Clinical trial results:
Safety and Efficacy of Low Molecular Weight Heparin for 72 Hours Followed by Dabigatran for the Treatment of Acute Intermediate-Risk Pulmonary Embolism.

Summary

EudraCT number	2015-001830-12
Trial protocol	DE ES BE NL AT SI FR IT
Global end of trial date	12 February 2021

Results information

Result version number	v1 (current)
This version publication date	11 January 2022
First version publication date	11 January 2022
Summary attachment (see zip file)	PEITHO-2_Report Synopsis_2021-01-21 (PEITHO-2_Ergebnisbericht § 42b AMG V3.0_2021-01-21_final sign.pdf)

Trial information

Trial identification

Sponsor protocol code	CTH C007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02596555
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	Center for Thrombosis and Hemostasis (CTH), University Medical Center of the Johannes Gutenberg University Mainz, +49 6131 17-8382, stavros.konstantinides@unimedizin-mainz.de
Scientific contact	Center for Thrombosis and Hemostasis (CTH), 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	22 December 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 December 2020
Global end of trial reached?	Yes
Global end of trial date	12 February 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to determine whether treatment of acute intermediate-risk PE (as defined by the inclusion and exclusion criteria) with parenteral anticoagulation for at least 72 hours after diagnosis, followed by dabigatran over 6 months, is effective and safe.

Protection of trial subjects:

N/A

Background therapy:

N/A

Evidence for comparator:

N/A

Actual start date of recruitment	29 January 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 18
Country: Number of subjects enrolled	Slovenia: 16
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	Austria: 20
Country: Number of subjects enrolled	Belgium: 36
Country: Number of subjects enrolled	France: 64
Country: Number of subjects enrolled	Germany: 112
Country: Number of subjects enrolled	Italy: 99
Country: Number of subjects enrolled	Romania: 22
Worldwide total number of subjects	402
EEA total number of subjects	402

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	148
From 65 to 84 years	222
85 years and over	32

Subject disposition

Recruitment

Recruitment details:

Date of first enrolment: 29.01.2016
Date of lastenrolment: 31.07.2019
Date of last completed: 12.02.2020

Pre-assignment

Screening details:

1,418 patients diagnosed with acute PE were screened at 42 sites in 9 countries.
Reasons for non-enrolment:
419 patients not in intermediate-risk PE category
223 contraindications to IMP
155 outside time window for participation/reduced life expectancy
127 inability to understand/expected non-adherence/other trial
92 no IC provided/possible

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 study.

Arm type	Experimental
Investigational medicinal product name	Substance name: Dabigatran
Investigational medicinal product code	ATC code: B01AE07
Other name	Brand name: Pradaxa
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

After diagnosis of acute intermediate-risk PE and enrolment in the study, patients started or continued to receive therapeutic-dose LMWH, or unfractionated heparin if LMWH was not available. Heparin was continued over 72 hours from the moment of the PE diagnosis. At that time, parenteral anticoagulation was switched to oral dabigatran following a standardised clinical evaluation by the investigator. Dabigatran (Boehringer Ingelheim, Ingelheim am Rhein, Germany) was administered at the approved dose of 150 mg twice daily. In patients with elevated bleeding risk or with an estimated glomerular filtration rate below 50 ml/min, a dose of 110 mg twice daily could be given at the discretion of the investigator and according to the drug’s European summary of product characteristics. Oral anticoagulation with dabigatran was continued for 6 months. After this period, continuation of anticoagulation and the choice of the anticoagulant drug were left to the discretion of the treating physicia

Number of subjects in period 1	Treatment arm
Started	402
Completed	402

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	402	402	
Age categorical Units: Subjects			
Adults (18-64 years)	148	148	
From 65-84 years	222	222	
85 years and over	32	32	
Gender categorical Units: Subjects			
Female	192	192	
Male	210	210	

Subject analysis sets

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 form.

Reporting group values	Intention-to-treat population		
Number of subjects	402		
Age categorical Units: Subjects			
Adults (18-64 years)	148		
From 65-84 years	222		
85 years and over	32		
Gender categorical Units: Subjects			
Female	192		
Male	210		

End points

End points reporting groups

Reporting group title	Treatment arm
Reporting group description: This is a single-arm study.	
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 form.	

Primary: Symptomatic VTE or PE-related death within 6 months

End point title	Symptomatic VTE or PE-related death within 6 months
End point description: The primary outcome is whether symptomatic venous thromboembolism (VTE) or pulmonary embolism (PE)-related death occurs within the first 6 months of anticoagulation therapy (yes/no). The primary analysis will be for intention to treat.	
End point type	Primary
End point timeframe: Within the first 6 months of anticoagulation therapy	

End point values	Treatment arm	Intention-to-treat population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	402	402		
Units: deaths	7	7		

Statistical analyses

Statistical analysis title	Primary outcome analysis
Statistical analysis description: Based on existing data, we tested the null hypothesis (π ≥ 0.061; 6.1%) against the alternative hypothesis (π < 0.061), using a one-sided exact binomial test in a two-stage Pocock group sequential design, with interim analysis after enrolment and after 20% of patients had completed 6-months follow-up. The significance level was chosen as an α of 5%.	
Comparison groups	Treatment arm v Intention-to-treat population
Number of subjects included in analysis	804
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.000022
Method	Exact binomial test
Parameter estimate	relative frequency
Point estimate	0.0174

Confidence interval	
level	95 %
sides	1-sided
upper limit	0.032
Variability estimate	Standard error of the mean
Dispersion value	0.65

Secondary: Recovery of RV function as assessed by echocardiography

End point title	Recovery of RV function as assessed by echocardiography

End point description:

RV recovery is defined as:
(i) complete recovery: normalization of all echocardiographic signs of RV pressure overload/dysfunction as defined by the inclusion criteria;
(ii) partial recovery: normalization of some echocardiographic signs of RV pressure overload/dysfunction as defined by the inclusion criteria, but at least one sign remaining;
(iii) no recovery: all echocardiographic signs of RV pressure overload/dysfunction as defined by the inclusion criteria established at baseline, are still present;
(iv) deterioration: appearance of additional signs of RV pressure overload/dysfunction during follow-up as defined by the inclusion criteria to those established at baseline;

End point type	Secondary

End point timeframe:

at 6±1 days or upon discharge (whichever comes first)

End point values	Treatment arm	Intention-to-treat population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	402	402		
Units: Study patients per category				
Complete recovery	40	40		
Partial recovery	171	171		
No recovery	136	136		
Deterioration	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Recovery of RV function as assessed by echocardiography

End point title	Recovery of RV function as assessed by echocardiography

End point description:

RV recovery is defined as:
(i) complete recovery: normalization of all echocardiographic signs of RV pressure overload/dysfunction as defined by the inclusion criteria;
(ii) partial recovery: normalization of some echocardiographic signs of RV pressure overload/dysfunction as defined by the inclusion criteria, but at least one sign remaining;
(iii) no recovery: all echocardiographic signs of RV pressure overload/dysfunction as defined by the inclusion criteria established at baseline, are still present;

(iv) deterioration: appearance of additional signs of RV pressure overload/dysfunction during follow-up as defined by the inclusion criteria to those established at baseline;

End point type	Secondary

End point timeframe:

at 6-month follow-up

End point values	Treatment arm	Intention-to-treat population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	402	402		
Units: Patients per reporting group				
Complete recovery	57	57		
Partial recovery	177	177		
No recovery	113	113		
Deterioration	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Temporal pattern of changes in NT-proBNP levels

End point title	Temporal pattern of changes in NT-proBNP levels

End point description:

NT-proBNP threshold levels:
(i) normalization: NT-proBNP levels below the age and gender dependent normal threshold at follow-up;
(ii) improvement: NT-proBNP levels >600 pg/ml at baseline that have decreased to ≤600 pg/ml but are still above the age and gender dependent normal threshold at follow-up;
(iii) no improvement: NT-proBNP levels ≤600 pg/ml but still above the age and gender dependent normal threshold at all three measurements; or NT-proBNP levels >600 pg/ml at follow-up;
(iv) deterioration: normal NT-proBNP levels at baseline but abnormal during follow-up; or baseline NT-proBNP levels ≤600 pg/ml, but above the age and gender dependent normal threshold, that increase to >600 pg/ml during follow-up;

End point type	Secondary

End point timeframe:

6±1 days or discharge (whichever comes first) versus baseline

End point values	Treatment arm	Intention-to-treat population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	402	402		
Units: percent				
number (not applicable)				
Normalization	12.66	12.66		
Improvement	15.38	15.38		

No improvement	27.30	27.30		
Deterioration	3.23	3.23		

Statistical analyses

No statistical analyses for this end point

Secondary: Temporal pattern of changes in NT-proBNP levels

End point title	Temporal pattern of changes in NT-proBNP levels

End point description:

NT-proBNP threshold levels:
(i) normalization: NT-proBNP levels below the age and gender dependent normal threshold at follow-up;
(ii) improvement: NT-proBNP levels >600 pg/ml at baseline that have decreased to ≤600 pg/ml but are still above the age and gender dependent normal threshold at follow-up;
(iii) no improvement: NT-proBNP levels ≤600 pg/ml but still above the age and gender dependent normal threshold at all three measurements; or NT-proBNP levels >600 pg/ml at follow-up;
(iv) deterioration: normal NT-proBNP levels at baseline but abnormal during follow-up; or baseline NT-proBNP levels ≤600 pg/ml, but above the age and gender dependent normal threshold, that increase to >600 pg/ml during follow-up;

End point type	Secondary

End point timeframe:

at 6 months versus baseline

End point values	Treatment arm	Intention-to-treat population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	402	402		
Units: percent				
number (not applicable)				
Normalization	23.03	23.03		
Improvement	17.12	17.12		
No improvement	15.63	15.63		
Deterioration	0.99	0.99		

Statistical analyses

No statistical analyses for this end point

Secondary: Death from any cause, or hemodynamic collapse or decompensation

End point title	Death from any cause, or hemodynamic collapse or decompensation

End point description:

End point type	Secondary

End point timeframe:
within 30 days from enrolment

End point values	Treatment arm	Intention-to-treat population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	402	402		
Units: percent				
number (not applicable)	1.2	1.2		

Statistical analyses

No statistical analyses for this end point

Secondary: PE-related death or hemodynamic collapse or decompensation

End point title	PE-related death or hemodynamic collapse or decompensation

End point description:

End point type	Secondary

End point timeframe:
within 30 days from enrolment

End point values	Treatment arm	Intention-to-treat population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	402	402		
Units: percent				
number (not applicable)	0.7	0.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall duration of hospital stay

End point title	Overall duration of hospital stay

End point description:
Index event and repeated hospitalizations due to PE [index or recurrent event] or to a bleeding event

End point type	Secondary

End point timeframe:
within 6 months

End point values	Treatment arm	Intention-to-treat population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	402	402		
Units: Days				
median (inter-quartile range (Q1-Q3))	8 (5.5 to 12)	8 (5.5 to 12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Death from any cause

End point title	Death from any cause

End point description:

End point type	Secondary

End point timeframe:

within 6 months

End point values	Treatment arm	Intention-to-treat population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	402	402		
Units: Deaths	8	8		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Major bleeding

End point title	Major bleeding

End point description:

Major bleeding, based on the International Society of Thrombosis and Haemostasis (ISTH) definition, i.e., any bleeding resulting in death; symptomatic bleeding in a critical organ including intracranial, intraspinal, intraocular, retroperitoneal, intraarticular and pericardial bleeding and muscle bleeding resulting in compartment syndrome; symptomatic bleeding resulting in a decrease in the hemoglobin concentration of at least 2g/dl or resulting in the transfusion of at least two packs of blood red cells

End point type	Other pre-specified

End point timeframe:

at 6 months from enrolment

End point values	Treatment arm	Intention-to-treat population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	402	402		
Units: percent				
number (confidence interval 95%)	2.7 (1.4 to 4.8)	2.7 (1.4 to 4.8)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Major bleeding

End point title	Major bleeding

End point description:

Major bleeding, based on the International Society of Thrombosis and Haemostasis (ISTH) definition, i.e., any bleeding resulting in death; symptomatic bleeding in a critical organ including intracranial, intraspinal, intraocular, retroperitoneal, intraarticular and pericardial bleeding and muscle bleeding resulting in compartment syndrome; symptomatic bleeding resulting in a decrease in the hemoglobin concentration of at least 2g/dl or resulting in the transfusion of at least two packs of blood red cells

End point type	Other pre-specified

End point timeframe:

at 7 months from enrolment

End point values	Treatment arm	Intention-to-treat population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	402	402		
Units: percent				
number (confidence interval 95%)	2.7 (1.4 to 4.8)	2.7 (1.4 to 4.8)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Clinically relevant bleeding

End point title	Clinically relevant bleeding

End point description:

Clinically relevant bleeding, defined as a composite of major or clinically relevant non-major bleeding. Clinically relevant non-major bleeding is defined as bleeding fulfilling at least one of the following criteria:
- spontaneous skin hematoma of at least 25 cm2;

- spontaneous nose bleeding of more than 5 minutes duration;
- macroscopic hematuria, either spontaneous or, if associated with intervention, lasting more than 24 hours;
- spontaneous rectal bleeding;
- gingival bleeding for more than 5 minutes;
- bleeding leading to hospitalization and/or requiring surgical treatment;
- bleeding leading to transfusion of less than 2 units of whole blood or red cells;
- any other bleeding event considered clinically relevant by the investigator.

End point type	Other pre-specified

End point timeframe:

at 6 months from enrolment

End point values	Treatment arm	Intention-to-treat population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	402	402		
Units: percent				
number (confidence interval 95%)	4.0 (2.3 to 6.4)	4.0 (2.3 to 6.4)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Clinically relevant bleeding

End point title	Clinically relevant bleeding

End point description:

Clinically relevant bleeding, defined as a composite of major or clinically relevant non-major bleeding. Clinically relevant non-major bleeding is defined as bleeding fulfilling at least one of the following criteria:
- spontaneous skin hematoma of at least 25 cm2;
- spontaneous nose bleeding of more than 5 minutes duration;
- macroscopic hematuria, either spontaneous or, if associated with intervention, lasting more than 24 hours;
- spontaneous rectal bleeding;
- gingival bleeding for more than 5 minutes;
- bleeding leading to hospitalization and/or requiring surgical treatment;
- bleeding leading to transfusion of less than 2 units of whole blood or red cells;
- any other bleeding event considered clinically relevant by the investigator.

End point type	Other pre-specified

End point timeframe:

at 7 months from enrolment

End point values	Treatment arm	Intention-to-treat population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	402	402		
Units: percent				
number (confidence interval 95%)	4.2 (2.5 to 6.7)	4.2 (2.5 to 6.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The period of observation for collection of adverse events extends from the time the subject has signed the informed consent document up to 30 days after the end of treatment (Visit 6 at 6 months from enrolment).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Intention-to-treat population

Reporting group description:

All analyses for the safety outcomes are conducted using the ITT analysis set.

Serious adverse events	Intention-to-treat population		
Total subjects affected by serious adverse events			
subjects affected / exposed	77 / 402 (19.15%)		
number of deaths (all causes)	8		
number of deaths resulting from adverse events	8		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	1 / 402 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemangioma			
subjects affected / exposed	1 / 402 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myeloproliferative neoplasm			
subjects affected / exposed	1 / 402 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Non-Hodgkin's lymphoma			

subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung adenocarcinoma				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Prostate cancer				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Clear cell renal cell carcinoma				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal cell carcinoma				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Basal cell carcinoma				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Hypertensive crisis				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Aortic stenosis				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhage				

subjects affected / exposed	1 / 402 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Deep vein thrombosis			
subjects affected / exposed	3 / 402 (0.75%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pelvic venous thrombosis			
subjects affected / exposed	1 / 402 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Nephrectomy			
subjects affected / exposed	1 / 402 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin neoplasm excision			
subjects affected / exposed	1 / 402 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vena cava filter removal			
subjects affected / exposed	1 / 402 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Embolism venous			
subjects affected / exposed	1 / 402 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Death			
subjects affected / exposed	2 / 402 (0.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		

Sudden death			
subjects affected / exposed	1 / 402 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pre-existing condition improved			
subjects affected / exposed	1 / 402 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infusion site thrombosis			
subjects affected / exposed	1 / 402 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chest discomfort			
subjects affected / exposed	1 / 402 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	4 / 402 (1.00%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Drug ineffective			
subjects affected / exposed	1 / 402 (0.25%)		
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 / 402 (0.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	1 / 402 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 402 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea exertional			
subjects affected / exposed	1 / 402 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory distress			
subjects affected / exposed	1 / 402 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Asthma			
subjects affected / exposed	1 / 402 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 402 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	1 / 402 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			
subjects affected / exposed	1 / 402 (0.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Epistaxis			
subjects affected / exposed	1 / 402 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Interstitial lung disease			
subjects affected / exposed	1 / 402 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary alveolar haemorrhage			
subjects affected / exposed	1 / 402 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 402 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary hypertension			
subjects affected / exposed	5 / 402 (1.24%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Pulmonary oedema			
subjects affected / exposed	1 / 402 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	6 / 402 (1.49%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 2		
Acute respiratory failure			
subjects affected / exposed	1 / 402 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung disorder			
subjects affected / exposed	2 / 402 (0.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			

Depression				
subjects affected / exposed	2 / 402 (0.50%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Panic disorder				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Liver function test increased				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Transaminases increased				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Troponin increased				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Multiple fractures				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Femoral neck fracture				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Humerus fracture				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin injury				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Atrioventricular block complete				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ischaemic cardiomyopathy				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Coronary artery disease				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	3 / 402 (0.75%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Cardiogenic shock				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Angina pectoris				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Left ventricular dysfunction				

subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocarditis				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	2 / 402 (0.50%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardio-respiratory arrest				
subjects affected / exposed	2 / 402 (0.50%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Nervous system disorders				
Haemorrhage intracranial				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Haemorrhagic stroke				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dementia				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Carpal tunnel syndrome				

subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Paraesthesia				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	1 / 402 (0.25%)			
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 / 402 (0.50%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Gastric polyps				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal polyp				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastric ulcer				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastritis				

subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastritis haemorrhagic				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhoids				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower gastrointestinal haemorrhage				
subjects affected / exposed	2 / 402 (0.50%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Melaena				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Dermatitis allergic				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Skin ulcer				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urticaria				

subjects affected / exposed	1 / 402 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urinary bladder polyp			
subjects affected / exposed	1 / 402 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute kidney injury			
subjects affected / exposed	3 / 402 (0.75%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	1 / 402 (0.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 402 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematoma muscle			
subjects affected / exposed	1 / 402 (0.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Rheumatoid arthritis			
subjects affected / exposed	1 / 402 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 402 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Respiratory tract infection				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	5 / 402 (1.24%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Pneumonia respiratory syncytial viral				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal sepsis				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	2 / 402 (0.50%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Staphylococcal bacteraemia				
subjects affected / exposed	1 / 402 (0.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				

Hyperuricaemia			
subjects affected / exposed	1 / 402 (0.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Intention-to-treat population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	146 / 402 (36.32%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 402 (1.00%)		
occurrences (all)	4		
Gamma-glutamyltransferase increased			
subjects affected / exposed	5 / 402 (1.24%)		
occurrences (all)	5		
Transaminases increased			
subjects affected / exposed	6 / 402 (1.49%)		
occurrences (all)	6		
N-terminal prohormone brain natriuretic peptide increased			
subjects affected / exposed	4 / 402 (1.00%)		
occurrences (all)	4		
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 402 (1.00%)		
occurrences (all)	4		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	8 / 402 (1.99%)		
occurrences (all)	8		
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 402 (1.24%)		
occurrences (all)	5		
General disorders and administration			

site conditions			
Fatigue			
subjects affected / exposed	8 / 402 (1.99%)		
occurrences (all)	8		
Oedema peripheral			
subjects affected / exposed	8 / 402 (1.99%)		
occurrences (all)	8		
Chest pain			
subjects affected / exposed	6 / 402 (1.49%)		
occurrences (all)	6		
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	8 / 402 (1.99%)		
occurrences (all)	8		
Abdominal pain upper			
subjects affected / exposed	6 / 402 (1.49%)		
occurrences (all)	6		
Constipation			
subjects affected / exposed	7 / 402 (1.74%)		
occurrences (all)	7		
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	4 / 402 (1.00%)		
occurrences (all)	4		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	7 / 402 (1.74%)		
occurrences (all)	7		
Dyspnoea exertional			
subjects affected / exposed	4 / 402 (1.00%)		
occurrences (all)	4		
Cough			
subjects affected / exposed	4 / 402 (1.00%)		
occurrences (all)	4		
Haemoptysis			

subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Pulmonary hypertension subjects affected / exposed occurrences (all)	4 / 402 (1.00%) 4 7 / 402 (1.74%) 7 4 / 402 (1.00%) 4		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 7 / 402 (1.74%) 7 6 / 402 (1.49%) 6		
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	 6 / 402 (1.49%) 6		
Infections and infestations Pneumonia subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	 5 / 402 (1.24%) 5 4 / 402 (1.00%) 4 5 / 402 (1.24%) 5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 June 2016	Study Design: Adapted to two-step identification of eligible population: first diagnosis of acute PE and then confirmation of intermediate risk Reason: Adaptation to guidelines and clinical practice, also allowing more time for eligibility checks; Study duration and schedule: Updated Reason: Duration of study is 7 months per patient and recruitment time is approximately 2.5 years; Exclusion criterion no. 2: Period of contraception corrected Reason: Period of contraception is from trial start until 1 month after last application of trial drug, i.e., until "end of trial visit" (and not 1 month after end of trial); Inclusion criterion no. 4: Deletion of sPESI (score ≥ 1) as part of assessment of risk classification Reason: "Hard criteria", imaging and/or biomarker findings, are considered to be reliable tools for identification of intermediate risk, independently from sPESI score; Exclusion criterion no. 7: Deleted Reason: Criterion unintentionally excluded patients who, based on clinical suspicion and according to guideline recommendations in case of intermediate or high pre-test clinical probability of PE, were put on anticoagulation before the definitive diagnosis of acute PE; Exclusion criterion no. 8: Replacement of "index PE episode" with "VTE" Reason: Replaced to include not only PE but also deep vein thrombosis (VTE) as an indication for chronic therapeutic anticoagulation. Dosage schedule: Clear statement on switch from LMWH to dabigatran to occur 72 hours after confirmation of PE diagnosis; time window of +12 hours was added; Reason: Since sequential approach to diagnosis of first acute PE and then intermediate risk is specified, it must be made clear that 72 hours count from PE diagnosis (and not from confirmation of intermediate risk). In addition, for administrative, "practical" reasons, e.g., if 72-hour time point is reached at night, when switch to oral drug is impractical and undesirable, time window of

15 January 2018	Risk-benefit assessment: - Change of follow-up period from 30 days to 6 months, correction of p for rejection of H0 from >6.1 to >0.061 Reason: Correction of typographical errors; - Inclusion of additional possible DSMB recommendations after completion of first interim analysis Reason: Interim results may suggest that reduced sample size is sufficient for rejection of H0; Safety outcomes: 7 months added Reason: To align time for safety outcomes with foreseen visits and analysis of safety outcomes; Exclusion criteria No. 4: corrected for interventional clinical trials Reason: Criterion unintentionally also excluded patients participating in non-interventional clinical trials (e.g. registries); Drug storage, supplies and accountability: Deletion of storage of the trial medication at room temperature Reason: There is no storage temperature limit according to manufacturer´s manual or SmPC; Sample size calculation: Recalculation of sample size including rationale.; sample size confirmed by addition of further data Reason: Consideration of recently published data allowing for more solid justification of calculated sample size; Interim analysis - Change of follow-up period from 30 days to 6 months; correction of p for the rejection of H0 from >6.1 to >0.061 Reason: Correction of typographical errors - Inclusion of additional possible DSMB recommendations after completion of first interim analysis Reason: Interim results may suggest that a reduced sample size is sufficient for rejection of H0;

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported