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 Hals-Nasen-Ohrenklinik und Poliklinik, 49 89 4140 2390,
Scientific contact	PD Dr. med. Ulrich Strassen, Klinikum rechts der Isar der TU München Hals-Nasen-Ohrenklinik und Poliklinik, 49 89 4140 2390, 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:

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)	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 wer 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
Arm title	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.

Arm title	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.

Number of subjects in period 1	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 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	75	67	
standard deviation	± 11.3	± 11.1	-
Gender categorical Units: Subjects			
Female	6	4	10
Male	10	10	20
Earlier episodes of ACE-induced angioedema Units: Subjects			
yes	4	3	7
no	12	11	23
Concomitant diseases Units: Subjects			
yes	16	14	30
no	0	0	0

End points

End points 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.

Primary: TCER

End point title	TCER

End point description:

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:

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:

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.
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 [1]
Method	Wilcoxon (Mann-Whitney)

Notes:

[1] - Exact test

Statistical analysis title	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[2]
P-value	= 0.0852 [3]
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

Statistical analysis title	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[4]
P-value	= 0.1354 [5]
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

Statistical analysis title	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[6]
P-value	= 0.184 [7]
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

Statistical analysis title	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 [8]
Method	Wilcoxon (Mann-Whitney)

Notes:

[8] - exact

Statistical analysis title	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 [9]
Method	Wilcoxon (Mann-Whitney)

Notes:

[9] - exact

Statistical analysis title	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 [10]
Method	Wilcoxon (Mann-Whitney)

Notes:

[10] - exact

Statistical analysis title	Sensitivity analysis actual ignoring 1h on PP

Statistical analysis description:

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 [11]
Method	Wilcoxon (Mann-Whitney)

Notes:

[11] - exact

Secondary: TOR

End point title	TOR

End point description:

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:

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

Statistical analysis title	Scheduled TOR on ITT

Statistical analysis description:

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 [12]
Method	Wilcoxon (Mann-Whitney)

Notes:

[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 %

Non-serious adverse events	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:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

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