Name of Sponsor/Company: Universitätsklinikum Erlangen Medizinische Fakultät	Individual Study Table Referring to Part of the Dossier Volume:	(For National Authority Use only)
Name of Finished Product: Gadovist® Approval-Nr.: 40252.00.00		
Name of Active Ingredient: Gadobutrol	Page:	

Title of Study:
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

Investigator(s):
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Study centre(s):
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Publication:
Schmidt MA, Knott M, Hoelter P, Engelhorn T, Larsson EM, Nguyen T, Essig M, Doerfler A. Standardized acquisition and post-processing of dynamic susceptibility contrast perfusion in patients with brain tumors, cerebrovascular disease and dementia: comparability of post-processing software. Br J Radiol. 2020 Jan;93(1105):20190543.

Study period (years):	**Phase of development:**
From: NOV-2012 To: JAN - 2016	IV

Objectives:

Primary Objective:

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

Secondary Objective:

- To assess regional perfusion abnormalities with dynamic susceptibility weighted (DSC-) MR perfusion in subjects with MCI and minor AD compared with mentally healthy subjects serving as a reference.
- To identify areas of reduced perfusion as marker for a dementing disorder.
- To compare the technical performance of both DSC-MRP and ASL-MRP in a cohort of subjects with MCI or minor AD – in regard of image quality and image artifacts.
- To assess the diagnostic value of Gadobutrol as a contrast media in DSC-MRP in subjects with MCI or minor AD.
- To compare the quantitative results of cerebral blood flow measures in both DSC- and ASL-MRP in an intraindividual comparison.

Methodology:
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
Arm 1: 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 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.

Number of patients:
Planned: 40 subjects, 10 mentally healthy volunteers.
Analysed: 44 subjects, 21 mentally healthy volunteers.

Diagnosis and main criteria for inclusion:

Subjects with clinical diagnosed minor congnitive impairment or minor Alzheimers Disease based on neuropsychological testing and the MMSE score.

1. Adult subjects, age >45 years
2. 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
3. Willing to undergo all study procedures
4. Subjects who have completed a neuropsychologic assessment or a MMSE with a score that allows full understanding of the study procedures and ability to give informed consent – for control subjects a normal MMSE is required.
5. Subject has voluntarily given written informed consent

Test product, dose and mode of administration, batch number:
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.

Patient ID	Gadovist Batch	Patient ID	Gadovist Batch
05-01	11551C	05-35	31545B
05-02	11551C	05-36	24582C
05-03	not applied	05-37	24582C
05-04	11550C	05-38	24582C
05-05	11550C	05-39	24582C
05-06	11550C	05-40	31584B
05-07	23579B	05-41	31584B
05-08	23579B	05-42	31584B
05-09	23579B	05-43	31584B
05-10	23579B	05-44	31584B
05-11	not applied	05-45	31584B
05-12	24582C	05-46	31584B
05-13	24582C	05-47	31584B
05-14	31584B	05-48	32596F
05-15	31584B	05-49	33599J
05-16	31584B	05-50	33599J
05-17	31584B	05-51	33599J
05-18	31584B	05-52	34604N
05-19	31584B	05-53	34604N
05-20	31584B	05-54	34604N
05-21	not applied	05-55	34604N
05-22	31584B	05-56	34604N
05-23	31584B	05-57	34604N
05-24	31584B	05-58	34604N
05-25	31584B	05-59	43614D
05-26	31545B	05-60	43614D
05-27	31545B	05-61	43614D
05-28	31584B	05-62	43614D
05-29	31584B	05-63	43614D
05-30	31545B	05-64	43614D
05-31	31584B	05-65	43559A
05-32	31545B	05-66	51621B
05-33	31584B	05-67	51621B
05-34	31584B	05-68	51621B

Duration of treatment:

The total duration of the active treatment was at maximum 1 day from screening to visit.

Criteria for evaluation

Efficacy:

All images will be evaluated for technical adequacy by on site and off site readers to check their eligibility. A blinded read will be performed off site using appropriate technology and equipment. The preparation of the reading will be adhering to international quality standards and documented accordingly. On site, the MR perfusion source data will be analyzed in a standardized way using the Siemens "MRPerf" software. This software generates color-coded parameter maps of mean transit time (MTT), time to peak (TTP), relative cerebral blood volume (rCBV) and relative cerebral blood flow (rCBF). Furthermore, a global bolus plot (GBP) is calculated, showing the time course of the global T2* signal. CE-MRA will be reconstructed on site as rotating thick slice maximum intensity projections (MIP). The blinded readers will have access to the source data, as well as the MIPs. For both DSC- and ALS-MRP, the visual (qualitative) image analysis in the blinded read will comprise a dedicated simultaneous matched-pairs assessment from both examinations together. The blinded readers will assess the technical adequacy of the each examination. Images will be rated as

- 1 = excellent,
- 2 = adequate (with artefacts but tolerable for assessment)
- 3 = inadequate (not tolerable for further evaluation).

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

Safety:

AEs will be listed only along with intensity, relationship, and seriousness. Separate listings will be generated for serious AEs. 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). Any medical occurrence that happens between the time when the informed consent form is signed and the first intake of IP(s) is an AE and has to be documented in the subject`s file and in the CRF AE report form. New AEs reported to the investigator during the observational period, after the last administration of IP(s), must be documented, treated, and followed up like all other AEs.

AEs will not be followed up after the final study visit/safety visit, which is scheduled 30 min after last administration of IP(s).

Pre-existing conditions that do not worsen during the course of the study are not reportable as AEs. To determine whether a condition has worsened, it is compared to the condition of the subject at screening.

Statistical methods:

Differences in white matter/cortical perfusion ratios between patients and controls were assessed by unpaired student’s t-tests after verification of normal distribution of the data.

The potential of a Gadobutrol enhanced dynamic susceptibility perfusion MRI (DSC-MRP) and a non contrast arterial spin labeling perfusion MRI (ASL-MRP) to predict hypoperfusion was tested using receiver operating characteristics.

Statistical analysis were performed using SPSS version 19 (IBM, Ehningen, Germany). The value $p < 0.05$ was considered statistically significant.

SUMMARY - CONCLUSION

EFFICACY RESULTS:

Patients showed markedly decreased cortical perfusion in the bilateral frontal lobe compared to controls. Diagnostic performance of relative cerebral blood volume (corrected for T1

effects, rBVc) was highest compared to ASL for frontal hypoperfusion (sensitivity 83%, specificity 80%, $p < 0.05$) in FTD and MCI. For non-leakage corrected rBV and rBF sensitivity of frontal hypoperfusion was above 80% (rBV: sensitivity 83%, specificity 75%, $p < 0.05$; rBF: sensitivity 83%, specificity 65%,$p < 0.05$).

SAFETY RESULTS:
Overall 4.4% subjects experienced AEs related to system organ class - Nervous system disorders. One event was headache, the other 2 events were vertigo. Vertigo was considered not to be related to study drug, headache had a possible study drug relationship.

CONCLUSION:
DSC-MR-perfusion using advanced deconvolution models can detect brain hypoperfusion in variety of subtypes of dementia. Hence, this widely accessible technique has the potential to improve the diagnosis of early dementia as part of an interdisciplinary work-up.

Date of the report:
02/03/2020