# Clinical trial results:
# Intraindividual cross-over comparison of Gadobutrol and Gadoterate enhanced combined DSC-MR-Perfusion and MR-Angiography in patients with cerebrovascular disease

## Summary

| | |
|---|---|
| EudraCT number | 2012-001582-33 |
| Trial protocol | DE |
| Global end of trial date | 01 November 2016 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 10 May 2020 |
| First version publication date | 10 May 2020 |
| Summary attachment (see zip file) | Synopsis (Synopse Stroke neu 2020.pdf) |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | Er-01-Perf-Stroke |

### Additional study identifiers

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

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Universitätsklinikum Erlangen |
| Sponsor organisation address | Schwabachanlage 6, Erlangen, Germany, 91054 |
| Public contact | Prof. Dr. Arnd Dörfler, University Hospital Erlangen, 49 091318539388, neuroradiologie@uk-erlangen.de |
| Scientific contact | Prof. Dr. Arnd Dörfler, University Hospital Erlangen, 49 091318539388, neuroradiologie@uk-erlangen.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 | 06 October 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 06 October 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 01 November 2016 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To prove that Gadobutrol provides superior characteristics as compared to Gadoterate in DSC-MR perfusion imaging and contrast-enhanced MR angiography in acute stroke patients and/or patients harboring an intracranial stenosis or extracranial ICA stenosis, assessed by two independent blinded readers.

Protection of trial subjects:

There are no measures necessary for the examination.
For minimise distress they get earphones for sound noising. If patients are scared or had claustrophobic the can get sedatives.
We monitor patients with video and they all have a button for emergency cases

Background therapy:

no background therapy

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 02 July 2012 |
| 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: 73 |
| Worldwide total number of subjects | 73 |
| EEA total number of subjects | 73 |

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) | 35 |
| From 65 to 84 years | 37 |

| | |
|---|---|
| 85 years and over | 1 |

## Subject disposition

### Recruitment

Recruitment details:

We recruited 73 Patients into the trial from november 2012 until january 2016

### Pre-assignment

Screening details:

Inclusion of Subjects from 18-85 years with with clinically suspected or definite ischemic stroke or an intracranial stenosis (> 50% degree) or extracranial stenosis of the internal carotid artery (> 70%). Also clinically indicated initial and follow-up MR examinations of the brain with contrast injection. Written inform consent

### Period 1

| | |
|---|---|
| Period 1 title | overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Single blind |
| Roles blinded | Assessor[1] |

Blinding implementation details:

The blinded readers will have access to the source data and the MIPs. For both CE-MRA and DSC-MRP, the visual (qualitative) image analysis in the blinded read will comprise a dedicated simultaneous matched-pairs assessment from both examinations. The blinded readers will assess the technical adequacy of each examination.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | No |
| **Arm title** | ARM 1 |

Arm description:

Patients receive 2 MRI brain examinations to assess cerebrovascular disease 1. MRI with contrast agent Gadovist® (Gadobutrol, 1.0 M gadolinium chelate, Bayer Healthcare) 2. MRI with contrast agent Dotarem® (Gadoterate, 0.5 M gadolinium chelate, Guerbet

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Gadovist |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Gadobutrol, 1.0 M gadolinium chelate, Bayer Healthcare

| | |
|---|---|
| Investigational medicinal product name | Dotarem |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Gadoterate, 0.5 M gadolinium chelate, Guerbet GmbH

| | |
|---|---|
| **Arm title** | ARM 2 |

Arm description:

Patients receive 2 MRI brain examinations 1. MRI with contrast agent Dotarem® (Gadoterate, 0.5 M gadolinium chelate, Guerbet GmbH); 2. MRI with contrast agent Gadovist® (Gadobutrol, 1.0 M gadolinium chelate, Bayer Healthcare)

| | |
|---|---|
| Arm type | Experimental |

| | |
|---|---|
| Investigational medicinal product name | Gadovist |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Gadobutrol, 1.0 M gadolinium chelate, Bayer Healthcare

| | |
|---|---|
| Investigational medicinal product name | Dotarem |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Gadoterate, 0.5 M gadolinium chelate, Guerbet GmbH

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: only a blinded read by assessor was done

| **Number of subjects in period 1** | ARM 1 | ARM 2 |
|---|---|---|
| Started | 34 | 36 |
| Completed | 28 | 29 |
| Not completed | 6 | 7 |
| Physician decision | 6 | 7 |

## Baseline characteristics

| Reporting groups[1] | |
|---|---|
| Reporting group title | overall trial |
| Reporting group description: - | |

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: there are at least 54 patients included. We indicated 57 but 3 hat to many major motion artefact

| Reporting group values | overall trial | Total | |
|---|---|---|---|
| Number of subjects | 57 | 57 | |
| Age categorical | | | |
| 1 patient were included at the group of 85 years or older<br>27patients were included at the group of 65-84 years<br>29 patients were included at the group of 18-64 years<br>The mean Age is 64 years | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 29 | 29 | |
| From 65-84 years | 27 | 27 | |
| 85 years and over | 1 | 1 | |
| Age continuous | | | |
| 73 Patients analysed with a mean age of 64 and a median age of 65<br>The youngest patient was 26 years and the oldest was 85 years at inclusion | | | |
| Units: years | | | |
| median | 65 | | |
| full range (min-max) | 26 to 85 | - | |
| Gender categorical | | | |
| 60% (36) male and 40% (21) female patients included | | | |
| Units: Subjects | | | |
| Female | 36 | 36 | |
| Male | 21 | 21 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | ARM 1 |

Reporting group description:

Patients receive 2 MRI brain examinations to assess cerebrovascular disease 1. MRI with contrast agent Gadovist® (Gadobutrol, 1.0 M gadolinium chelate, Bayer Healthcare) 2. MRI with contrast agent Dotarem® (Gadoterate, 0.5 M gadolinium chelate, Guerbet

| | |
|---|---|
| Reporting group title | ARM 2 |

Reporting group description:

Patients receive 2 MRI brain examinations 1. MRI with contrast agent Dotarem® (Gadoterate, 0.5 M gadolinium chelate, Guerbet GmbH); 2. MRI with contrast agent Gadovist® (Gadobutrol, 1.0 M gadolinium chelate, Bayer Healthcare)

### Primary: Image quality

| | |
|---|---|
| End point title | Image quality |

End point description:

As primary efficacy endpoint, an overall assessment of image quality will be performed by the blinded readers for both CE-MRA and DSC-MRP images combined:
MR study 1 better than MR study 2
Both MR studies equal
MR study 2 better than MR study 1

| | |
|---|---|
| End point type | Primary |

End point timeframe:

no timeframe applicable

| End point values | ARM 1 | ARM 2 | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 28[1] | 26[2] | | |
| Units: arbitary unit | | | | |
| MR study 1 better than MR study 2 | 10 | 12 | | |
| Both MR studies equal | 12 | 11 | | |
| MR study 2 better than MR study 1 | 6 | 3 | | |

Notes:

[1] - finally 28 patients performed visit 2 from 34 patients who started at this ARM

[2] - finally 29 patients startet visit 2 from 36. 3 patients who started Visit 2 get no 2nd infjection

### Statistical analyses

| | |
|---|---|
| **Statistical analysis title** | Primary Efficacy |
| Comparison groups | ARM 1 v ARM 2 |

| | |
|---|---|
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | < 0.05 |
| Method | ANOVA |
| Parameter estimate | Mean difference (net) |

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| The adverse events where reported earliest after written inform consent and latest 30 minutes after last examination | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 19 |

| Reporting groups | |
|---|---|
| Reporting group title | Headache |
| Reporting group description: | |
| The event was headache. It was considered not to be related to study drug | |

| Serious adverse events | Headache | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Headache | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | | |
| Nervous system disorders | | | |
| Headache | Additional description: Patient get headache after Dotarem injection | | |
| subjects affected / exposed | 1 / 1 (100.00%) | | |
| occurrences (all) | 1 | | |

## 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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

In this study there was a drop out rate of 22% as 16 patients of 73 screened patients did not complete the 2nd MRI.

Notes:

## Online references

http://www.ncbi.nlm.nih.gov/pubmed/28913611