



Clinical trial results: Ultrasound Accelerated Thrombolysis 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 Conshohocken, 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