Clinical trial results:
Prospective, open-label, two-arm, parallel-group, single center phase IV clinical trial to evaluate the diagnostic value of a Gadobutrol enhanced dynamic susceptibility perfusion MRI (DSC-MRP) and a non contrast arterial spin labeling perfusion MRI (ASL-MRP) in subjects with minor cognitive impairment or minor Alzheimer's disease compared to age matched mentally healthy subjects

Summary

EudraCT number	2012-001583-29
Trial protocol	DE
Global end of trial date	05 October 2016

Results information

Result version number	v1 (current)
This version publication date	03 May 2020
First version publication date	03 May 2020
Summary attachment (see zip file)	Synopsis (Synopse Alzheimer neu.pdf)

Trial information

Trial identification

Sponsor protocol code	Er-02-Perf-AD

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	EudraCT: 2012-001583-29

Notes:

Sponsors

Sponsor organisation name	Universitätsklinikum Erlangen
Sponsor organisation address	Schwabachanlage 6, Erlangen, Germany, 91054
Public contact	Prof. Dr. Arnd Dörfler, University of Erlangen, 49 091318539388, neuroradiologie@uk-erlangen.de
Scientific contact	Prof. Dr. Arnd Dörfler, University of 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	05 October 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 January 2016
Global end of trial reached?	Yes
Global end of trial date	05 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the robustness of Gadobutrol enhanced DSC-MRP with spin-labeling perfusion studies in subjects with MCI and minor Alzheimer´s disease (AD)

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: 65
Worldwide total number of subjects	65
EEA total number of subjects	65

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)	39
From 65 to 84 years	26
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The recruitment started on November 2012 and ended on January 2016. The Recruitment was only at university hospital erlangen at the department of neuroradiology

Pre-assignment

Screening details:

Subjects with clinical diagnosed minor congnitive impairment or minor Alzheimers Disease based on neuropsychological testing and the MMSE score.
Main criterias was adult subjects, age >45 years, Subjects with symptoms of MCI or minor AD referred for diagnostic work-up with MRI - or mentally healthy control subjects in the same age range

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

no blinding done

Arms

Are arms mutually exclusive?	Yes
Arm title	ARM 1

Arm description:

40 Subjects with MCI or minor AD will undergo a single MRI study with two types of perfusion measurements: Gadobutrol enhanced DSC-MRP and ASL-MRP.

Arm type	Experimental
Investigational medicinal product name	Gadovist
Investigational medicinal product code	
Other name	Gadobutrol
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Gadovist® (Gadobutrol, 1.0 M gadolinium chelate, Bayer Healthcare)
contrast agent is given intravenous with a dose of 0,1mmol/kg of BW via injector.

Arm title	ARM 2

Arm description:

Arm 2: 10 mentally healthy subjects will serve as a reference and will undergo a single MRI study with two types of perfusion measurements: Gadobutrol enhanced DSC-MRP and ASL-MRP.

Arm type	Experimental
Investigational medicinal product name	Gadovist
Investigational medicinal product code	
Other name	Gadobutrol
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Gadovist® (Gadobutrol, 1.0 M gadolinium chelate, Bayer Healthcare)
contrast agent is given intravenous with a dose of 0,1mmol/kg of BW via injector.

Number of subjects in period 1	ARM 1	ARM 2
Started	44	21
Completed	44	21

Baseline characteristics

Reporting groups

Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	65	65	
Age categorical			
33 males (48.5%) and 35 females (51.5%) were enrolled in this study. The mean age was 64 years, the mean weight 79.67kg and the mean height 169.1cm. All subjects in the study were of Caucasian origin. The youngest patient was 46 years at and the oldest 83 years			
Units: Subjects			
Adults (18-64 years)	39	39	
From 65-84 years	26	26	
Age continuous			
In this study patients have to be at least 45 years. Therefore we had an age enrollment range from 46 years to 83 years			
Units: years			
median	62		
full range (min-max)	46 to 83	-	
Gender categorical			
33 males (48.5%) and 35 females (51.5%) were enrolled in this study. The mean age was 64 years, the mean weight 79.67kg and the mean height 169.1cm. All subjects in the study were of Caucasian origin.			
Units: Subjects			
Female	32	32	
Male	33	33	

Subject analysis sets

Subject analysis set title	Demographics
Subject analysis set type	Full analysis

Subject analysis set description:

33 males (48.5%) and 35 females (51.5%) were enrolled in this study. The mean age was 64 years, the mean weight 79.67kg and the mean height 169.1cm.
All subjects in the study were of Caucasian origin.

Subject analysis set title	Medical History
Subject analysis set type	Full analysis

Subject analysis set description:

All relevant medical history was recorded at the screening visit. Table 7 provides the summary of patient`s medical history classified by involved System Organ Class (SOC) and MedDRA preferred term (PT) for the population.
10 (14.7%) subjects had a medical history of Cerebral endovascular aneurysm repair in the study. That is because for the reference group patients were randomized who became a control MRI.

Subject analysis set title	Baseline findings
Subject analysis set type	Full analysis

Subject analysis set description:

All relevant Baseline findings were recorded at the screening visit. Table 8 provides the summary of patient`s Baseline findings classified by involved System Organ Class (SOC) and MedDRA preferred term (PT) for the population.
40 (58.8%) and 30 (44.1%) subjects had a Baseline finding of Cognitive disorder and Hypertension in

the study.

Subject analysis set title	MMSE
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects will undergo a detailed neuropsychological testing and Mini-Mental Score Examination (MMSE) before entering the study protocol. The mean MMSE for all patients was 26.8, for only the subjects 25.6 and for the control group 29.5. Table 10 provides the MMSE scores.

Subject analysis set title	Analysis of Efficacy
Subject analysis set type	Full analysis

Subject analysis set description:

Averaged values for cortex, deep white matter and hippocampus in both hemispheres are presented. DSC-MRP results in a more robust perfusion assessment compared to ASL-MRP. There was no statistical significant difference when comparing image quality of DSC-MRP to ASL-MRP (p > 0.12).

Reporting group values	Demographics	Medical History	Baseline findings
Number of subjects	65	65	65
Age categorical			
33 males (48.5%) and 35 females (51.5%) were enrolled in this study. The mean age was 64 years, the mean weight 79.67kg and the mean height 169.1cm. All subjects in the study were of Caucasian origin. The youngest patient was 46 years at and the oldest 83 years			
Units: Subjects			
Adults (18-64 years)	39	39	39
From 65-84 years	26	26	26
Age continuous			
In this study patients have to be at least 45 years. Therefore we had an age enrollment range from 46 years to 83 years			
Units: years			
median	62	62	62
full range (min-max)	46 to 83	46 to 83	46 to 83
Gender categorical			
33 males (48.5%) and 35 females (51.5%) were enrolled in this study. The mean age was 64 years, the mean weight 79.67kg and the mean height 169.1cm. All subjects in the study were of Caucasian origin.			
Units: Subjects			
Female	32	32	32
Male	33	33	33

Reporting group values	MMSE	Analysis of Efficacy	
Number of subjects	65	65	
Age categorical			
33 males (48.5%) and 35 females (51.5%) were enrolled in this study. The mean age was 64 years, the mean weight 79.67kg and the mean height 169.1cm. All subjects in the study were of Caucasian origin. The youngest patient was 46 years at and the oldest 83 years			
Units: Subjects			
Adults (18-64 years)	39	39	
From 65-84 years	26	26	
Age continuous			
In this study patients have to be at least 45 years. Therefore we had an age enrollment range from 46 years to 83 years			
Units: years			
median	62	62	
full range (min-max)	46 to 83	46 to 83	

Gender categorical			
33 males (48.5%) and 35 females (51.5%) were enrolled in this study. The mean age was 64 years, the mean weight 79.67kg and the mean height 169.1cm. All subjects in the study were of Caucasian origin.			
Units: Subjects			
Female	32	32	
Male	33	33	

End points

End points reporting groups

Reporting group title	ARM 1

Reporting group description:

40 Subjects with MCI or minor AD will undergo a single MRI study with two types of perfusion measurements: Gadobutrol enhanced DSC-MRP and ASL-MRP.

Reporting group title	ARM 2

Reporting group description:

Arm 2: 10 mentally healthy subjects will serve as a reference and will undergo a single MRI study with two types of perfusion measurements: Gadobutrol enhanced DSC-MRP and ASL-MRP.

Subject analysis set title	Demographics
Subject analysis set type	Full analysis

Subject analysis set description:

33 males (48.5%) and 35 females (51.5%) were enrolled in this study. The mean age was 64 years, the mean weight 79.67kg and the mean height 169.1cm.
All subjects in the study were of Caucasian origin.

Subject analysis set title	Medical History
Subject analysis set type	Full analysis

Subject analysis set description:

All relevant medical history was recorded at the screening visit. Table 7 provides the summary of patient`s medical history classified by involved System Organ Class (SOC) and MedDRA preferred term (PT) for the population.
10 (14.7%) subjects had a medical history of Cerebral endovascular aneurysm repair in the study. That is because for the reference group patients were randomized who became a control MRI.

Subject analysis set title	Baseline findings
Subject analysis set type	Full analysis

Subject analysis set description:

All relevant Baseline findings were recorded at the screening visit. Table 8 provides the summary of patient`s Baseline findings classified by involved System Organ Class (SOC) and MedDRA preferred term (PT) for the population.
40 (58.8%) and 30 (44.1%) subjects had a Baseline finding of Cognitive disorder and Hypertension in the study.

Subject analysis set title	MMSE
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects will undergo a detailed neuropsychological testing and Mini-Mental Score Examination (MMSE) before entering the study protocol. The mean MMSE for all patients was 26.8, for only the subjects 25.6 and for the control group 29.5. Table 10 provides the MMSE scores.

Subject analysis set title	Analysis of Efficacy
Subject analysis set type	Full analysis

Subject analysis set description:

Averaged values for cortex, deep white matter and hippocampus in both hemispheres are presented. DSC-MRP results in a more robust perfusion assessment compared to ASL-MRP. There was no statistical significant difference when comparing image quality of DSC-MRP to ASL-MRP ($p > 0.12$).

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 DSC- and ASL-MRP images combined:
DSC-MRP better than ASL-MRP
Both equal
ASL-MRP better than DSC-MRP

End point type	Primary

End point timeframe:

The period of observation extends from the time when the informed consent form was signed until 30 min after last administration of IP(s)

End point values	ARM 1	ARM 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	21		
Units: arbitrary unit				
DSC-MRP better than ASL-MRP	14	7		
Both equal	24	10		
ASL-MRP better than DSC-MRP	6	4		

Statistical analyses

Statistical analysis title	Primary Efficacy

Statistical analysis description:

Three populations were considered for the analyses: the modified intention-to-treat (MITT) the per-protocol (PP) and the safety population. All efficacy endpoints were analyzed for the MITT and PP population of which the MITT population analysis was the primary and PP was the secondary analyses sets and all safety endpoints was analyzed for the safety population

Comparison groups	ARM 1 v ARM 2
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05 [1]
Method	ANOVA

Notes:

[1] - statistically significant.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
The period of observation for an AE extends from the time when the informed consent form was signed until 30 min after last administration of IP(s)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19

Reporting groups	
Reporting group title	Headache
Reporting group description: -	
Reporting group title	Vertigo
Reporting group description:	
Vertigo was considered not to be related to study drug	

Serious adverse events	Headache	Vertigo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	0 / 2 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Headache	Vertigo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	2 / 2 (100.00%)	
Nervous system disorders			
Vertigo	Additional description: Vertigo was considered not to be related to study drug. 2 Patients reported vertigo		
subjects affected / exposed	1 / 1 (100.00%)	2 / 2 (100.00%)	
occurrences (all)	1	2	
Headache	Additional description: Headache had a possible study drug relationship 1 Patient reported headache		
subjects affected / exposed	1 / 1 (100.00%)	2 / 2 (100.00%)	
occurrences (all)	1	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

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

65 patients were in the PP population as 3 patients were drop-outs.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31617743