



## Clinical trial results:

### Angiotensin Converting Enzyme Inhibitor (ACE) Induced Angioedema BERINERT

### Randomized, double-blind, two arms, multicenter, Phase III study of Berinert for treatment of ACE induced Angioedema

#### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2012-001670-28    |
| Trial protocol           | DE                |
| Global end of trial date | 30 September 2018 |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 21 May 2020  |
| First version publication date | 21 May 2020  |

#### Trial information

##### Trial identification

|                       |                 |
|-----------------------|-----------------|
| Sponsor protocol code | BER-1272-0058-I |
|-----------------------|-----------------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Technische Universität München, Fakultät für Medizin  |
| Sponsor organisation address | Ismaninger Str. 22, München, Germany, 81675   |
| Public contact               | PD Dr. med. Ulrich Strassen, Klinikum rechts der Isar der TU München<br>Hals-Nasen-Ohrenklinik und Poliklinik, 49 89 4140 2390,                     |
| Scientific contact           | PD Dr. med. Ulrich Strassen, Klinikum rechts der Isar der TU München<br>Hals-Nasen-Ohrenklinik und Poliklinik, 49 89 4140 2390,<br>murat.bas@tum.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                       | 24 September 2019 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 05 September 2018 |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 30 September 2018 |
| Was the trial ended prematurely?                     | Yes               |

Notes:

## General information about the trial

Main objective of the trial:

Primary Objective:

To show that Berinert shortens the time to complete resolution of signs and symptoms of acute ACE-induced angioedema of the upper airway tract compared to placebo when given on top standard treatment

Protection of trial subjects:

The conduct of this clinical study met the local legal and regulatory requirements. The study was conducted in accordance the ethical principles of Good Clinical Practice (GCP). Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. The study was regularly monitored by the Sponsor and all investigators connected to the study were GCP trained.

Background therapy:

Standard of care.

Evidence for comparator:

ACE inhibitors are the most common cause of drug-induced angioedema (0.2 to 0.7% of patients receiving ACEi). ACEi are used widely in the treatment of hypertension, heart failure, myocardial infarction, renal failure, and diabetic nephropathy. Over the last several years, the use of ACEi has increased enormously, which could lead to a greater prevalence of angioedema. ACE inhibitors block ACE, the enzyme that among other actions, degrades bradykinin. In ACE induced angioedema a local imbalance between production and breakdown of bradykinin exists. C1 inhibitor is believed to suppress the local over-production of bradykinin under these circumstances.

Berinert® is a plasma-derived C1 esterase inhibitor concentrate, which is approved for the indication of acute hereditary angioedema (HAE). It is able to act as a substitute for the missing protein or the functional deficit it causes in patients with type I or II HAE. Berinert® has been successfully used also in single cases of very severe ACE-induced angioedema for more than 10 years and additional cases of a successful treatment response to Berinert have been reported since then.

However, a placebo-controlled trial to demonstrate the efficacy of Berinert® for ACE induced angioedema has not been performed.

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 14 October 2013 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | No              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |             |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Germany: 30 |
|--------------------------------------|-------------|

|                                    |    |
|------------------------------------|----|
| Worldwide total number of subjects | 30 |
| EEA total number of subjects       | 30 |

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|---|----|
| 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)                      | 11 |
| From 65 to 84 years                       | 14 |
| 85 years and over                         | 5  |

## Subject disposition

### Recruitment

Recruitment details:

Between 22.12.2013 and 05.09.2018 30 patients were randomised. All 30 patients were analysed in the "Intent-to Treat Population", 21 patients were analysed in the "Per-Protocol Population".

### Pre-assignment

Screening details:

Patients arrive at the emergency department of the clinic with an acute angioedema of the head and neck area and are admitted. The admission of the patient, study suitability assessment and randomisation take place according to the clinical study protocol. Patients were enrolled to the study, if eligibility was confirmed.

### Pre-assignment period milestones

|                              |    |
|------------------------------|----|
| Number of subjects started   | 30 |
| Number of subjects completed |    |

### Period 1

|                              |  |
|------------------------------|--|
| Period 1 title               | Overall trial (overall period)               |
| Is this the baseline period? | Yes  |
| Allocation method            | Randomised - controlled                      |
| Blinding used                | Double blind                                 |
| Roles blinded                | Subject, Investigator, Monitor, Data analyst |

Blinding implementation details:

Due to many aspects, a classical double blinding procedure was not possible. It was not possible to create a placebo solution similar to the Berinert® solution since the specific solution properties of this substance cannot be unrecognizably copied with corresponding placebo powder. The lyophilised Berinert® must be dissolved and have to be prepared in the time limit prescribed. Therefore was necessary to have one unblinded physician. Appropriate working procedures have been established.

### Arms

|                              |                     |
|------------------------------|---------------------|
| Are arms mutually exclusive? | Yes                 |
| <b>Arm title</b>             | Standard + Berinert |

Arm description:

Standard + Berinert

Standard (prednisolone-21-hydrogensuccinat / Clemastinfumarat i.v.) + Body weight adjusted 20IU/kg b.w. Berinert® rounded to the next 500 IU vial.

|  |   |
|--|---|
| Arm type                               | Experimental  |
| Investigational medicinal product name | Berinert  |
| Investigational medicinal product code | B02AB03   |
| Other name                             | C1-Esterase-Inhibitor   |
| Pharmaceutical forms                   | Powder and solvent for solution for injection/skin-prick test |
| Routes of administration               | Intravenous use   |

Dosage and administration details:

Body weight adjusted 20IU/kg b.w. Berinert® rounded to the next 500 IU vial.

If no improvement of the symptoms has occurred within six hours after the first administration of the medicine, then in both the patient groups a second administration of Berinert 500 mg prednisolone-21-hydrogensuccinat and Clemastinfumarat i.v. is possible.

|  |                                 |
|--|---------------------------------|
| Investigational medicinal product name | Prednisolon-21-hydrogensuccinat |
| Investigational medicinal product code |                                 |
| Other name                             |                                 |
| Pharmaceutical forms                   | Solution for injection          |

|   |                        |
|---|------------------------|
| Routes of administration  | Intravenous use        |
| Dosage and administration details:  |                        |
| One Dose of Prednisolone-21-hydrogensuccinat 500 mg i.v (reconstituted in 5ml of sterile water for injection)               |                        |
| After 6 hours decision whether a second dose of Cortisone should be administered.   |                        |
| Investigational medicinal product name  | Clemastinfumarat       |
| Investigational medicinal product code  |                        |
| Other name  |                        |
| Pharmaceutical forms  | Solution for injection |
| Routes of administration  | Intravenous use        |
| Dosage and administration details:  |                        |
| One dose 2,68 mg milligram(s) Clemastinfumarat i.v (Baseline Visite 0)  |                        |
| After 6 hours decision whether a second dose of Clemastin should be administered.   |                        |
| <b>Arm title</b>  | Standard + Placebo     |
| Arm description:  |                        |
| Standard + Placebo  |                        |
| Standard (prednisolone-21-hydrogensuccinat / Clemastinfumarat i.v.) + Placebo (10ml 0,9% NaCl ) rounded to next 10 ml step. |                        |

|   |                                 |
|---|---------------------------------|
| Arm type  | Placebo                         |
| Investigational medicinal product name  | NaCl                            |
| Investigational medicinal product code  |                                 |
| Other name  |                                 |
| Pharmaceutical forms  | Solution for infusion           |
| Routes of administration  | Intravenous use                 |
| Dosage and administration details:  |                                 |
| One dose Placebo (10ml 0, 9% NaCl)  |                                 |
| Investigational medicinal product name  | Prednisolon-21-hydrogensuccinat |
| Investigational medicinal product code  |                                 |
| Other name  |                                 |
| Pharmaceutical forms  | Solution for injection          |
| Routes of administration  | Intravenous use                 |
| Dosage and administration details:  |                                 |
| One Dose of Prednisolone-21-hydrogensuccinat 500 mg i.v (reconstituted in 5ml of sterile water for injection) |                                 |
| After 6 hours decision whether a second dose of Cortisone should be administered.                             |                                 |
| Investigational medicinal product name  | Clemastinfumarat                |
| Investigational medicinal product code  |                                 |
| Other name  |                                 |
| Pharmaceutical forms  | Solution for injection          |
| Routes of administration  | Intravenous use                 |
| Dosage and administration details:  |                                 |
| One dose 2,68 mg milligram(s) Clemastinfumarat i.v (Baseline Visite 0)  |                                 |
| After 6 hours decision whether a second dose of Clemastin should be administered.                             |                                 |

| <b>Number of subjects in period 1</b> | Standard + Berinert | Standard + Placebo |
|---------------------------------------|---------------------|--------------------|
| Started                               | 16                  | 14                 |
| Completed                             | 14                  | 11                 |
| Not completed                         | 2                   | 3                  |
| Adverse event, non-fatal              | 1                   | -                  |
| Lost to follow-up                     | 1                   | 3                  |

## Baseline characteristics

### Reporting groups

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Standard + Berinert |
|-----------------------|---------------------|

Reporting group description:

Standard + Berinert

Standard (prednisolone-21-hydrogensuccinat / Clemastinfumarat i.v.) + Body weight adjusted 20IU/kg b.w. Berinert® rounded to the next 500 IU vial.

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Standard + Placebo |
|-----------------------|--------------------|

Reporting group description:

Standard + Placebo

Standard (prednisolone-21-hydrogensuccinat / Clemastinfumarat i.v.) + Placebo (10ml 0,9% NaCl ) rounded to next 10 ml step.

| Reporting group values   | Standard + Berinert | Standard + Placebo | Total |
|--|---------------------|--------------------|-------|
| Number of subjects   | 16                  | 14                 | 30    |
| Age categorical<br>Units: Subjects                               |                     |                    |       |
| In utero   |                     |                    | 0     |
| Preterm newborn infants<br>(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<br>Units: years                                   |                     |                    |       |
| arithmetic mean  | 75                  | 67                 |       |
| standard deviation   | ± 11.3              | ± 11.1             | -     |
| Gender categorical<br>Units: Subjects                            |                     |                    |       |
| Female   | 6                   | 4                  | 10    |
| Male   | 10                  | 10                 | 20    |
| Earlier episodes of ACE-induced<br>angioedema<br>Units: Subjects |                     |                    |       |
| yes  | 4                   | 3                  | 7     |
| no   | 12                  | 11                 | 23    |
| Concomitant diseases<br>Units: Subjects                          |                     |                    |       |
| yes  | 16                  | 14                 | 30    |
| no   | 0                   | 0                  | 0     |

## End points

### End points reporting groups

|   |                     |
|---|---------------------|
| Reporting group title   | Standard + Berinert |
| Reporting group description:<br>Standard + Berinert<br>Standard (prednisolone-21-hydrogensuccinat / Clemastinfumarat i.v.) + Body weight adjusted 20IU/kg b.w. Berinert® rounded to the next 500 IU vial. |                     |
| Reporting group title   | Standard + Placebo  |
| Reporting group description:<br>Standard + Placebo<br>Standard (prednisolone-21-hydrogensuccinat / Clemastinfumarat i.v.) + Placebo (10ml 0,9% NaCl ) rounded to next 10 ml step.                         |                     |

### Primary: TCER

|  |         |
|--|---------|
| End point title  | TCER    |
| End point description:<br>TCER is set to the first visit time, according to the visit schedule, at which complete resolution is marked to be present. As this potentially leads to equal TCER for some subjects (called `bindings' in statistics), the exact p-value are computed for the Wilcoxon-Mann-Whitney-U test. Missing TCER in the treatment group are imputed by the longest TCER observed for all patients. In the control group, complete resolution is assumed to have taken place instantly after the last known observation of the respective patients. |         |
| End point type   | Primary |
| End point timeframe:<br>Time to complete edema restitution (TCER)  |         |

| End point values              | Standard + Berinert | Standard + Placebo |  |  |
|-------------------------------|---------------------|--------------------|--|--|
| Subject group type            | Reporting group     | Reporting group    |  |  |
| Number of subjects analysed   | 16                  | 14                 |  |  |
| Units: hours                  |                     |                    |  |  |
| median (full range (min-max)) | 24 (6 to 48)        | 15 (4 to 30)       |  |  |

### Statistical analyses

|  |  |
|--|--|
| Statistical analysis title   | Primary endpoint analysis on ITT         |
| Statistical analysis description:<br>Scheduled imputed TCER on ITT. The ITT population contains all randomized patients with results attributed to the treatment group they were randomized to and who received at least one dose of study medication.<br>Exact Wilcoxon-Mann-Whitney U test |  |
| Comparison groups  | Standard + Berinert v Standard + Placebo |



|   |                         |
|---|-------------------------|
| Number of subjects included in analysis | 30                      |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | = 0.0457 <sup>[1]</sup> |
| Method                                  | Wilcoxon (Mann-Whitney) |

Notes:

[1] - Exact test

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Sensitivity analysis actual imputed on ITT |
|-----------------------------------|--|

Statistical analysis description:

Actual imputed TCER on ITT. The ITT population contains all randomized patients with results attributed to the treatment group they were randomized to and who received at least one dose of study medication.

Exact Wilcoxon-Mann-Whitney U test

|   |  |
|---|--|
| Comparison groups                       | Standard + Berinert v Standard + Placebo |
| Number of subjects included in analysis | 30                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority <sup>[2]</sup>               |
| P-value                                 | = 0.0852 <sup>[3]</sup>                  |
| Method                                  | Wilcoxon (Mann-Whitney)                  |

Notes:

[2] - Analysis is performed using the actual TCER as an outcome instead of the visit schedule based TCER.

[3] - exact

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Sensitivity analysis scheduled ignoring 1h on ITT |
|-----------------------------------|---|

Statistical analysis description:

Scheduled TCER ignoring the 1h rule on ITT. The ITT population contains all randomized patients with results attributed to the treatment group they were randomized to and who received at least one dose of study medication.

Exact Wilcoxon-Mann-Whitney-U test

|   |  |
|---|--|
| Comparison groups                       | Standard + Berinert v Standard + Placebo |
| Number of subjects included in analysis | 30                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority <sup>[4]</sup>               |
| P-value                                 | = 0.1354 <sup>[5]</sup>                  |
| Method                                  | Wilcoxon (Mann-Whitney)                  |

Notes:

[4] - As there were seven patients without confirmation of TCER after one hour, additional analyses are conducted while ignoring the one hour rule in the actual and scheduled TCER.

[5] - exact

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Sensitivity analysis actual ignoring 1h on ITT |
|-----------------------------------|--|

Statistical analysis description:

Actual TCER ignoring the 1h rule on ITT. The ITT population contains all randomized patients with results attributed to the treatment group they were randomized to and who received at least one dose of study medication.

Exact Wilcoxon-Mann-Whitney-U test

|                   |  |
|-------------------|--|
| Comparison groups | Standard + Berinert v Standard + Placebo |
|-------------------|--|

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 30                         |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[6]</sup> |
| P-value                                 | = 0.184 <sup>[7]</sup>     |
| Method                                  | Wilcoxon (Mann-Whitney)    |

Notes:

[6] - Analysis is performed using the actual TCER as an outcome instead of the visit schedule based TCER. As there were seven patients without confirmation of TCER after one hour, additional analyses are conducted while ignoring the one hour rule in the actual and scheduled TCER.

[7] - exact

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Sensitivity analysis scheduled imputed on PP |
|-----------------------------------|--|

Statistical analysis description:

Scheduled imputed TCER on PP. The PP population contains all patients in the ITT population except for those with major protocol violations and those who received per-protocol rescue medication.

Exact Wilcoxon-Mann-Whitney U test

|   |  |
|---|--|
| Comparison groups                       | Standard + Berinert v Standard + Placebo |
| Number of subjects included in analysis | 30                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.4718 <sup>[8]</sup>                  |
| Method                                  | Wilcoxon (Mann-Whitney)                  |

Notes:

[8] - exact

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Sensitivity analysis actual imputed on PP |
|-----------------------------------|---|

Statistical analysis description:

Actual imputed TCER on PP. The PP population contains all patients in the ITT population except for those with major protocol violations and those who received per-protocol rescue medication.

Exact Wilcoxon-Mann-Whitney-U test

|   |  |
|---|--|
| Comparison groups                       | Standard + Berinert v Standard + Placebo |
| Number of subjects included in analysis | 30                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.6511 <sup>[9]</sup>                  |
| Method                                  | Wilcoxon (Mann-Whitney)                  |

Notes:

[9] - exact

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Sensitivity analysis scheduled ignoring 1h on PP |
|-----------------------------------|--|

Statistical analysis description:

Scheduled TCER ignoring the 1h rule on PP. The PP population contains all patients in the ITT population except for those with major protocol violations and those who received per-protocol rescue medication.

Exact Wilcoxon-Mann-Whitney-U test

|   |  |
|---|--|
| Comparison groups                       | Standard + Berinert v Standard + Placebo |
| Number of subjects included in analysis | 30                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.2869 <sup>[10]</sup>                 |
| Method                                  | Wilcoxon (Mann-Whitney)                  |

Notes:

[10] - exact

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Sensitivity analysis actual ignoring 1h on PP |
| Statistical analysis description:<br>Actual TCER ignoring the 1h rule on PP. The PP population contains all patients in the ITT population except for those with major protocol violations and those who received per-protocol rescue medication. Exact Wilcoxon-Mann-Whitney-U test |   |
| Comparison groups  | Standard + Berinert v Standard + Placebo      |
| Number of subjects included in analysis  | 30  |
| Analysis specification   | Pre-specified                                 |
| Analysis type  | superiority                                   |
| P-value  | = 0.4561 <sup>[11]</sup>                      |
| Method   | Wilcoxon (Mann-Whitney)                       |
| Notes:<br>[11] - exact   |   |

## Secondary: TOR

|  |           |
|--|-----------|
| End point title  | TOR       |
| End point description:<br>Time between start of study medication administration and time of onset of relief (TOR), defined as at least one point reduction of the sum-score of the edema severity scale. |           |
| End point type   | Secondary |
| End point timeframe:<br>Time to onset of relief  |           |

| End point values              | Standard + Berinert | Standard + Placebo |  |  |
|-------------------------------|---------------------|--------------------|--|--|
| Subject group type            | Reporting group     | Reporting group    |  |  |
| Number of subjects analysed   | 16                  | 14                 |  |  |
| Units: hours                  |                     |                    |  |  |
| median (full range (min-max)) | 2 (2 to 12)         | 2 (2 to 6)         |  |  |

## Statistical analyses

|  |  |
|--|--|
| <b>Statistical analysis title</b>  | Scheduled TOR on ITT                     |
| Statistical analysis description:<br>Scheduled TOR on ITT. The ITT population contains all randomized patients with results attributed to the treatment group they were randomized to and who received at least one dose of study medication. Exact Wilcoxon-Mann-Whitney-U test |  |
| Comparison groups  | Standard + Berinert v Standard + Placebo |
| Number of subjects included in analysis  | 30                                       |
| Analysis specification   | Pre-specified                            |
| Analysis type  | superiority                              |
| P-value  | = 0.4443 <sup>[12]</sup>                 |
| Method   | Wilcoxon (Mann-Whitney)                  |
| Notes:<br>[12] - exact   |  |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AEs and SAEs were documented in the timeframe from signed informed consent till the end of the follow-up period.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |    |
|--------------------|----|
| Dictionary version | 17 |
|--------------------|----|

### Reporting groups

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Standard + Berinert |
|-----------------------|---------------------|

Reporting group description:

Standard + Berinert

Standard (prednisolone-21-hydrogensuccinat / Clemastinfumarat i.v.) + Body weight adjusted 20IU/kg b.w. Berinert® rounded to the next 500 IU vial.

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Standard + Placebo |
|-----------------------|--------------------|

Reporting group description:

Standard + Placebo

Standard (prednisolone-21-hydrogensuccinat / Clemastinfumarat i.v.) + Placebo (10ml 0,9% NaCl ) rounded to next 10 ml step.

| Serious adverse events                            | Standard + Berinert | Standard + Placebo |  |
|---|---------------------|--------------------|--|
| Total subjects affected by serious adverse events |                     |                    |  |
| subjects affected / exposed                       | 2 / 16 (12.50%)     | 2 / 14 (14.29%)    |  |
| number of deaths (all causes)                     | 0                   | 0                  |  |
| number of deaths resulting from adverse events    | 0                   | 0                  |  |
| Investigations                                    |                     |                    |  |
| Troponin T increased                              |                     |                    |  |
| subjects affected / exposed                       | 0 / 16 (0.00%)      | 1 / 14 (7.14%)     |  |
| occurrences causally related to treatment / all   | 0 / 0               | 0 / 1              |  |
| deaths causally related to treatment / all        | 0 / 0               | 0 / 0              |  |
| Vascular disorders                                |                     |                    |  |
| Hypertension                                      |                     |                    |  |
| subjects affected / exposed                       | 1 / 16 (6.25%)      | 0 / 14 (0.00%)     |  |
| occurrences causally related to treatment / all   | 0 / 1               | 0 / 0              |  |
| deaths causally related to treatment / all        | 0 / 0               | 0 / 0              |  |
| Contusion   |                     |                    |  |
| subjects affected / exposed                       | 0 / 16 (0.00%)      | 1 / 14 (7.14%)     |  |
| occurrences causally related to treatment / all   | 0 / 0               | 0 / 1              |  |
| deaths causally related to treatment / all        | 0 / 0               | 0 / 0              |  |

|   |                |                |  |
|---|----------------|----------------|--|
| Nervous system disorders                        |                |                |  |
| Syncope   |                |                |  |
| subjects affected / exposed                     | 1 / 16 (6.25%) | 0 / 14 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

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

| <b>Non-serious adverse events</b>                     | Standard + Berinert | Standard + Placebo |  |
|---|---------------------|--------------------|--|
| Total subjects affected by non-serious adverse events |                     |                    |  |
| subjects affected / exposed                           | 5 / 16 (31.25%)     | 4 / 14 (28.57%)    |  |
| Cardiac disorders                                     |                     |                    |  |
| Angina pectoris                                       |                     |                    |  |
| subjects affected / exposed                           | 1 / 16 (6.25%)      | 0 / 14 (0.00%)     |  |
| occurrences (all)                                     | 1                   | 0                  |  |
| General disorders and administration site conditions  |                     |                    |  |
| Device dislocation                                    |                     |                    |  |
| subjects affected / exposed                           | 1 / 16 (6.25%)      | 0 / 14 (0.00%)     |  |
| occurrences (all)                                     | 1                   | 0                  |  |
| Gastrointestinal disorders                            |                     |                    |  |
| Diarrhoea   |                     |                    |  |
| subjects affected / exposed                           | 1 / 16 (6.25%)      | 0 / 14 (0.00%)     |  |
| occurrences (all)                                     | 1                   | 0                  |  |
| Skin and subcutaneous tissue disorders                |                     |                    |  |
| Angioedema  |                     |                    |  |
| subjects affected / exposed                           | 0 / 16 (0.00%)      | 1 / 14 (7.14%)     |  |
| occurrences (all)                                     | 0                   | 1                  |  |
| Infections and infestations                           |                     |                    |  |
| Influenza   |                     |                    |  |
| subjects affected / exposed                           | 0 / 16 (0.00%)      | 1 / 14 (7.14%)     |  |
| occurrences (all)                                     | 0                   | 1                  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date         | Amendment  |
|--------------|--|
| 18 July 2014 | Clarification of 1 inclusion Criterion : Patients with ACE induced angioedema (grade II-III in at least one severity scale) with imminent airway obstruction admitted to an Emergency department |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/27886906>