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 27patients were included at the group of 65-84 years 29 patients were included at the group of 18-64 years 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 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