 (0.00%)	0 / 16 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Tremor			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Microcytic anaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 16 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Vertigo			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 12 (0.00%)	1 / 16 (6.25%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Abdominal distension			
subjects affected / exposed	0 / 12 (0.00%)	1 / 16 (6.25%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Abdominal pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 16 (6.25%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Anal haemorrhage			
subjects affected / exposed	1 / 12 (8.33%)	0 / 16 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	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			

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			
subjects affected / exposed	0 / 12 (0.00%)	1 / 16 (6.25%)	2 / 20 (10.00%)
occurrences (all)	0	1	2
Metabolism and nutrition disorders			
Folate deficiency			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Hyperphosphataemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 16 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Hypokalaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 16 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0

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

subjects affected / exposed	0 / 22 (0.00%)	0 / 17 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Hypotension			
subjects affected / exposed	0 / 22 (0.00%)	0 / 17 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Surgical and medical procedures			
Sinus operation			
subjects affected / exposed	0 / 22 (0.00%)	0 / 17 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 17 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Feeling cold			
subjects affected / exposed	1 / 22 (4.55%)	0 / 17 (0.00%)	0 / 38 (0.00%)
occurrences (all)	1	0	0
Feeling hot			
subjects affected / exposed	0 / 22 (0.00%)	0 / 17 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
Infusion site extravasation			
subjects affected / exposed	1 / 22 (4.55%)	0 / 17 (0.00%)	0 / 38 (0.00%)
occurrences (all)	1	0	0
Infusion site phlebitis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 17 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	0 / 22 (0.00%)	0 / 17 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 17 (0.00%)	2 / 38 (5.26%)
occurrences (all)	0	0	2
Peripheral swelling			
subjects affected / exposed	0 / 22 (0.00%)	0 / 17 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	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	0 / 22 (0.00%)	0 / 17 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Liver function test increased			
subjects affected / exposed	0 / 22 (0.00%)	0 / 17 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
Mean cell volume increased			
subjects affected / exposed	1 / 22 (4.55%)	0 / 17 (0.00%)	0 / 38 (0.00%)
occurrences (all)	1	0	0
Occult blood positive			
subjects affected / exposed	0 / 22 (0.00%)	0 / 17 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
Urobilinogen urine increased			
subjects affected / exposed	1 / 22 (4.55%)	0 / 17 (0.00%)	0 / 38 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	0 / 22 (0.00%)	0 / 17 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
Skin abrasion			
subjects affected / exposed	0 / 22 (0.00%)	0 / 17 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
Synovial rupture			
subjects affected / exposed	1 / 22 (4.55%)	0 / 17 (0.00%)	0 / 38 (0.00%)
occurrences (all)	1	0	0
Urinary retention postoperative			
subjects affected / exposed	0 / 22 (0.00%)	0 / 17 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 22 (0.00%)	1 / 17 (5.88%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Bundle branch block right			
subjects affected / exposed	0 / 22 (0.00%)	1 / 17 (5.88%)	0 / 38 (0.00%)
occurrences (all)	0	1	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	0 / 22 (0.00%)	0 / 17 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	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	0 / 22 (0.00%)	0 / 17 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
Paraesthesia oral			
subjects affected / exposed	0 / 22 (0.00%)	0 / 17 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 22 (0.00%)	0 / 17 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Hepatocellular injury			
subjects affected / exposed	0 / 22 (0.00%)	0 / 17 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Hypertransaminasaemia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 17 (0.00%)	1 / 38 (2.63%)
occurrences (all)	1	0	1
Skin and subcutaneous tissue disorders			
Ecchymosis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 17 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Night sweats			
subjects affected / exposed	1 / 22 (4.55%)	0 / 17 (0.00%)	0 / 38 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	0 / 22 (0.00%)	0 / 17 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 22 (0.00%)	0 / 17 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
Haematuria			
subjects affected / exposed	0 / 22 (0.00%)	0 / 17 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Ketonuria			
subjects affected / exposed	1 / 22 (4.55%)	0 / 17 (0.00%)	0 / 38 (0.00%)
occurrences (all)	1	0	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			

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:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported