Clinical trial results:
Open label, single arm safety prospective cohort study of dabigatran etexilate for secondary prevention of venous thromboembolism in children from 0 to less than 18 years

Summary

EudraCT number	2014-000583-18
Trial protocol	ES FI AT GR IT LT CZ BE SK SE BG FR HU DK DE
Global end of trial date	19 November 2019

Results information

Result version number	v1 (current)
This version publication date	23 May 2020
First version publication date	23 May 2020

Trial information

Trial identification

Sponsor protocol code	1160.108

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02197416
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	Boehringer Ingelheim Call Center, Boehringer Ingelheim, +1 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim Call Center, Boehringer Ingelheim, +1 8002430127, clintriage.rdg@boehringer-ingelheim.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000081-PIP01-11
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 December 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 October 2019
Global end of trial reached?	Yes
Global end of trial date	19 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this paediatric prospective cohort trial is to assess the safety of dabigatran etexilate for secondary prevention of venous thromboembolism in children from 0 to less than 18 years of age.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. Rescue medication was allowed for all patients as required.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 May 2015
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	Taiwan: 1
Country: Number of subjects enrolled	Thailand: 2
Country: Number of subjects enrolled	Czech Republic: 24
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	Lithuania: 5
Country: Number of subjects enrolled	Russian Federation: 59
Country: Number of subjects enrolled	Turkey: 17
Country: Number of subjects enrolled	Ukraine: 5
Country: Number of subjects enrolled	Brazil: 6
Country: Number of subjects enrolled	Mexico: 3
Country: Number of subjects enrolled	Canada: 17
Country: Number of subjects enrolled	United States: 29
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Italy: 16
Country: Number of subjects enrolled	Norway: 6

Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	Switzerland: 3
Country: Number of subjects enrolled	Israel: 3
Worldwide total number of subjects	231
EEA total number of subjects	86

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)	12
Children (2-11 years)	45
Adolescents (12-17 years)	174
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This open label, single arm prospective cohort study was designed to assess the safety of dabigatran etexilate (DE) for secondary prevention of paediatric venous thromboembolism (VTE) with 12-month (365 days) treatment period followed by 28 days end of treatment follow-up. Results of participants were reported via 3 mutually exclusive age groups.

Pre-assignment

Screening details:

All subjects were screened for eligibility prior to participation in the trial. Subjects attended a specialist site which ensured that they (the subjects) strictly met all inclusion and none of the exclusion criteria. 1 enrolled subject was withdrawn before treated due to unable to swallow the capsules.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	dabigatran etexilate (0 to < 2 years)

Arm description:

Single oral dose of dabigatran etexilate (DE) oral liquid formulation (OLF) ranging from 6.25 milligram(mg) to 143.75mg was administrated twice daily in the morning and evening for participants aged less than 12 months. Single oral dose of DE pellets ranging from 20mg to 330mg was administrated twice daily in the morning and evening for participants aged less than 8 years. Dosage of DE was adjusted by age and weight of participants intending to achieve trough plasma dabigatran concentrations between 50 and <250 nanogram(ng)/mL. The DE dose limit was 22.2 mg/kilogram (kg)/day.The maximal DE single dose was 330 mg. This arm includes participants aged between 0 to <2

Arm type	Experimental
Investigational medicinal product name	Dabigatran etexilate pellets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Single oral dose of DE pellets ranging from 20mg to 330mg was administrated twice daily in the morning and evening for participants aged less than 8 years. Dosage of DE was adjusted by age and weight of participants. Granules stands for pellets.

Investigational medicinal product name	Dabigatran etexilate oral liquid formulation
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

Single oral dose of dabigatran etexilate (DE) oral liquid formulation (OLF) ranging from 6.25 milligram(mg) to 143.75mg was administrated twice daily in the morning and evening for participants aged less than 12 months .Dosage of DE was adjusted by age and weight of participants.

Arm title	dabigatran etexilate (2 to <12 years)

Arm description:

Single oral dose of DE pellets ranging from 20mg to 330mg was administrated twice daily in the morning and evening for participants aged less than 8 years and who cannot take capsules between 8 to <12 years. Single oral dose of DE capsule ranging from 50 mg to 330mg was administrated twice daily in the morning and evening for participants aged at least 8 years. Dosage of DE was adjusted by age

and weight of participants intending to achieve trough plasma dabigatran concentrations between 50 and <250 ng/mL. The DE dose limit was 22.2 mg/kg/day.The maximal DE single dose was 330 mg. This arm includes participants aged between 2 to <12 years.

Arm type	Experimental
Investigational medicinal product name	Dabigatran etexilate capsules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Single oral dose of DE capsule ranging from 50 mg to 330mg was administrated twice daily in the morning and evening for participants aged at least 8 years. Dosage of DE was adjusted by age and weight of participants

Investigational medicinal product name	Dabigatran etexilate pellets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Single oral dose of DE pellets ranging from 20mg to 330mg was administrated twice daily in the morning and evening for participants aged less than 8 years and who cannot take capsules between 8 to <12 years. Dosage of DE was adjusted by age and weight of participants. Granules stands for pellets.

Arm title	dabigatran etexilate (12 to <18 years)

Arm description:

Single oral dose of DE capsule ranging from 50 mg to 330mg was administrated twice daily in the morning and evening for participants aged at least 8 years. Dosage of DE was adjusted by age and weight of participants intending to achieve trough plasma dabigatran concentrations between 50 and <250 ng/mL. The DE dose limit was 22.2 mg/kg/day.The maximal DE single dose was 330 mg. This arm includes participants aged between 12 to <18 years.

Arm type	Experimental
Investigational medicinal product name	Dabigatran etexilate capsules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Single oral dose of DE capsule ranging from 50 mg to 330mg was administrated twice daily in the morning and evening for participants aged at least 8 years. Dosage of DE was adjusted by age and weight of participants.

Number of subjects in period 1[1]	dabigatran etexilate (0 to < 2 years)	dabigatran etexilate (2 to <12 years)	dabigatran etexilate (12 to <18 years)
Started	9	43	161
Completed	8	39	153
Not completed	1	4	8
Consent withdrawn by subject	-	2	1
Adverse event, non-fatal	-	-	1
Other reasons	-	2	5
Protocol deviation	1	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The enrolled set included all patients with signed informed consent. The enrolled set was used for disposition summaries. The baseline characteristic were reported on the entered set including all patients with signed informed consent who were eligible to enter the trial, regardless whether they took trial medication.

Baseline characteristics

Reporting groups	
Reporting group title	dabigatran etexilate (0 to < 2 years)
Reporting group description:	
Single oral dose of dabigatran etexilate (DE) oral liquid formulation (OLF) ranging from 6.25 milligram(mg) to 143.75mg was administrated twice daily in the morning and evening for participants aged less than 12 months. Single oral dose of DE pellets ranging from 20mg to 330mg was administrated twice daily in the morning and evening for participants aged less than 8 years. Dosage of DE was adjusted by age and weight of participants intending to achieve trough plasma dabigatran concentrations between 50 and <250 nanogram(ng)/mL. The DE dose limit was 22.2 mg/kilogram (kg)/day.The maximal DE single dose was 330 mg. This arm includes participants aged between 0 to <2	
Reporting group title	dabigatran etexilate (2 to <12 years)
Reporting group description:	
Single oral dose of DE pellets ranging from 20mg to 330mg was administrated twice daily in the morning and evening for participants aged less than 8 years and who cannot take capsules between 8 to <12 years. Single oral dose of DE capsule ranging from 50 mg to 330mg was administrated twice daily in the morning and evening for participants aged at least 8 years. Dosage of DE was adjusted by age and weight of participants intending to achieve trough plasma dabigatran concentrations between 50 and <250 ng/mL. The DE dose limit was 22.2 mg/kg/day.The maximal DE single dose was 330 mg. This arm includes participants aged between 2 to <12 years.	
Reporting group title	dabigatran etexilate (12 to <18 years)
Reporting group description:	
Single oral dose of DE capsule ranging from 50 mg to 330mg was administrated twice daily in the morning and evening for participants aged at least 8 years. Dosage of DE was adjusted by age and weight of participants intending to achieve trough plasma dabigatran concentrations between 50 and <250 ng/mL. The DE dose limit was 22.2 mg/kg/day.The maximal DE single dose was 330 mg. This arm includes participants aged between 12 to <18 years.	

Reporting group values	dabigatran etexilate (0 to < 2 years)	dabigatran etexilate (2 to <12 years)	dabigatran etexilate (12 to <18 years)
Number of subjects	9	43	161
Age categorical			
The treated set (TS) included all patients who were dispensed trial medication and were documented to have taken at least one dose of investigational treatment.			
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)	9	0	0
Children (2-11 years)	0	43	0
Adolescents (12-17 years)	0	0	161
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
The treated set (TS) included all patients who were dispensed trial medication and were documented to have taken at least one dose of investigational treatment.			
Units: years			
arithmetic mean	0.6	6.8	15.1
standard deviation	± 0.5	± 3.1	± 1.6

Sex: Female, Male			
The treated set (TS) included all patients who were dispensed trial medication and were documented to have taken at least one dose of investigational treatment.			
Units: Participants			
Female	4	22	70
Male	5	21	91
Race (NIH/OMB)			
The treated set (TS) included all patients who were dispensed trial medication and were documented to have taken at least one dose of investigational treatment.			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	1	6
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	4	4
White	8	37	149
More than one race	1	1	1
Unknown or Not Reported	0	0	1
Ethnicity (NIH/OMB)			
The treated set (TS) included all patients who were dispensed trial medication and were documented to have taken at least one dose of investigational treatment.			
Units: Subjects			
Hispanic or Latino	0	2	7
Not Hispanic or Latino	9	41	153
Unknown or Not Reported	0	0	1

Reporting group values	Total		
Number of subjects	213		
Age categorical			
The treated set (TS) included all patients who were dispensed trial medication and were documented to have taken at least one dose of investigational treatment.			
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)	9		
Children (2-11 years)	43		
Adolescents (12-17 years)	161		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age Continuous			
The treated set (TS) included all patients who were dispensed trial medication and were documented to have taken at least one dose of investigational treatment.			
Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
The treated set (TS) included all patients who were dispensed trial medication and were documented to have taken at least one dose of investigational treatment.			
Units: Participants			
Female	96		

Male	117		

Race (NIH/OMB)			
The treated set (TS) included all patients who were dispensed trial medication and were documented to have taken at least one dose of investigational treatment.			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	7		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	8		
White	194		
More than one race	3		
Unknown or Not Reported	1		
Ethnicity (NIH/OMB)			
The treated set (TS) included all patients who were dispensed trial medication and were documented to have taken at least one dose of investigational treatment.			
Units: Subjects			
Hispanic or Latino	9		
Not Hispanic or Latino	203		
Unknown or Not Reported	1		

End points

End points reporting groups

Reporting group title	dabigatran etexilate (0 to < 2 years)

Reporting group description:

Single oral dose of dabigatran etexilate (DE) oral liquid formulation (OLF) ranging from 6.25 milligram(mg) to 143.75mg was administrated twice daily in the morning and evening for participants aged less than 12 months. Single oral dose of DE pellets ranging from 20mg to 330mg was administrated twice daily in the morning and evening for participants aged less than 8 years. Dosage of DE was adjusted by age and weight of participants intending to achieve trough plasma dabigatran concentrations between 50 and <250 nanogram(ng)/mL. The DE dose limit was 22.2 mg/kilogram (kg)/day.The maximal DE single dose was 330 mg. This arm includes participants aged between 0 to <2

Reporting group title	dabigatran etexilate (2 to <12 years)

Reporting group description:

Single oral dose of DE pellets ranging from 20mg to 330mg was administrated twice daily in the morning and evening for participants aged less than 8 years and who cannot take capsules between 8 to <12 years. Single oral dose of DE capsule ranging from 50 mg to 330mg was administrated twice daily in the morning and evening for participants aged at least 8 years. Dosage of DE was adjusted by age and weight of participants intending to achieve trough plasma dabigatran concentrations between 50 and <250 ng/mL. The DE dose limit was 22.2 mg/kg/day.The maximal DE single dose was 330 mg. This arm includes participants aged between 2 to <12 years.

Reporting group title	dabigatran etexilate (12 to <18 years)

Reporting group description:

Single oral dose of DE capsule ranging from 50 mg to 330mg was administrated twice daily in the morning and evening for participants aged at least 8 years. Dosage of DE was adjusted by age and weight of participants intending to achieve trough plasma dabigatran concentrations between 50 and <250 ng/mL. The DE dose limit was 22.2 mg/kg/day.The maximal DE single dose was 330 mg. This arm includes participants aged between 12 to <18 years.

Primary: Event-free probability of recurrence of venous thromboembolism (VTE) at 6 and 12 months

End point title	Event-free probability of recurrence of venous thromboembolism (VTE) at 6 and 12 months[1]

End point description:

The event-free probability of first recurrence of VTE were provided by Kaplan-Meier estimation with its 95% confidence intervals (CIs) at 6 and 12 months.
Patients who did not experience recurrent VTE at the time of analysis, dropped out from the trial early, were lost to follow-up, or had died from non-VTE related cause were considered as non-events and censored. On treatment period was from first DE administration to 3 days of residual effect period after last DE administration. The treated set (TS) included all patients who were dispensed trial medication and
were documented to have taken at least one dose of investigational treatment. The treated set was used to assess safety endpoints

End point type	Primary

End point timeframe:

At month 6 (Week 26) and 12 (Week 52) of on treatment period

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: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis were tested.

End point values	dabigatran etexilate (0 to < 2 years)	dabigatran etexilate (2 to <12 years)	dabigatran etexilate (12 to <18 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	43	161	
Units: Probability				
number (confidence interval 95%)				
6 months	1.000 (1.000 to 1.000)	1.000 (1.000 to 1.000)	0.979 (0.937 to 0.993)	
12 months	1.000 (1.000 to 1.000)	1.000 (1.000 to 1.000)	0.979 (0.937 to 0.993)	

Statistical analyses

No statistical analyses for this end point

Primary: Event-free probability of major or minor (including Clinically relevant non-major (CRNM)) bleeding events at 6 and 12 months

End point title	Event-free probability of major or minor (including Clinically relevant non-major (CRNM)) bleeding events at 6 and 12 months[2]

End point description:

The event-free probability of major or minor (including CRNM) bleeding event were provided by Kaplan-Meier estimation with its 95% confidence intervals (CIs) at 6 and 12 months.
Patients who did not experience major or minor (including CRNM) bleeding event at the time of analysis, dropped out from the trial early, were lost to follow-up, or had died from non-bleeding related cause were considered as non-events and censored. On treatment period was from first DE administration to 3 days of residual effect period after last DE administration. The treated set (TS) included all patients who were dispensed trial medication and were documented to have taken at least one dose of investigational treatment.

End point type	Primary

End point timeframe:

At month 6 (Week 26) and month 12 (Week 52) of on treatment period

Notes:

[2] - 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: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis were tested.

End point values	dabigatran etexilate (0 to < 2 years)	dabigatran etexilate (2 to <12 years)	dabigatran etexilate (12 to <18 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	43	161	
Units: Probability				
number (confidence interval 95%)				
6 months	0.889 (0.433 to 0.984)	0.894 (0.706 to 0.965)	0.753 (0.675 to 0.815)	
12 months	0.889 (0.433 to 0.984)	0.831 (0.592 to 0.936)	0.691 (0.603 to 0.763)	

Statistical analyses

No statistical analyses for this end point

Primary: Event-free probability of mortality overall and related to thrombotic or thromboembolic events at 6 and 12 months

End point title	Event-free probability of mortality overall and related to thrombotic or thromboembolic events at 6 and 12 months[3]

End point description:

The event-free probability of mortality overall and related to thrombotic or thromboembolic events were provided by Kaplan-Meier estimation with its 95% confidence intervals (CIs) at 6 and 12 months. Patients who did not experience mortality overall and related to thrombotic or thromboembolic events at the time of analysis, dropped out from the trial early, were lost to follow-up, were considered as non-events and censored. On treatment period was from first DE administration to 3 days of residual effect period after last DE administration. The treated set (TS) included all patients who were dispensed trial medication and were documented to have taken at least one dose of investigational treatment.

End point type	Primary

End point timeframe:

At month 6 (Week 26) and 12 (Week 52) of on treatment period

Notes:

[3] - 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: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis were tested.

End point values	dabigatran etexilate (0 to < 2 years)	dabigatran etexilate (2 to <12 years)	dabigatran etexilate (12 to <18 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	43	161	
Units: Probability				
number (confidence interval 95%)				
6 months	1.000 (1.000 to 1.000)	1.000 (1.000 to 1.000)	1.000 (1.000 to 1.000)	
12 months	1.000 (1.000 to 1.000)	1.000 (1.000 to 1.000)	1.000 (1.000 to 1.000)	

Statistical analyses

No statistical analyses for this end point

Secondary: Event-free probability of occurrence of post-thrombotic syndrome (PTS) at 6 and 12 months

End point title	Event-free probability of occurrence of post-thrombotic syndrome (PTS) at 6 and 12 months

End point description:

The event-free probability of PTS were provided by Kaplan-Meier estimation with its 95% confidence intervals (CIs) at 6 and 12 months. Patients who did not experience PTS at the time of analysis, dropped out from the trial early, were lost to follow-up, or had died from non-PTS related cause were considered as non-events and censored. On treatment period was from first DE administration to 3 days of residual effect period after last DE administration. The treated set (TS) included all patients who were dispensed trial medication and
were documented to have taken at least one dose of investigational treatment.

End point type	Secondary

End point timeframe:

At month 6 (Week 26) and 12 (Week 52) of on treatment period

End point values	dabigatran etexilate (0 to < 2 years)	dabigatran etexilate (2 to <12 years)	dabigatran etexilate (12 to <18 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	43	161	
Units: Probability				
number (confidence interval 95%)				
6 months	1.000 (1.000 to 1.000)	1.000 (1.000 to 1.000)	0.979 (0.935 to 0.993)	
12 months	1.000 (1.000 to 1.000)	1.000 (1.000 to 1.000)	0.979 (0.935 to 0.993)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with dabigatran etexilate (DE) dose adjustments during on treatment period

End point title	Percentage of participants with dabigatran etexilate (DE) dose adjustments during on treatment period

End point description:

On treatment period was from first DE administration to 3 days of residual effect period after last DE administration. The treated set (TS) included all patients who were dispensed trial medication and were documented to have taken at least one dose of investigational treatment.

End point type	Secondary

End point timeframe:

From first DE administration to 3 days of residual effect period after last DE administration, up to 52 weeks+ 3 days

End point values	dabigatran etexilate (0 to < 2 years)	dabigatran etexilate (2 to <12 years)	dabigatran etexilate (12 to <18 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	43	161	
Units: Percentage of participants				
number (not applicable)	66.7	39.5	21.1	

Statistical analyses

No statistical analyses for this end point

Secondary: Central measurement of Activated partial thromboplastin time (aPTT) at Visit 3 (after at least six consecutive dabigatran etexilate (DE) doses)

End point title	Central measurement of Activated partial thromboplastin time (aPTT) at Visit 3 (after at least six consecutive dabigatran etexilate (DE) doses)

End point description:

The pharmacodynamics (PD) set (PDS) included all treated patients who provided at least one evaluable PD observation and had no protocol deviations relevant to the evaluation of PD endpoints. Only those with non-missing endpoint values were included in this analysis.

End point type	Secondary

End point timeframe:

At Visit 3 (day 4 after first dose of trial medication)

End point values	dabigatran etexilate (0 to < 2 years)	dabigatran etexilate (2 to <12 years)	dabigatran etexilate (12 to <18 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	23	105	
Units: Second (s)				
arithmetic mean (standard deviation)	46.6 (± 18.1)	57.1 (± 70.4)	56.8 (± 64.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Central measurement of Activated partial thromboplastin time (aPTT) at post-titration (after at least 3 days following any dabigatran etexilate (DE) dose adjustment)

End point title	Central measurement of Activated partial thromboplastin time (aPTT) at post-titration (after at least 3 days following any dabigatran etexilate (DE) dose adjustment)

End point description:

The pharmacodynamics (PD) set (PDS) included all treated patients who provided at least one evaluable PD observation and had no protocol deviations relevant to the evaluation of PD endpoints. Only those with non-missing endpoint values were included in this analysis.

End point type	Secondary

End point timeframe:

Pharmacodynamics (PD) samples were collected from first dose of trial medication at day 1 and day 4, 22, 43, 85, 127, 183, 239, and 295 until last dose at day 365 and at post-titration (at least 3 days after dose adjustment) if needed, up to 365 days.

End point values	dabigatran etexilate (0 to < 2 years)	dabigatran etexilate (2 to <12 years)	dabigatran etexilate (12 to <18 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	16	31	
Units: Second (s)				
arithmetic mean (standard deviation)	49.1 (± 26.8)	57.3 (± 23.9)	59.0 (± 80.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Central measurement of Ecarin clotting time (ECT) at Visit 3 (after at least six consecutive dabigatran etexilate (DE) doses)

End point title	Central measurement of Ecarin clotting time (ECT) at Visit 3 (after at least six consecutive dabigatran etexilate (DE) doses)

End point description:

The pharmacodynamics (PD) set (PDS) included all treated patients who provided at least one evaluable PD observation and had no protocol deviations relevant to the evaluation of PD endpoints. Only those with non-missing endpoint values were included in this analysis.

End point type	Secondary

End point timeframe:

At Visit 3 (day 4 after first dose of trial medication)

End point values	dabigatran etexilate (0 to < 2 years)	dabigatran etexilate (2 to <12 years)	dabigatran etexilate (12 to <18 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	24	105	
Units: Second (s)				
arithmetic mean (standard deviation)	52.7 (± 17.6)	64.3 (± 55.7)	69.5 (± 30.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Central measurement of Ecarin clotting time (ECT) at post-titration (after at least 3 days following any dabigatran etexilate (DE) dose adjustment)

End point title	Central measurement of Ecarin clotting time (ECT) at post-titration (after at least 3 days following any dabigatran etexilate (DE) dose adjustment)

End point description:

The pharmacodynamics (PD) set (PDS) included all treated patients who provided at least one evaluable PD observation and had no protocol deviations relevant to the evaluation of PD endpoints. Only those with non-missing endpoint values were included in this analysis.

End point type	Secondary

End point timeframe:

PD samples were collected from first dose of trial medication at day 1 and day 4, 22, 43, 85, 127, 183, 239, and 295 until last dose at day 365 and at post-titration (at least 3 days after dose adjustment) if needed, up to 365 days.

End point values	dabigatran etexilate (0 to < 2 years)	dabigatran etexilate (2 to <12 years)	dabigatran etexilate (12 to <18 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	16	32	
Units: Second (s)				
arithmetic mean (standard deviation)	53.3 (± 19.4)	66.6 (± 23.6)	69.2 (± 28.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Central measurement of Diluted thrombin time (dTT) at Visit 3 (after at least six consecutive dabigatran etexilate (DE) doses)

End point title	Central measurement of Diluted thrombin time (dTT) at Visit 3 (after at least six consecutive dabigatran etexilate (DE) doses)

End point description:

The pharmacodynamics (PD) set (PDS) included all treated patients who provided at least one evaluable PD observation and had no protocol deviations relevant to the evaluation of PD endpoints. Only those with non-missing endpoint values were included in this analysis.

End point type	Secondary

End point timeframe:

At Visit 3 (day 4 after first dose of trial medication)

End point values	dabigatran etexilate (0 to < 2 years)	dabigatran etexilate (2 to <12 years)	dabigatran etexilate (12 to <18 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	17	64	
Units: Second (s)				
arithmetic mean (standard deviation)	37.9 (± 19.5)	40.5 (± 14.6)	45.3 (± 17.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Central measurement of Diluted thrombin time (dTT) at post-titration (after at least 3 days following any dabigatran etexilate (DE) dose adjustment)

End point title	Central measurement of Diluted thrombin time (dTT) at post-titration (after at least 3 days following any dabigatran etexilate (DE) dose adjustment)

End point description:

The pharmacodynamics (PD) set (PDS) included all treated patients who provided at least one evaluable

PD observation and had no protocol deviations relevant to the evaluation of PD endpoints. Only those with non-missing endpoint values were included in this analysis.

End point type	Secondary

End point timeframe:

dTT values were collected at day 4, 22, 43, 85, 127, 183, 239, and 295 until last dose at day 365 and at post-titration (at least 3 days after dose adjustment) if needed, up to 365 days.

End point values	dabigatran etexilate (0 to < 2 years)	dabigatran etexilate (2 to <12 years)	dabigatran etexilate (12 to <18 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	12	26	
Units: Second (s)				
arithmetic mean (standard deviation)	40.0 (± 24.3)	46.0 (± 18.6)	43.4 (± 17.7)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose until end of trial + 28 days of follow-up, up to 52 weeks+28 days for all cause death. From first dose until last dose of study drug + 3 days of residual effect period, up to 52 weeks + 3 days for other adverse events.

Adverse event reporting additional description:

The treated set (TS) included all patients who were dispensed trial medication and had taken at least 1 dose of investigational treatment, which was used to assess safety endpoints. The adverse events were reported with single arm align with the study design.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Dabigatran etexilate

Reporting group description:

Single oral dose of dabigatran etexilate (DE) oral liquid formulation (OLF) ranging from 6.25 milligram(mg) to 143.75 mg was administrated twice daily in the morning and evening for participants aged less than 12 months.
Single oral dose of DE pellets ranging from 20mg to 330mg was administrated twice daily in the morning and evening for participants aged less than 8 years.
Single oral dose of DE capsule ranging from 50 mg to 330mg was administrated twice daily in the morning and evening for participants aged at least 8 years.
Dosage of DE was adjusted by age and weight of participants intending to achieve trough plasma dabigatran concentrations between 50 and <250 ng/mL. The DE dose limit was 22.2 mg/kg/day.The maximal DE single dose was 330 mg.

Serious adverse events	Dabigatran etexilate		
Total subjects affected by serious adverse events			
subjects affected / exposed	30 / 213 (14.08%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute lymphocytic leukaemia			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ewing's sarcoma recurrent			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			

Bleeding varicose vein				
subjects affected / exposed	1 / 213 (0.47%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Deep vein thrombosis				
subjects affected / exposed	2 / 213 (0.94%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Haematoma				
subjects affected / exposed	1 / 213 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lupus vasculitis				
subjects affected / exposed	1 / 213 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Phlebitis superficial				
subjects affected / exposed	1 / 213 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombosis				
subjects affected / exposed	1 / 213 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chest pain				
subjects affected / exposed	1 / 213 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oedema peripheral				
subjects affected / exposed	1 / 213 (0.47%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Reproductive system and breast disorders			
Menstrual disorder			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pelvic adhesions			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sleep apnoea syndrome			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Post-traumatic stress disorder			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood bilirubin increased			

subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic enzyme increased			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metal poisoning			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post procedural haematoma			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Congenital anomaly			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Cardiac disorders			
Atrial flutter			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocarditis			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pericardial effusion			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ventricular pre-excitation			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Migraine			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain upper			

subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal perforation			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic vein stenosis			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Lupus nephritis			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Catheter site infection			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			

subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Encephalitis			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 213 (0.94%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pulpitis dental			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tonsillitis			
subjects affected / exposed	2 / 213 (0.94%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 213 (0.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Dabigatran etexilate		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	113 / 213 (53.05%)		
Nervous system disorders			
Headache			
subjects affected / exposed	34 / 213 (15.96%)		
occurrences (all)	54		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	15 / 213 (7.04%)		
occurrences (all)	20		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	13 / 213 (6.10%)		
occurrences (all)	13		
Diarrhoea			
subjects affected / exposed	15 / 213 (7.04%)		
occurrences (all)	21		
Dyspepsia			
subjects affected / exposed	15 / 213 (7.04%)		
occurrences (all)	18		
Nausea			
subjects affected / exposed	17 / 213 (7.98%)		
occurrences (all)	25		
Vomiting			
subjects affected / exposed	15 / 213 (7.04%)		
occurrences (all)	17		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	14 / 213 (6.57%)		
occurrences (all)	17		
Epistaxis			
subjects affected / exposed	14 / 213 (6.57%)		
occurrences (all)	17		
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	11 / 213 (5.16%)		
occurrences (all)	13		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	11 / 213 (5.16%)		
occurrences (all)	14		
Pain in extremity			
subjects affected / exposed	13 / 213 (6.10%)		
occurrences (all)	17		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	34 / 213 (15.96%)		
occurrences (all)	54		
Upper respiratory tract infection			
subjects affected / exposed	14 / 213 (6.57%)		
occurrences (all)	14		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 October 2014	With Global Amendment 1, recruitment of patients with a body weight >40 kg was temporarily suspended. It was projected that, because of the performed capping of the maximum single starting dose at 220 mg, a considerable proportion of patients with a body weight >40 kg will have dabigatran plasma levels falling below 50 ng/mL. Of note, with Global Amendment 2 (see below) a two times daily regimen using actual calculated dosages (according to Hayton equation) was implemented instead of capped dosages.
28 January 2015	A twice daily dosing regimen using actual calculated dosages (according to Hayton equation) was implemented. This dosing regimen also included the additional safeguard of up- or down-titration to achieve a trough plasma level of 50 to <250 ng/mL. The temporary suspension of recruitment of patients with a body weight >40 kg was terminated. It was explained that the maximal daily dose level does neither exceed a daily dose level of 22.2 mg/kg nor a single dose of 330 mg, resulting in a maximal daily dose of 660 mg in the higher age/body weight group. With this amendment, only one dose adjustment was allowed. Consequently, patients not reaching the target trough plasma concentrations after one dose adjustment were to discontinue DE and were to receive subsequently SoC at the investigator's discretion. The extent of up-titration was modified from initially 85 - 100% to 15 -100% to not exceed maximum daily dosages based on acceptable toxicology limits. Dosing and dose adjustment nomograms were incorporated in Appendix 10.4 of the CTP. It was clarified that patients aged 6 months to <8 years and those who cannot take capsule were to receive pellets while patients aged 0 to <6 months and those who cannot take pellets at an age of 6 to <12 months were to receive OLF. For clarification, it was added to inclusion criterion 2 that patients who were switched from DE to the SoC arm during the treatment phase of trial 1160.106 for any reason were not eligible for this trial. An additional exclusion criterion was introduced: Patients in age group 0 to <2 years with gestational age at birth <37 weeks or with a body weight lower than the 3rd percentile (according to the WHO Child growth standards) were not to be entered in the trial. It was clarified that use of a specific reversal agent to counteract the antithrombotic activity of DE is allowed as soon as available in a framework of clinical investigation.
27 November 2015	The up-titration dosing nomograms for capsules and pellets were updated. It was stated that the dosing nomograms for the OLF will be revised as well in light of the errors identified for the capsule and pellet nomograms and to reflect the acceptable daily intake of tartaric acid. It was defined that this revision will be done before opening the youngest age group (0 to <2 years).

16 March 2016	The assessment of acceptability of all age-appropriate formulations (capsules, pellets, OLF) was added. Randomisation in a 1:1 ratio to an OLF with either a flavoured or an unflavoured solvent for reconstitution was introduced. A summary of the Phase I bioavailability trial 1160.194 was added to provide background information on the interchangeability of the different DE formulations. Information on the Phase IIa trial 1160.89 was updated. In the inclusion criteria, it was added that a temporary interruption of the anticoagulant therapy for the index VTE event or prior to the start of secondary VTE prophylaxis was acceptable, if one of the defined pre-requisites was met. In the exclusion criteria, it was clarified that central venous line insertion is not considered a major surgery and that patients with a history of asymptomatic petechial or microbleeds are eligible for the trial. The threshold when to remove patients from the trial because of low eGFR was decreased to <50 mL/min/1.73 m^2. The threshold for inclusion into the trial remained at ≥80 mL/min/1.73 m^2. A precise definition of the eGFR Schwarz formula was added. The 150 mg DE capsule was introduced to reduce the number of capsules taken by a patient at a single time point. The derived DE target doses based on Hayton calculations for newborns aged <1 month and with a body weight <3 kg were added. Dose adjustment step ranges for up-titration were corrected to 10-100% and for downtitration to 25-50% to reflect the respective dosing nomograms. The dosing nomograms for the OLF were updated. It was explained that as soon as a clinical trial with a specific reversal agent in paediatric patients is initiated, eligible patients from trial 1160.108 can be entered in this trial and receive the reversal agent. Cross reporting of laboratory results between trials is then allowed to limit the blood volume required for analysis.

30 November 2016	In the section on sample size, it was clarified that recruitment can be kept open after 100 patients have been recruited. The final results of the completed Phase IIa PK/PD trials 1160.89 and 1160.105, which were relevant for the patients to be included in second age group (2 to<12 years) and in the youngest age group (0 to <2 years), were provided. To reflect the sequential introduction of age-appropriate formulations (and OLF in particular), it was clarified that patients in age group 2 to <12 years are to be entered and treated considering the availability of the age-appropriate DE formulations. The 60 mg and 70 mg strengths, which were not planned to be used in the trial, were removed from the dosing nomograms for DE pellets. The eGFR threshold for exclusion from the trial was changed to <60 mL/min/1.73m^2 for patients aged 12 to <18 years. For patients aged 0 to <12 years, the eGFR threshold for exclusion from the trial remained unchanged at <80 mL/min/1.73m^2. It was clarified that patients with a heart valve prosthesis requiring anticoagulation are not to be included in the trial. The analysis set for PK analyses was defined; it was specified that this analysis set will also be used for PK/PD analyses. It was defined that multiple PK/PD and safety interim analyses for any of the age groups may be considered. It was clarified that interim analyses based on selected or partial clinical trial data may be conducted for regulatory purposes. It was added that all deaths are to be considered as non-events for occurrence of PTS and therefore are to be censored. The recommendation to use a proton pump inhibitor such as pantoprazole in case of development of gastrointestinal symptoms was replaced by the recommendation to use a proton pump inhibitor according to the local standard of care in accordance with local labelling recommendations.
19 January 2018	Active meningitis, encephalitis, and intracranial abscess at Visit 2 were added as exclusion criteria. Furthermore, patients who developed active meningitis, encephalitis, or intracranial abscess were to be discontinued from the trial medication.

10 September 2018	The option to administer pellets was expanded to patients <6 months of age. It was explained that the use of OLF is preferred over pellets in patients <12 months of age, provided that OLF supplies are available to the site. The time window from Visit 1 (screening) to Visit 2 (first administration of trial medication) was expanded to 14 days to facilitate screening procedures. It was clarified that the discontinuation from trial medication is required if a drug-related SAE occurred. Accordingly, the option to re-start DE after a major bleeding event was deleted. Reaching steady state of the currently assigned DE formulation (i.e. at least 6 consecutive DE doses taken) was introduced as a prerequisite for considering a switch to another formulation. It was deleted that the primary analysis can only be conducted after all patients have completed the 12-month evaluation or otherwise dropped out from the trial. The requirement not to publish any trial data prior to the finalisation of CTRs was deleted. The definition of the PD endpoints was modified: PD assessments at Visit 3 (after at least 6 consecutive DE doses) and after at least 3 days following any DE dose adjustment were to be considered instead of PD assessments at Visit 4. It was clarified that the PD sample Aliquot 1, if not needed for DE concentration measurement guiding dose adjustment, can be used for the central analysis of PD and PK based on dTT (Anti-Factor IIa activity), aPTT and/or ECT. An explanation was added that the secondary endpoint of 'number of DE dose adjustments during the treatment period' is equivalent to the number of patients with DE adjustments during the treatment period since only one dose adjustment was allowed per patient.
07 February 2019	The eGFR threshold in exclusion criterion 2 was lowered to <50 mL/min/1.73m^2 for all patients, irrespective of their age.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported