Clinical trial results:
Home Treatment of Patients with Low-Risk Pulmonary Embolism with the Oral Factor Xa Inhibitor Rivaroxaban: Prospective Management Trial (HoT-PE)

Summary

EudraCT number	2013-001657-28
Trial protocol	DE PT FI ES NL GR IT
Global end of trial date	26 November 2019

Results information

Result version number	v1 (current)
This version publication date	29 November 2021
First version publication date	29 November 2021
Summary attachment (see zip file)	HoT-PE_Report Synopsis_2020-07-09 (HoT-PE_Report Synopsis_2020-07-09_final_sign.pdf)

Trial information

Trial identification

Sponsor protocol code	CTHC002

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	University Medical Center of the Johannes Gutenberg University Mainz
Sponsor organisation address	Langenbeckstrasse 1, Mainz, Germany, 55131
Public contact	Prof. Dr. S. Konstantinides, University Medical Center of the Johannes Gutenberg University Mainz, +49 6131 17-8382, stavros.konstantinides@unimedizin-mainz.de
Scientific contact	Prof. Dr. S. Konstantinides, University Medical Center of the Johannes Gutenberg University Mainz, +49 6131 17-8382, stavros.konstantinides@unimedizin-mainz.de

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 May 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 November 2019
Global end of trial reached?	Yes
Global end of trial date	26 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether early discharge and out-of-hospital treatment of patients with low-risk acute PE (as defined by the inclusion and exclusion criteria) with the new oral factor Xa inhibitor rivaroxaban is feasible, effective, and safe.

Protection of trial subjects:

N/A

Background therapy:

This is a single-arm trial

Evidence for comparator:

N/A

Actual start date of recruitment	27 May 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	Netherlands: 16
Country: Number of subjects enrolled	Portugal: 17
Country: Number of subjects enrolled	Spain: 29
Country: Number of subjects enrolled	Finland: 28
Country: Number of subjects enrolled	Germany: 339
Country: Number of subjects enrolled	Greece: 12
Country: Number of subjects enrolled	Italy: 135
Worldwide total number of subjects	576
EEA total number of subjects	576

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	359
From 65 to 84 years	206
85 years and over	11

Subject disposition

Recruitment

Recruitment details:

Date of first enrolment: 27.05.2014
Date of last enrolment: 27.11.2018

Pre-assignment

Screening details:

2,854 patients diagnosed with acute PE were screened for enrolment at 49 centres in 7 European countries.

Period 1

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

Arms

Arm title	Treatment arm

Arm description:

This is a single-arm trial.

Arm type	Experimental
Investigational medicinal product name	Substance name: Rivaroxaban
Investigational medicinal product code	ATC code: B01AF01
Other name	Brand name: Xarelto
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients received 15 mg rivaroxaban twice daily for the first 3 weeks, followed by 20 mg once daily for the duration of the study, but for no less than 3 months.

Number of subjects in period 1	Treatment arm
Started	576
Completed	554
Not completed	22
Adverse event, serious fatal	3
Physician decision	5
Consent withdrawn by subject	4
Adverse event, non-fatal	4
Excluded medication	1
Adminisitrative/regulatory reasons	1
Lost to follow-up	4

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	576	576	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	359	359	
From 65-84 years	206	206	
85 years and over	11	11	
Gender categorical Units: Subjects			
Female	266	266	
Male	310	310	

Subject analysis sets	
Subject analysis set title	Per-protocol population
Subject analysis set type	Per protocol

Subject analysis set description:

All patients, who received at least one dose of study drug and fulfilled the protocol requirements for early discharge from the hospital.

Subject analysis set title	Intention-to-treat population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients who signed the informed consent.

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients, who received at least one dose of study drug.

Reporting group values	Per-protocol population	Intention-to-treat population	Safety population
Number of subjects	547	576	569
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0

Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	341	359	355
From 65-84 years	197	206	203
85 years and over	9	11	11
Gender categorical Units: Subjects			
Female	251	266	263
Male	296	310	306

End points

End points reporting groups

Reporting group title	Treatment arm
Reporting group description:	
This is a single-arm trial.	
Subject analysis set title	Per-protocol population
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients, who received at least one dose of study drug and fulfilled the protocol requirements for early discharge from the hospital.	
Subject analysis set title	Intention-to-treat population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients who signed the informed consent.	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients, who received at least one dose of study drug.	

Primary: Symptomatic recurrent venous thromboembolism, or pulmonary embolism-related death

End point title	Symptomatic recurrent venous thromboembolism, or pulmonary embolism-related death
End point description:	
The primary efficacy outcome was symptomatic recurrent venous thromboembolism, or pulmonary embolism-related death within three months of enrolment.	
End point type	Primary
End point timeframe:	
Within 3 months of enrolment	

End point values	Treatment arm	Intention-to-treat population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	576	576		
Units: Deaths	3	3		

Statistical analyses

Statistical analysis title	Primary outcome analysis
Statistical analysis description:	
The null hypothesis (H0) that $p \geq 0.03$ (where p=probability for recurrent VTE or death within 3 months) was tested against the alternative hypothesis (H1) that $p < 0.03$, using a binomial test (2-stage adaptive design based on an O'Brien Fleming design).	
Comparison groups	Treatment arm v Intention-to-treat population

Number of subjects included in analysis	1152
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	≥ 0.03
Method	Binomial test (O'Brien Fleming design)

Secondary: All-cause mortality within 7 days

End point title	All-cause mortality within 7 days

End point description:

End point type	Secondary

End point timeframe:

Within 7 days of enrolment

End point values	Treatment arm	Intention-to-treat population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	576	576		
Units: Deaths	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: All-cause mortality within 3 weeks

End point title	All-cause mortality within 3 weeks

End point description:

End point type	Secondary

End point timeframe:

Within 3 weeks from enrolment

End point values	Treatment arm	Intention-to-treat population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	576	576		
Units: Deaths	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: All-cause mortality within 3 months

End point title	All-cause mortality within 3 months

End point description:

End point type	Secondary

End point timeframe:

Within 3 months from enrolment

End point values	Treatment arm	Intention-to-treat population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	576	576		
Units: Deaths	3	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall duration of hospital stay within 3 months

End point title	Overall duration of hospital stay within 3 months

End point description:

Duration of hospital stay due to index event and repeated hospitalizations due to PE [index or recurrent event] or to a bleeding event) within 3 months

End point type	Secondary

End point timeframe:

Within 3 months from enrolment

End point values	Treatment arm	Intention-to-treat population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	576	576		
Units: days	927	927		

Statistical analyses

No statistical analyses for this end point

Secondary: Rehospitalization due to PE or to a bleeding event

End point title	Rehospitalization due to PE or to a bleeding event

End point description:

Rehospitalization due to index or recurrent PE or to a bleeding event

End point type	Secondary

End point timeframe:

Within 3 months of hospitailzation

End point values	Treatment arm	Intention-to-treat population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	576	576		
Units: hospitalizations	19	19		

Statistical analyses

No statistical analyses for this end point

Secondary: Generic quality of life

End point title	Generic quality of life

End point description:

Data on generic quality of life (QoL) were collected by use of the EQ-5D-5L questionnaires.

End point type	Secondary

End point timeframe:

At baseline

End point values	Treatment arm	Intention-to-treat population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	473	473		
Units: EQ-5D-5L score				
number (not applicable)	0.82	0.82		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment satisfaction

End point title	Treatment satisfaction

End point description:

Treatment satisfaction was analysed by the Anti-Clot Treatment Scale (ACTS).

End point type	Secondary

End point timeframe:

At 3 weeks

End point values	Treatment arm	Intention-to-treat population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	421	421		
Units: ACTS burden score				
number (not applicable)	40.5	40.5		

Statistical analyses

No statistical analyses for this end point

Secondary: All-cause mortality at one year

End point title	All-cause mortality at one year

End point description:

End point type	Secondary

End point timeframe:

Within 1 year of enrolment

End point values	Treatment arm	Intention-to-treat population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	576	576		
Units: Deaths	5	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment satisfaction

End point title	Treatment satisfaction

End point description:

End point type	Secondary

End point timeframe:

At 3 months after enrolment

End point values	Treatment arm	Intention-to-treat population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	421	421		
Units: ACTS burden scale				
number (not applicable)	42.5	42.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Generic quality of life

End point title	Generic quality of life

End point description:

End point type	Secondary

End point timeframe:

At 1 week after enrolment

End point values	Treatment arm	Intention-to-treat population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	473	473		
Units: EQ-5D-5L score				
number (not applicable)	0.86	0.86		

Statistical analyses

No statistical analyses for this end point

Secondary: Generic quality of life

End point title	Generic quality of life

End point description:

End point type	Secondary

End point timeframe:

At 3 months after enrolment

End point values	Treatment arm	Intention-to-treat population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	473	473		
Units: EQ-5D-5L score				
number (not applicable)	0.91	0.91		

Statistical analyses

No statistical analyses for this end point

Secondary: Generic quality of life

End point title	Generic quality of life

End point description:

End point type	Secondary

End point timeframe:

At 3 weeks after enrolment

End point values	Treatment arm	Intention-to-treat population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	473	473		
Units: EQ-5D-5L score				
number (not applicable)	0.89	0.89		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease-specific quality of life (QoL)

End point title	Disease-specific quality of life (QoL)

End point description:

End point type	Secondary

End point timeframe:

At baseline

End point values	Treatment arm	Intention-to-treat population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	425	425		
Units: PEmb-QoL score				
number (not applicable)	37.0	37.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease-specific quality of life (QoL)

End point title	Disease-specific quality of life (QoL)

End point description:

End point type	Secondary

End point timeframe:

At 3 weeks after enrolment

End point values	Treatment arm	Intention-to-treat population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	425	425		
Units: PEmb-QoL score				
number (not applicable)	28.9	28.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease-specific quality of life (QoL)

End point title	Disease-specific quality of life (QoL)

End point description:

End point type	Secondary

End point timeframe:

At 3 months after enrolment

End point values	Treatment arm	Intention-to-treat population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	425	425		
Units: PEmb-QoL score				
number (not applicable)	19.9	19.9		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Major bleeding

End point title	Major bleeding

End point description:

The safety outcomes included major bleeding (defined by the criteria of the International Society on Thrombosis and Haemostasis, ISTH).

End point type	Other pre-specified

End point timeframe:

Within 3 months of enrolment

End point values	Treatment arm	Safety population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	569	569		
Units: Bleedings	6	6		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Clinically relevant non-major bleeding

End point title	Clinically relevant non-major bleeding

End point description:

Clinically relevant non-major bleeding as defined by the criteria of the International Society on Thrombosis and Haemostasis

End point type	Other pre-specified

End point timeframe:

Within 3 months of enrolment

End point values	Treatment arm	Safety population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	569	569		
Units: Bleedings	30	30		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Serious adverse events (SAEs)

End point title	Serious adverse events (SAEs)

End point description:

End point type	Other pre-specified

End point timeframe:

Within 3 months of enrolment

End point values	Treatment arm	Safety population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	576	569		
Units: events	68	68		

Statistical analyses

Statistical analysis title	Safety outcome analysis

Statistical analysis description:

Safety analysis was conducted in the safety population, including all patients who received at least one dose of study drug. Absolute (N) and relative (%) frequencies and Kaplan-Meier curves including a table with the number of patients under risk were calculated.

Comparison groups	Treatment arm v Safety population
Number of subjects included in analysis	1145
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001 [1]
Method	Binomial test (1-sided)
Parameter estimate	absolute risk
Point estimate	0.52
Confidence interval	
level	95 %
sides	1-sided
upper limit	1.34
Variability estimate	Standard error of the mean
Dispersion value	0.3

Notes:

[1] - The primary efficacy endpoint (symptomatic recurrent venous thromboembolism [VTE] or death related to pulmonary embolism within 3 months after enrolment) is a safety endpoint, therefore the corresponding test from the main analysis is reported here.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time the subject has signed the informed consent document up to 3 months after enrolment (Visit 4)

Adverse event reporting additional description:

If the investigator detects a serious adverse event in a trial subject after the end of the period of observation, and considers the event possibly related to the prior trial, he should contact the Sponsor to determine how the adverse event should be documented and reported.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Safety population

Reporting group description:

All patients, who received at least one dose of study medication.

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	70 / 569 (12.30%)		
number of deaths (all causes)	14		
number of deaths resulting from adverse events	7		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Mesothelioma			
subjects affected / exposed	1 / 569 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Metastases to central nervous system			
subjects affected / exposed	1 / 569 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma			
subjects affected / exposed	1 / 569 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Neoplasm progression			

subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Oesophageal neoplasm				
subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatic carcinoma				
subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Prostate cancer				
subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchial carcinoma				
subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Shock haemorrhagic				
subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhage				
subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pelvic venous thrombosis				
subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Deep vein thrombosis				

subjects affected / exposed	1 / 569 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	1 / 569 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Removal of external fixation			
subjects affected / exposed	1 / 569 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 569 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Disease progression			
subjects affected / exposed	2 / 569 (0.35%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Chest discomfort			
subjects affected / exposed	2 / 569 (0.35%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	5 / 569 (0.88%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	1 / 569 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 569 (0.18%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	2 / 569 (0.35%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 569 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea exertional			
subjects affected / exposed	1 / 569 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Asthma			
subjects affected / exposed	2 / 569 (0.35%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 569 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleurisy			
subjects affected / exposed	1 / 569 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute respiratory distress syndrome			

subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pulmonary embolism				
subjects affected / exposed	3 / 569 (0.53%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Anxiety				
subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Schizoaffective disorder				
subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute stress disorder				
subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Panic attack				
subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Echocardiogram abnormal				
subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ultrasound pancreas abnormal				

subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Troponin increased				
subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Troponin T increased				
subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Electrocardiogram change				
subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Subdural haematoma				
subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ankle fracture				
subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tibia fracture				
subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Coronary artery disorders NEC				
subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Acute myocardial infarction				
subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Angina pectoris				
subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bradycardia				
subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tachycardia				
subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebral haemorrhage				
subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Cerebrovascular accident				
subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Aphasia				
subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Syncope				

subjects affected / exposed	1 / 569 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	1 / 569 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Demyelinating polyneuropathy			
subjects affected / exposed	1 / 569 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 569 (0.35%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Normochromic normocytic anaemia			
subjects affected / exposed	1 / 569 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	1 / 569 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 569 (0.18%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	1 / 569 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Gastric ulcer				
subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrooesophageal reflux disease				
subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterovesical fistula				
subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				
subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ureterolithiasis				
subjects affected / exposed	1 / 569 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal colic				

subjects affected / exposed	2 / 569 (0.35%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Intervertebral discitis			
subjects affected / exposed	1 / 569 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cytomegalovirus mononucleosis			
subjects affected / exposed	1 / 569 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enterococcal bacteraemia			
subjects affected / exposed	1 / 569 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Large intestine infection			
subjects affected / exposed	1 / 569 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 569 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 569 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	8 / 569 (1.41%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 1		
Bacteraemia			

subjects affected / exposed	1 / 569 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 569 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	1 / 569 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	1 / 569 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	2 / 569 (0.35%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	220 / 569 (38.66%)		
Injury, poisoning and procedural complications			
Wound			
subjects affected / exposed	6 / 569 (1.05%)		
occurrences (all)	6		
Vascular disorders			
Haematoma			
subjects affected / exposed	11 / 569 (1.93%)		
occurrences (all)	17		
Nervous system disorders			

Headache			
subjects affected / exposed	8 / 569 (1.41%)		
occurrences (all)	11		
Dizziness			
subjects affected / exposed	6 / 569 (1.05%)		
occurrences (all)	6		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	8 / 569 (1.41%)		
occurrences (all)	8		
Chest pain			
subjects affected / exposed	16 / 569 (2.81%)		
occurrences (all)	22		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	9 / 569 (1.58%)		
occurrences (all)	10		
Gastrointestinal disorders			
Mouth haemorrhage			
subjects affected / exposed	10 / 569 (1.76%)		
occurrences (all)	10		
Gingival bleeding			
subjects affected / exposed	38 / 569 (6.68%)		
occurrences (all)	38		
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	14 / 569 (2.46%)		
occurrences (all)	14		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	15 / 569 (2.64%)		
occurrences (all)	15		
Haemoptysis			
subjects affected / exposed	9 / 569 (1.58%)		
occurrences (all)	9		
Epistaxis			

subjects affected / exposed occurrences (all)	36 / 569 (6.33%) 46		
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	 9 / 569 (1.58%) 9		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 7 / 569 (1.23%) 7 11 / 569 (1.93%) 11		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 7 / 569 (1.23%) 7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 September 2013	Inclusion Criterion no. 4: Acceptable method of contraception for fertile women updated to not recommend the use of hormone-based contraceptives and to request the performance of a pregnancy test in case menstruation is delayed during therapy. Reason: hormonal contraception is not suitable for women with a history of DVT / PE Inclusion Criteria - Additional Criterion no. 6: Absence of right ventricular (RV) enlargement or dysfunction, and of free floating thrombi in the right atrium or right ventricle, detected by echocardiography or on computed tomography. [with definitions] Exclusion Criteria – Removal of Criterion no. 6: Right ventricular (RV) enlargement or dysfunction, or free floating thrombi in the right atrium or right ventricle, detected by echocardiography or on computed tomography. Reason: To emphasize that right ventricular function must be properly assessed by either CT or echocardiography Exclusion Criterion no. 14: specified that GFR should be calculated by the MDRD formula Reason: To assure that the calculation of GFR is done in the same manner across all study sites Change of procedures for collecting data gathered with patient questionnaires Reason: A more safe and streamlined process has been agreed upon to assure that this data is being collected.
24 June 2014	Trial Schedule, Visit 2: Time window re-specified to say Day 7-11 Reason: To allow for scheduling of telephone interviews around weekends and bank holidays 3.6.2 Exclusion criterion no. 6: Rewording of text on limits for pre-treatment of index episode with anticoagulants 3.6.2 Exclusion criterion no. 7: Rewording of text on concurrent anticoagulation treatment for previous indications Reason: Previous text was confusing, partly incorrect and difficult to interpret at study sites. 4.1.4 Dosage Schedule, 1st Para.: Rewording of text to align with the changes in Excl. Criteria 6 and 7

09 November 2015	Number of sites has been changed to 40-50 not only in Germany but in Europe. Reason: The recruitment rate in Germany remain very stable, indicating that an increase in recruitment rate is not possible among German sites. Trial Schedule: - The Computer Assisted Telephone Interview (CATI) is done with patients recruited at German sites only. In other countries, a structured telephone call to the patients will be made by the respective study group. Reason: An operational computerized system is not available in the foreseen non-German countries. The contact with patients will be ensured by phone calls by the site's study team - Utilization of health care resources will be assesed in German patients only. Reason: There is no good model available to compare or co-analyze health costs across national health care systems. Duration of the trial has been changed from 28 to 60 months. Reason: A lower than anticipated recruitment rate Inclusion Criterion 6: Absence of right ventricular (RV) enlargement or dysfunction, and of free floating thrombi in the right atrium or right ventricle on echocardiography or computed tomography. In the amendment, RV dysfunction is absent on echocardiography when both criteria listed below are met: - Right/left ventricular end-diastolic diameter ratio < 0.9 (apical or subcostal 4-chamber view) - No paradoxical motion of the interventricular septum. The remaining echocardiographic criteria have been deleted. Reason: Based on updated Recommendations for Cardiac Chamber Quantification in Adults by the American Society of Echocardiography and the European Society of Cardiovascular Imaging in 2015, all outdated or controversial criteria of RV dysfunction were deleted and only the "simple" criterion, validated in the most recent pulmonary embolism trials , i.e. right/left ventricular end-diastolic diameter ratio < 0.9, is kept.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported