Clinical trial results:
Open label study comparing efficacy and safety of dabigatran etexilate to standard of care in paediatric patients with venous thromboembolism (VTE)

Summary

EudraCT number	2013-002114-12
Trial protocol	CZ LT BE ES SE FI SK GR NO IT AT BG Outside EU/EEA FR HU DK DE
Global end of trial date	14 November 2019

Results information

Result version number	v3 (current)
This version publication date	14 November 2021
First version publication date	28 May 2020
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	1160.106

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01895777
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Dr. Boehringer-Gasse 5-11, Vienna, Austria, 1121
Public contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 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?	No

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	14 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The 2 main objectives were to assess the efficacy and safety of dabigatran etexilate (DE) relative to standard of care (SoC) and to document the appropriateness of the proposed DE dosing algorithm

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	18 February 2014
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	Argentina: 3
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Brazil: 6
Country: Number of subjects enrolled	Canada: 32
Country: Number of subjects enrolled	Czechia: 54
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	Finland: 3
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Lithuania: 4
Country: Number of subjects enrolled	Mexico: 3
Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Russian Federation: 92
Country: Number of subjects enrolled	Spain: 1

Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	Thailand: 5
Country: Number of subjects enrolled	Turkey: 21
Country: Number of subjects enrolled	Ukraine: 6
Country: Number of subjects enrolled	United States: 37
Worldwide total number of subjects	328
EEA total number of subjects	117

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	8
Infants and toddlers (28 days-23 months)	40
Children (2-11 years)	75
Adolescents (12-17 years)	205
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A multi-centre, open-label, randomised, parallel-group, active-controlled, non-inferiority trial of dabigatran etexilate (DE) versus standard of care (SoC) in children from birth to less than 18 years of age.

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. Subjects were not to be allocated to a treatment group if any of the entry criteria were violated.

Period 1

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

Blinding implementation details:

It was an open-label trial

Arms

Are arms mutually exclusive?	Yes
Arm title	Dabigatran etexilate

Arm description:

Oral administration of dabigatran etexilate (DE) twice daily. Patients aged ≥8 years: age- and weight-adjusted DE dosing via capsules using 50 milligram (mg), 75 mg, 110 mg, and 150 mg capsules. Patients aged <8 years or for patients who cannot take capsules even if older than 8 (but <12 years of age): age- and weight-adjusted dosing via DE pellets. Patients aged <12 months: age- and weight-adjusted dosing via DE oral liquid formulation (OLF).

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

Dosage and administration details:

Oral administration of dabigatran etexilate (DE) twice daily. Patients aged ≥8 years: age- and weight-adjusted DE dosing via capsules using 50 milligram (mg), 75 mg, 110 mg, and 150 mg capsules. Patients aged <8 years or for patients who cannot take capsules even if older than 8 (but <12 years of age): age- and weight-adjusted dosing via DE pellets. Patients aged <12 months: age- and weight-adjusted dosing via DE oral liquid formulation (OLF).

Arm title	Standard of care

Arm description:

Investigators decided on SoC treatment at time of randomisation: either low molecular weight heparin (LMWH) or vitamin K antagonists (VKA) or fondaparinux.

Arm type	Active comparator
Investigational medicinal product name	Low molecular weight heparin (LMWH) or vitamin K antagonists (VKA) or fondaparinux.
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Injection
Routes of administration	Oral use, Subcutaneous use

Dosage and administration details:

Investigators decided on SoC treatment at time of randomisation: either low molecular weight heparin

(LMWH) or vitamin K antagonists (VKA) or fondaparinux.

Number of subjects in period 1[1]	Dabigatran etexilate	Standard of care
Started	177	90
Treated	176	90
Completed	168	85
Not completed	9	5
Adverse event, non-fatal	1	2
Other reasons	3	2
Lost to follow-up	2	-
Not treated	1	-
Non-compliance with the CTP	2	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: This table is based on the randomized set and not on the subjects enrolled

Baseline characteristics

Reporting groups	
Reporting group title	Dabigatran etexilate
Reporting group description:	
Oral administration of dabigatran etexilate (DE) twice daily. Patients aged ≥8 years: age- and weight-adjusted DE dosing via capsules using 50 milligram (mg), 75 mg, 110 mg, and 150 mg capsules. Patients aged <8 years or for patients who cannot take capsules even if older than 8 (but <12 years of age): age- and weight-adjusted dosing via DE pellets. Patients aged <12 months: age- and weight-adjusted dosing via DE oral liquid formulation (OLF).	
Reporting group title	Standard of care
Reporting group description:	
Investigators decided on SoC treatment at time of randomisation: either low molecular weight heparin (LMWH) or vitamin K antagonists (VKA) or fondaparinux.	

Reporting group values	Dabigatran etexilate	Standard of care	Total
Number of subjects	177	90	267
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	4	0	4
Infants and toddlers (28 days-23 months)	18	13	31
Children (2-11 years)	43	21	64
Adolescents (12-17 years)	112	56	168
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	11.1	11.0	
standard deviation	± 6.1	± 6.1	-
Sex: Female, Male Units:			
Female	96	38	134
Male	81	52	133
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	10	3	13
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	3	4
White	163	82	245
More than one race	2	0	2
Unknown or Not Reported	1	2	3
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	8	3	11

Not Hispanic or Latino	169	86	255
Unknown or Not Reported	0	1	1

End points

End points reporting groups

Reporting group title	Dabigatran etexilate

Reporting group description:

Oral administration of dabigatran etexilate (DE) twice daily. Patients aged ≥8 years: age- and weight-adjusted DE dosing via capsules using 50 milligram (mg), 75 mg, 110 mg, and 150 mg capsules. Patients aged <8 years or for patients who cannot take capsules even if older than 8 (but <12 years of age): age- and weight-adjusted dosing via DE pellets. Patients aged <12 months: age- and weight-adjusted dosing via DE oral liquid formulation (OLF).

Reporting group title	Standard of care

Reporting group description:

Investigators decided on SoC treatment at time of randomisation: either low molecular weight heparin (LMWH) or vitamin K antagonists (VKA) or fondaparinux.

Primary: Composite primary endpoint

End point title	Composite primary endpoint

End point description:

The primary endpoint was the combined endpoint of the proportions of patients with: - Complete thrombus resolution - Freedom from recurrent VTE - Freedom from mortality related to VTE. The events outlined in the above combined primary endpoint were assessed by radiologists or other such qualified clinicians using an appropriate method such as ultrasound, echocardiography, venography, or CT scan, based on the location of the thrombus and the test used to perform the baseline assessment. The primary efficacy endpoint contained 3 components. Each component was evaluated separately, and only if the criteria for all 3 components were satisfied, the primary endpoint was considered achieved. The randomised set (RS) included all randomised patients in the treatment groups to which they were randomised, regardless whether they took trial medication

End point type	Primary

End point timeframe:

From the time of randomisation until Week 12, 84 days after randomisation including a visit window of 7 days.

End point values	Dabigatran etexilate	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	90		
Units: Participants				
Complete thrombus resolution	81	38		
Freedom from recurrent VTE	170	83		
Freedom from mortality related to VTE	177	89		
Composite endpoint met	81	38		

Statistical analyses

Statistical analysis title	Primary endpoint analysis

Statistical analysis description:

The primary analysis of the primary efficacy endpoint used the randomised set, following the intention-to-treat principle, based on adjudication-confirmed data. Age group was used as stratification factor

using a Mantel-Haenszel type weighted average of differences.

Comparison groups	Standard of care v Dabigatran etexilate
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0001 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Rates
Point estimate	-0.038
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.141
upper limit	0.066

Notes:

[1] - p-value for non-inferiority is actually <0.0001

Secondary: Freedom from major bleeding events (MBEs)

End point title	Freedom from major bleeding events (MBEs)

End point description:

Freedom from major bleeding events (MBEs), defined as either fatal bleeding, clinically overt bleeding associated with a decrease in haemoglobin of at least 20 g/L in a 24-hour period, bleeding that is retroperitoneal, pulmonary, intracranial or otherwise involves the central nervous system, or bleeding that requires intervention in an operating suite. The treated set (TS) includes all patients who were dispensed trial medication and were documented to have taken at least 1 dose of trial medication

End point type	Secondary

End point timeframe:

From first administration of trial medication until last administration of trial medication +6 days (residual effect period).

End point values	Dabigatran etexilate	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	176	90		
Units: Kaplan-meier estimate				
arithmetic mean (confidence interval 90%)	0.977 (0.948 to 0.990)	0.977 (0.929 to 0.993)		

Statistical analyses

Statistical analysis title	Time-to-event analysis

Statistical analysis description:

Time-to-event endpoint using Kaplan-Meier estimates based on adjudication-confirmed data. Due to the low event rate of major bleeding, age group stratification was not considered.

Comparison groups	Dabigatran etexilate v Standard of care

Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	
Method	Kaplan-Meier estimate
Parameter estimate	Kaplan-Meier estimate of rate difference
Point estimate	0
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.032
upper limit	0.032

Secondary: Freedom from thrombus progression at end of therapy compared with baseline

End point title	Freedom from thrombus progression at end of therapy compared with baseline

End point description:

Freedom from thrombus progression at end of therapy compared with baseline, based on adjudication-confirmed data. The randomised set (RS) included all randomised patients in the treatment groups to which they were randomised, regardless whether they took trial medication.

End point type	Secondary

End point timeframe:

From the time of randomisation until Week 12, 84 days after randomisation including a visit window of 7 days.

End point values	Dabigatran etexilate	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	90		
Units: Participants	148	73		

Statistical analyses

No statistical analyses for this end point

Secondary: All bleeding events

End point title	All bleeding events

End point description:

The incidence of bleeding events including major bleeding events (MBEs), clinically relevant non-major (CRNM) bleeding, minor bleeding events, any bleeding events, and the incidence of the combined endpoint of major and CRNM bleeding events was presented, based on adjudication-confirmed data. The treated set (TS) includes all patients who were dispensed trial medication and were documented to have taken at least 1 dose of trial medication.

End point type	Secondary

End point timeframe:

From first administration of trial medication until last adminstration of trial medication +6 days (residual effect period).

End point values	Dabigatran etexilate	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	176	90		
Units: Participants				
Any bleeding	38	22		
Major bleeding	4	2		
CRNM bleeding	2	1		
Minor bleeding	33	21		
Major and CRNM bleeding	6	3		

Statistical analyses

Statistical analysis title	Time-to-event analysis

Statistical analysis description:

Any bleeding events was analysed as time-to-event endpoint using a stratified Cox proportional hazard model with treatment as a covariate in the model and age group as the stratification factor. A pooling of age groups was performed as no events were observed in certain age group.

Comparison groups	Dabigatran etexilate v Standard of care
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6149
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.145
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.736
upper limit	1.78

Secondary: All-cause mortality

End point title	All-cause mortality

End point description:

Patients being alive at the end of observational period will be censored for all-cause mortality at the date of patients' last date known to be alive, or the date of data cut-off whichever comes first. The treated set (TS) includes all patients who were dispensed trial medication and were documented to have taken at least 1 dose of trial medication.

End point type	Secondary

End point timeframe:

From first administration of trial medication until last administration of trial medication +6 days (residual effect period).

End point values	Dabigatran etexilate	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	176	90		
Units: Participants	0	1		

Statistical analyses

Statistical analysis title	Time-to-event analysis

Statistical analysis description:

All-cause mortality was analyzed as time-to-event endpoint using a stratified Cox proportional hazard model with treatment as a covariate in the model.

Comparison groups	Dabigatran etexilate v Standard of care
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9976
Method	Cox proportional hazard model
Parameter estimate	Hazard ratio (HR)
Point estimate	6.99
Confidence interval	
level	90 %
sides	2-sided
lower limit	0
upper limit	99999.99

Secondary: Steady state plasma concentrations after at least 3 days following any dabigatran etexilate dose adjustment

End point title	Steady state plasma concentrations after at least 3 days following any dabigatran etexilate dose adjustment[2]

End point description:

Descriptive statistics for steady state plasma concentrations of total dabigatran etexilate after at least 3 days following any dabigatran etexilate dose adjustment. The pharmacokinetic set (PKS) included all patients treated with DE who had at least 1 evaluable PK measurement and had no protocol deviations relevant to the evaluation of PK endpoints. Only scheduled visits were considered.

End point type	Secondary

End point timeframe:

From the time of randomisation until Week 12, 84 days after randomisation including a visit window of 7 days.

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: For this end point only the Dabigatran etexilate group was defined for the statistical analysis.

End point values	Dabigatran etexilate			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: nanogram per milliliter				
geometric mean (geometric coefficient of variation)	81.7 (± 54.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of dose adjustment during the treatment phase

End point title	Frequency of dose adjustment during the treatment phase

End point description:

Frequency of dose adjustments (i.e. number of patients with dose adjustment), temporary and permanent discontinuation from therapy, and number of patients with laboratory monitoring requirements for dose. The treated set (TS) includes all patients who were dispensed trial medication and were documented to have taken at least 1 dose of trial medication.

End point type	Secondary

End point timeframe:

From first administration of trial medication until last administration of trial medication +6 days (residual effect period).

End point values	Dabigatran etexilate	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	176	90		
Units: Participants				
With dose adjustment	63	56		
With temporary interruption	25	6		
Laboratory monitoring required	175	82		

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of the acceptability of an age-appropriate formulation at end of therapy (Capsules)

End point title	Assessment of the acceptability of an age-appropriate formulation at end of therapy (Capsules)[3]

End point description:

Acceptability was defined as the overall ability and willingness of the patient to use the medicinal product. Questions regarding acceptability were to be answered by the patient and/or parent/caregiver (as applicable) and by the investigator/site staff. Investigator questionnaire capsules: What is your impression about the patient's acceptability of DE intake? The score is 1 (good), 2 (satisfactory), 3 (not satisfactory) and 4 (bad). Parents questionnaire capsules: How acceptable was the DE treatment for the child? The score is 1 (good), 2 (satisfactory), 3 (not satisfactory) and 4 (bad). Patients questionnaire

capsules: Was taking the study capsules easy or difficult? The score is 1 (Very easy), 2 (easy), 3 (neither easy nor difficult), 4 (difficult) and 5 (very difficult). Scores refers to the end of treatment. The treated set (TS) includes all patients who were dispensed trial medication and were documented to have taken at least 1 dose of trial medication.

End point type	Secondary

End point timeframe:

Assessment at the last study visit

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: For this end point only the Dabigatran etexilate group was defined for the statistical analysis.

End point values	Dabigatran etexilate			
Subject group type	Reporting group			
Number of subjects analysed	119			
Units: Score				
arithmetic mean (standard deviation)				
Investigator questionnaire capsules	1.0 (± 0.2)			
Parents questionnaire capsules	1.0 (± 0.0)			
Patient questionnaire capsules	1.6 (± 0.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of the acceptability of an age-appropriate formulation at end of therapy (Pellets)

End point title	Assessment of the acceptability of an age-appropriate formulation at end of therapy (Pellets)[4]

End point description:

Acceptability was defined as the overall ability and willingness of the patient to use the medicinal product. Questions regarding acceptability were to be answered by the patient and/or parent/caregiver (as applicable) and by the investigator/site staff. Investigator questionnaire pallets: What is your impression about the patient's acceptability of DE intake? The score is 1 (good), 2 (satisfactory), 3 (not satisfactory) and 4 (bad). Parents questionnaire pellets: Do you think that spitting occurs? The score is 1 (Never), 2 (sometimes) and 3 (often). Scores refers to the end of treatment. The treated set (TS) includes all patients who were dispensed trial medication and were documented to have taken at least 1 dose of trial medication

End point type	Secondary

End point timeframe:

Assessment at the last study visit

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: For this end point only the Dabigatran etexilate group was defined for the statistical analysis.

End point values	Dabigatran etexilate			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: Score				
arithmetic mean (standard deviation)				
Investigator questionnaire pellets	1.2 (± 0.6)			
Parents questionnaire pellets	1.2 (± 0.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of the acceptability of an age-appropriate formulation at end of therapy (Oral liquid formulation - OLF)

End point title	Assessment of the acceptability of an age-appropriate formulation at end of therapy (Oral liquid formulation - OLF)[5]

End point description:

Acceptability was defined as the overall ability and willingness of the patient to use the medicinal product. Questions regarding acceptability were to be answered by the patient and/or parent/caregiver (as applicable) and by the investigator/site staff. Investigator questionnaire flavoured OLF: What is your impression about the patient's acceptability of DE intake? The score is 1 (good), 2 (satisfactory), 3 (not satisfactory) and 4 (bad). Investigator questionnaire unflavoured OLF: What is your impression about the patient's acceptability of DE intake? The score is 1 (good), 2 (satisfactory), 3 (not satisfactory) and 4 (bad). Parents questionnaire for flavoured and unflavoured OLF.: Do you think spitting occurs? The score ranges form 1 (never), 2 (sometimes) to 3 (often). Scores refers to the end of treatment. The treated set (TS) includes all patients who were dispensed trial medication and were documented to have taken at least 1 dose of trial medication

End point type	Secondary

End point timeframe:

Assessment at the last study visit

Notes:

[5] - 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: For this end point only the Dabigatran etexilate group was defined for the statistical analysis.

End point values	Dabigatran etexilate			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Score				
arithmetic mean (standard deviation)				
Investigator questionnaire flavoured OLF	1.6 (± 0.8)			
Investigator questionnaire unflavoured OLF	1.2 (± 0.4)			
Parents questionnaire flavoured OLF	1.4 (± 0.5)			
Parents questionnaire unflavoured OLF	1.8 (± 0.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Steady state plasma concentrations of total dabigatran at visit 3

End point title	Steady state plasma concentrations of total dabigatran at visit 3[6]

End point description:

Descriptive statistics for steady state plasma concentrations of total dabigatran etexilate at visit 3. The pharmacokinetic set (PKS) included all patients treated with DE who had at least 1 evaluable PK measurement and had no protocol deviations relevant to the evaluation of PK endpoints. Only scheduled visits were considered.

End point type	Secondary

End point timeframe:

From the time of randomisation until visit 3

Notes:

[6] - 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: For this end point only the Dabigatran etexilate group was defined for the statistical analysis.

End point values	Dabigatran etexilate			
Subject group type	Reporting group			
Number of subjects analysed	139			
Units: nanogram per milliliter				
geometric mean (geometric coefficient of variation)	79.8 (± 68.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of patients switching the type of anti-coagulation therapy including Dabigatran etexilate to standard of care treatment and switching from one standard of care treatment to another

End point title	Frequency of patients switching the type of anti-coagulation therapy including Dabigatran etexilate to standard of care treatment and switching from one standard of care treatment to another

End point description:

Frequency of patients switching the type of anti-coagulation therapy including Dabigatran etexilate (DE) to standard of care (SoC) treatment and switching from one standard of care treatment to another. The treated set (TS) includes all patients who were dispensed trial medication and were documented to have taken at least 1 dose of trial medication. For DE arm, only the switch from DE to SoC was counted, while for the SoC arm, all switches among SoC treatments were counted.

End point type	Secondary

End point timeframe:

From first administration of trial medication until last administration of trial medication +6 days (residual effect period).

End point values	Dabigatran etexilate	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	176	90		
Units: Participants	22	2		

Statistical analyses

No statistical analyses for this end point

Secondary: All components of the primary efficacy endpoint

End point title	All components of the primary efficacy endpoint

End point description:

Patients with VTE-related death occurring between randomisation to Day 84 + 7 days were considered as not meeting the endpoint. The presence of recurrent VTE(s) was examined throughout the trial, and only the date of first occurrence was used for analysis. Assessment of index VTE status (best overall response) was scheduled on Day 84 ± 7 days (Visit 8) for patients who were alive without an early consent withdraw. In the case a Patient discontinued trial medication prematurely due to any reason the index VTE assessment took place at the early end of treatment visit. The randomised set (RS) included all randomised patients in the treatment groups to which they were randomised, regardless whether they took trial medication

End point type	Secondary

End point timeframe:

From the time of randomisation until Week 12, 84 days after randomisation including a visit window of 7 days.

End point values	Dabigatran etexilate	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	90		
Units: Participants				
Complete thrombus resolution by Day 84	81	38		
Recurrent VTE by Day 84	7	7		
VTE-related death by Day 84	0	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For DE patients all AEs recorded between first dabigatran etexilate (DE) intake until 6 days after the last administration of dabigatran etexilate. The Open-label treatment period with DE or SOC is from vist 2 defined as day 0 up to 84 days.

Adverse event reporting additional description:

For patients in standard of care arm, all AEs occurred between the first drug intake of standard of care (SOC) until 6 days after the last administration of any standard of care. The treated set (TS) includes all patients who were dispensed trial medication and were documented to have taken at least 1 dose of trial medication

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Standard of care (SoC)

Reporting group description:

Investigators decided on SoC treatment at time of randomisation: either low molecular weight heparin (LMWH) or vitamin K antagonists (VKA) or fondaparinux.

Reporting group title	Dabigatran etexilate

Reporting group description:

Oral administration of dabigatran etexilate (DE) twice daily. Patients aged ≥8 years: age- and weight-adjusted DE dosing via capsules using 50 milligram (mg), 75 mg, 110 mg, and 150 mg capsules. Patients aged <8 years or for patients who cannot take capsules even if older than 8 (but <12 years of age): age- and weight-adjusted dosing via DE pellets. Patients aged <12 months: age- and weight-adjusted dosing via DE oral liquid formulation (OLF).

Serious adverse events	Standard of care (SoC)	Dabigatran etexilate	
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 90 (20.00%)	25 / 176 (14.20%)	
number of deaths (all causes)	2	2	
number of deaths resulting from adverse events	2	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 90 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	3 / 90 (3.33%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Embolism venous			
subjects affected / exposed	1 / 90 (1.11%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic infarction			
subjects affected / exposed	1 / 90 (1.11%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Post thrombotic syndrome			
subjects affected / exposed	0 / 90 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	1 / 90 (1.11%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Takayasu's arteritis			
subjects affected / exposed	0 / 90 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			
subjects affected / exposed	0 / 90 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 90 (1.11%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Implant site necrosis			
subjects affected / exposed	0 / 90 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 90 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthmatic crisis			
subjects affected / exposed	1 / 90 (1.11%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 90 (1.11%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 90 (2.22%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 90 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachypnoea			
subjects affected / exposed	1 / 90 (1.11%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	1 / 90 (1.11%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			

subjects affected / exposed	1 / 90 (1.11%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Procedural haemorrhage			
subjects affected / exposed	0 / 90 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 90 (1.11%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 90 (1.11%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 90 (1.11%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Haemorrhage intracranial			
subjects affected / exposed	0 / 90 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	0 / 90 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tension headache			
subjects affected / exposed	1 / 90 (1.11%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 90 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 90 (0.00%)	3 / 176 (1.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 90 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sickle cell anaemia with crisis			
subjects affected / exposed	1 / 90 (1.11%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 90 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Papilloedema			
subjects affected / exposed	1 / 90 (1.11%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 90 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			

subjects affected / exposed	0 / 90 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 90 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 90 (1.11%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 90 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis chronic			
subjects affected / exposed	0 / 90 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal haemorrhage			
subjects affected / exposed	1 / 90 (1.11%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Proctitis haemorrhagic			
subjects affected / exposed	0 / 90 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Myositis			
subjects affected / exposed	0 / 90 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			

subjects affected / exposed	1 / 90 (1.11%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Erysipelas			
subjects affected / exposed	1 / 90 (1.11%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 90 (1.11%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis rotavirus			
subjects affected / exposed	1 / 90 (1.11%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 90 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastoiditis			
subjects affected / exposed	1 / 90 (1.11%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis herpes			
subjects affected / exposed	0 / 90 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 90 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			

subjects affected / exposed	1 / 90 (1.11%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 90 (1.11%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 90 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	0 / 90 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound sepsis			
subjects affected / exposed	0 / 90 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 90 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	0 / 90 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 90 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			

subjects affected / exposed	0 / 90 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoproteinaemia			
subjects affected / exposed	0 / 90 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Standard of care (SoC)	Dabigatran etexilate	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 90 (17.78%)	59 / 176 (33.52%)	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 90 (4.44%)	17 / 176 (9.66%)	
occurrences (all)	4	26	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 90 (3.33%)	11 / 176 (6.25%)	
occurrences (all)	3	12	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 90 (1.11%)	9 / 176 (5.11%)	
occurrences (all)	1	11	
Dyspepsia			
subjects affected / exposed	0 / 90 (0.00%)	10 / 176 (5.68%)	
occurrences (all)	0	10	
Vomiting			
subjects affected / exposed	1 / 90 (1.11%)	14 / 176 (7.95%)	
occurrences (all)	1	18	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	6 / 90 (6.67%)	8 / 176 (4.55%)	
occurrences (all)	13	9	

Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	7 / 90 (7.78%) 7	11 / 176 (6.25%) 12	

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.
28 January 2015	The age cut-offs for stratum 2 and 3 were changed based on the EMA PDCO opinion dated 29 Sep 2014 .A twice daily dosing regimen using actual calculated dosages (according to Hayton equation) was implemented. It was clarified that patients aged 6 months to <8 years and those who cannot take capsule at an age of 8 to <12 years were to receive pellets, and that patients aged 0 to <6 months and those who cannot take pellets at an age of 6 to <12 months were to receive OLF. In the benefit-risk section of the CTP, information on the Phase IIa trials was updated as these trials were a prerequisite for opening the second age group (2 to <12 years). 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 all patients who continued treatment for VTE, regardless of whether this was a switch from DE to SoC or from one SoC to another, are not considered early discontinued. A more detailed and age-specific description of the blood sample volumes collected during the trial was added.
26 November 2015	The up-titration dosing nomograms for capsules and pellets were updated to correct calculation errors. It was stated that the OLF dosing nomograms will need to be updated as well in advance of opening the youngest age group (0 to <2 years).
16 March 2016	The assessment of thrombus extension at Visit 5 was removed from the CTP, to better reflect the clinical routine for follow-up of patients with VTE and to eliminate potential unwarranted radiation exposure. A summary of Phase I bioavailability trial 1160.194 was added to provide background information for considering DE formulations to be used interchangeable, without the need for a conversion factor. It was clarified that patients requiring VTE therapy beyond 3 months have to be switched at Visit 8 (Day 84) to SoC treatment (if randomised to DE) or continue SoC treatment (if randomised to the SoC arm) and could be treated with SoC during the follow-up period. Randomisation in a 1:1 ratio to an OLF with either a flavoured or an unflavoured solvent for reconstitution was introduced. It was clarified that eGFR retesting was allowed once during the screening period. The criterion when to remove patients from the trial because of low eGFR was decreased to <50 mL/min/1.73m². The 150 mg DE capsule was introduced to reduce the number of capsules taken by patient at a single time point. It was explained that in case of gastrointestinal symptoms, DE was to be taken with a meal or concomitantly with a proton pump inhibitor. 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.

29 November 2016	The sample size was reduced from a minimum of 240 to a minimum of 180 evaluable patients for the efficacy component of the co-primary endpoint. The duration of the follow-up period was reduced from 9 months to 1 month after the last intake of trial medication. It was clarified that freedom from thrombus progression at the end of therapy (Day 84 after randomisation or eEOT whichever comes first) will be assessed in comparison with baseline. It was clarified that pre-treatment with VKAs during the initial parenteral treatment was acceptable if the INR had not reached a therapeutic level (INR <2.0) at the time of randomisation. To facilitate an expedited evaluation of the risk of bleeding in patients <2 months of age, the first trough dabigatran concentration assessment (at Visit 3) was required to be supplemented by a local aPTT measurement for patients <2 months and a baseline aPTT was also required to be available for these patients. The final results of the completed Phase IIa PK/PD trials relevant for the patients to be included in second age group (2 to<12 years) and in youngest age group (0 to <2 years) were provided. The eGFR threshold for exclusion from the trial was changed to <60 mL/min/1.73m2 for patients aged 12 to <18 years. 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 SoC in accordance with local labelling recommendations. 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 analysis set for PK analyses was defined. It was clarified that interim analyses based on selected or partial clinical trial data may be conducted for regulatory purposes.
30 October 2017	The sample size was further reduced from a minimum of 180 to a minimum of 141 evaluable patients for the efficacy primary endpoint, but it was clarified that the recruitment of further patients could be continued if required by regulatory authorities. Based on FDA advice, freedom from major bleeding events was changed from the coprimary safety endpoint to a secondary endpoint. Fondaparinux was added as allowed SoC treatment based on therapeutic guidelines and EMA advice. The flow chart was amended with several clarifications regarding visit windows, the collection of post-dose samples, and follow-up periods.
16 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.
11 September 2018	The option to administer pellets was expanded to patients <6 months of age. A preference for usage of OLF over pellets in patients <12 months of age, provided that OLF supplies are available to the site, was implemented. The time window from Visit 1 (screening) to Visit 2 (first administration of trial medication)was expanded to 21 days to facilitate screening procedures. It was clarified that the discontinuation from trial medication is required if a drug-related SAE occurred. It was added that the type of SoC may be changed during the treatment period in patients randomised to SoC. The wording of several secondary endpoints was modified to clarify the meaning
06 February 2019	The eGFR threshold in exclusion criterion 2 was lowered to <50 mL/min/1.73 m² for all patients, irrespective of their age.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported