Clinical trial results:
Ultrasound Accelerated Thombolysis of Pulmonary Embolism

Summary

EudraCT number	2010-022468-11
Trial protocol	DE
Global end of trial date	12 April 2013

Results information

Result version number	v1 (current)
This version publication date	31 December 2016
First version publication date	31 December 2016
Summary attachment (see zip file)	Ultima study (Ultima study.pdf)

Trial information

Trial identification

Sponsor protocol code	ULTIMA

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01166997
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	BTG Pharmaceuticals
Sponsor organisation address	300 Barr Harbor Drive, West Conshohoken, United States, 19428
Public contact	Hans-Joachim Lau, Dr. Hans-Joachim Lau - Consultant, 0049 1608576962, hjlau@meddevconsult.de
Scientific contact	Hans-Joachim Lau, Dr. Hans-Joachim Lau - Consultant, 0049 1608576962, hjlau@meddevconsult.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	12 April 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 April 2013
Global end of trial reached?	Yes
Global end of trial date	12 April 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

In patients with documented PE and right heart dysfunction, determine if treatment with ultrasound accelerated thrombolysis will significantly improve right heart function at 24 hours compared to patients receiving anticoagulation alone.

Protection of trial subjects:

The study was approved by the ethics committees of the participating institutions and all patients provided written informed consent before enrollment.

Background therapy:

In patients with acute pulmonary embolism, systemic thrombolysis improves right ventricular (RV) dilatation,
is associated with major bleeding, and is withheld in many patients at risk. This multicenter randomized, controlled trial
investigated whether ultrasound-assisted catheter-directed thrombolysis (USAT) is superior to anticoagulation alone in
the reversal of RV dilatation in intermediate-risk patients.

Evidence for comparator:

UFH was administered immediately after randomization as an intravenous bolus of 80 IU/kg, followed by an infusion of 18 IU/kg per hour (with a maximum initial infusion rate of 1800 IU/h). For patients already receiving UFH, low-molecular-weight
heparin (LMWH), or fondaparinux before randomization, the initial UFH bolus was omitted. For patients who had received LMWH or fondaparinux at a weight-adjusted therapeutic dose, the start of the UFH infusion was delayed until 8 to 12 hours after the last LMWH injection and until 20 to 24 hours after the last fondaparinux injection.

Actual start date of recruitment	26 November 2010
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	Germany: 40
Country: Number of subjects enrolled	Switzerland: 19
Worldwide total number of subjects	59
EEA total number of subjects	40

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)	30
From 65 to 84 years	29
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From November 2010 to January 2013, 59 patients with intermediate-risk PE from 8 tertiary care hospitals in Germany and Switzerland.

Pre-assignment

Screening details:

Inclusion criteria included acute symptomatic PE confirmed by contrast-enhanced computed tomography with embolus located in at least 1 main or proximal lower lobe pulmonary artery and RV to left ventricular dimension ratio greater than or equal to 1 obtained from the echocardiographic apical 4-chamber view.

Period 1

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

Blinding implementation details:

Patients were randomized in an open-label fashion to receive unfractionated heparin (UFH) and an USAT regimen of 10 mg recombinant tissue plasminogen activator (rtPA) over 15 hours per treated lung via the EkoSonic Endovascular System (n=30; USAT group) or UFH alone (n=29; heparin group). Randomization was performed in blocks of 4 without stratification.

Arms

Are arms mutually exclusive?	Yes
Arm title	USAT group

Arm description:

10 to 20 mg recombinant tissue plasminogen activator over 15 hours plus unfractionated heparin (UFH)

Arm type	Experimental
Investigational medicinal product name	10 to 20 mg recombinant tissue plasminogen activator
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular and intravenous use

Dosage and administration details:

Mean total rtPA dose of 20.8±3.0 mg.

Arm title	Heparin group

Arm description:

Unfractionated heparin alone

Arm type	Active comparator
Investigational medicinal product name	unfractionated heparin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Intravenous bolus of UFH of 80 IU/kg, followed by an infusion of 18 IU/kg per hour

Number of subjects in period 1	USAT group	Heparin group
Started	30	29
Completed	30	27
Not completed	0	2
Adverse event, serious fatal	-	1
Adverse event, non-fatal	-	1

Baseline characteristics

Reporting groups	
Reporting group title	USAT group
Reporting group description:	
10 to 20 mg recombinant tissue plasminogen activator over 15 hours plus unfractionated heparin (UFH)	
Reporting group title	Heparin group
Reporting group description:	
Unfractionated heparin alone	

Reporting group values	USAT group	Heparin group	Total
Number of subjects	30	29	59
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	64	62	
standard deviation	± 15	± 13	-
Gender categorical			
Units: Subjects			
Female	19	12	31
Male	11	17	28

End points

End points reporting groups	
Reporting group title	USAT group
Reporting group description:	
10 to 20 mg recombinant tissue plasminogen activator over 15 hours plus unfractionated heparin (UFH)	
Reporting group title	Heparin group
Reporting group description:	
Unfractionated heparin alone	

Primary: RV/LV Ratio	
End point title	RV/LV Ratio
End point description:	
End point type	Primary
End point timeframe:	
24 hours	

End point values	USAT group	Heparin group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	29		
Units: 1.28 to 0.99	30	29		

Statistical analyses

Statistical analysis title	Fisher exact test
Statistical analysis description:	
Comparison of binary data between the groups was performed with the Fisher exact test.	
Comparison groups	Heparin group v USAT group
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [1]
Method	Mantel-Haenszel

Notes:

[1] - The estimated sample size was 24 per group with a power of 80% at a 2-sided P value of 0.05 by t test.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

90 days

Adverse event reporting additional description:

Patients were scheduled for a follow-up clinical visit and repeated echocardiography. Safety outcomes included death, hemodynamic decompensation, major and minor bleeding, recurrent venous thromboembolism, and serious adverse events up to 90 days after randomization.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	USAT group

Reporting group description:

10 to 20 mg recombinant tissue plasminogen activator over 15 hours plus unfractionated heparin (UFH)

Reporting group title	Heparin group

Reporting group description:

Unfractionated heparin alone

Serious adverse events	USAT group	Heparin group	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 30 (10.00%)	2 / 29 (6.90%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Surgical and medical procedures			
Postoperative wound infection			
subjects affected / exposed	1 / 30 (3.33%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	0 / 30 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Supraventricular tachycardia			

subjects affected / exposed	0 / 30 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Bronchopneumopathy			
subjects affected / exposed	0 / 30 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumonia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 30 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Musculoskeletal and connective tissue disorders			
Radius fracture			
subjects affected / exposed	1 / 30 (3.33%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	USAT group	Heparin group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 30 (0.00%)	2 / 29 (6.90%)	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	0 / 30 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported