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| **Name of Sponsor/Company:**<br><br>Universitätsklinikum Erlangen<br>Medizinische Fakultät | Individual Study Table Referring to Part of the Dossier<br><br>Volume:<br><br>Page: | (For National Authority Use only) |
| **Name of Finished Product:**<br>Gadovist® Approval-Nr.: 40252.00.00<br>Dotarem® Approval-Nr.: 56812.00.01 | | |
| **Name of Active Ingredient:**<br>Gadobutrol, Gadoterate | | |

**Title of Study:**
Intraindividual cross-over comparison of Gadobutrol and Gadoterate enhanced combined DSC-MR-Perfusion and MR-Angiography in patients with cerebrovascular disease

**Investigator(s):**
Prof. Dr. med. Arnd Dörfler

**Study centre(s):**
Universitätsklinikum Erlangen, Abteilung Neuroradiologie, Schwabachanlage 6, 91054 Erlangen

**Publication:**

- Hoelter P, Lang S, Weibart M, Schmidt M, Knott MFX, Engelhorn T, Essig M, Kloska S, Doerfler A. Prospective intraindividual comparison of gadoterate and gadobutrol for cervical and intracranial contrast-enhanced magnetic resonance angiography. Neuroradiology. 2017 Dec;59(12):1233-1239
- 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<br>To: JAN - 2016 | IV |

**Objectives:**

<u>Primary Objective:</u>

- To compare Gadobutrol to Gadoterate in DSC-MR perfusion imaging and contrast-enhanced MR angiography in acute stroke subjects and/or subjects harboring an intracranial stenosis or extracranial ICA stenosis

<u>Secondary Objective:</u>

- To assess the feasibility of a dual injection protocol in MRI in subjects with acute stroke or cerebrovascular diseases.
- To evaluate descriptively whether Gadobutrol enhanced study protocol provides superior information to guide and tailor further diagnostic and / or therapeutic decisions in this kind of subject population.
- To evaluate descriptively whether Gadobutrol has a superior vessel contrast and contrast-to-noise ratio in CE-MRA studies (quantitative analysis).
- To evaluate descriptively whether the vessel conspicuity and stenosis characterization with the use of Gadobutrol is superior (qualitative analysis).
- To evaluate whether the signal drop after gadobutrol injection in DSC-MRP is superior

based on a quantitative analysis of the signal intensity time curve.

- To assess the correlation between the cardiac ejection fraction (if available) and the DSC-MRP quality.

**Methodology:**
Single-center, open-label (due to different volumes of the study and reference medication), randomized, prospective, intraindividual comparative phase IV clinical trial.Cerebrovascular subjects will undergo two MRI studies with two types of measurements: Gadobutrol vs. Gadoterate for DSC-MRP and/or CE-MRA;

Arm 1: 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 GmbH);
The interval between the 2 examinations is 12 h to 7 days.
Both contrast agents are given intravenous with a dose of 0,1mmol/kg of BW via injector

Arm 2: 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)
The invervall between the 2 examinations is 12 h to 7 days.
Both contrast agents are given intravenous with a dose of 0,1mmol/kg of BW via injector

**Number of patients:**
Planned: 90
Analysed: 73

**Diagnosis and main criteria for inclusion:**
Subjects with clinically suspected or known cerebrovascular disease and ischemic stroke
1. adult subjects, age 18-85 years
2. with clinically suspected or definite ischemic stroke or an intracranial stenosis (> 50% degree) or extracranial stenosis of the internal carotid artery (> 70%)
3. clinically indicated initial and follow-up MR examinations of the brain with contrast injection
4. willing to undergo and comply with all study procedures
5. 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 |
|---|---|---|---|
| 01-01 | 13532C | 01-38 | 31584B |
| 01-02 | 23539B | 01-39 | 32596F |
| 01-03 | not applied | 01-40 | 32596F |
| 01-04 | 11551C | 01-41 | 32596F |
| 01-05 | 23541C | 01-42 | 33599J |
| 01-06 | 23541C | 01-43 | 33599J |
| 01-07 | 23541C | 01-44 | 33599J |
| 01-08 | 23541C | 01-45 | 33599J |
| 01-09 | 24543B | 01-46 | 34604N |
| 01-10 | 11551C | 01-47 | not applied |
| 01-11 | 31544A | 01-48 | 34604N |
| 01-12 | not applied | 01-49 | 34604N |
| 01-13 | 24543B | 01-50 | 34604N |
| 01-14 | not applied | 01-51 | 34604N |
| 01-15 | 24543B | 01-52 | 34604N |

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|---|---|---|---|
| 01-16 | 31545B | 01-53 | 32548F |
| 01-17 | 31544A | 01-54 | 43614D |
| 01-18 | 31544A | 01-55 | 43614D |
| 01-19 | 31545B | 01-56 | 43614D |
| 01-20 | 31545B | 01-57 | not applied |
| 01-21 | 31545B | 01-58 | 43559A |
| 01-22 | 31545B | 01-59 | 43614D |
| 01-23 | 31545B | 01-60 | 43614D |
| 01-24 | not applied | 01-61 | 43614D |
| 01-25 | not applied | 01-62 | 43614D |
| 01-26 | 31546B | 01-63 | not applied |
| 01-27 | 31546B | 01-64 | 43614D |
| 01-28 | 32548A | 01-65 | 43559A |
| 01-29 | 24582C | 01-66 | 51621B |
| 01-30 | 24582C | 01-67 | 51621B |
| 01-31 | 24582C | 01-68 | 51621B |
| 01-32 | 32599F | 01-69 | 51621B |
| 01-33 | 32599F | 01-70 | 51621B |
| 01-34 | 32599F | 01-71 | 51621B |
| 01-35 | 31584B | 01-72 | 51621B |
| 01-36 | not applied | 01-73 | not applied |
| 01-37 | 31584B | | |

**Duration of treatment:**

The total duration of the active treatment was at maximum 7 days from Screening to last visit.

**Reference therapy, dose and mode of administration, batch number:**

Dotarem® (Gadoterate 1.0 M gadolinium chelate, Bayer Healthcare)

| Patient ID | Dotarem Batch | Patient ID | Dotarem Batch |
|---|---|---|---|
| 01-01 | not applied | 01-38 | 136D071A |
| 01-02 | 126D079A | 01-39 | 136D071A |
| 01-03 | 126D080A | 01-40 | 136D084A |
| 01-04 | 126D080A | 01-41 | 136D071A |
| 01-05 | 126D1014 | 01-42 | 136D092A |
| 01-06 | 126D080A | 01-43 | 136D084A |
| 01-07 | not applied | 01-44 | 136D084A |
| 01-08 | 126D104A | 01-45 | 136F092A |
| 01-09 | 126D104A | 01-46 | 136D106A |
| 01-10 | 126D080A | 01-47 | 136D107A |
| 01-11 | 126D104A | 01-48 | not applied |
| 01-12 | not applied | 01-49 | 136D107A |
| 01-13 | 126D104A | 01-50 | 146D052A |
| 01-14 | 126D091B | 01-51 | 146D052A |
| 01-15 | not applied | 01-52 | 136D107A |
| 01-16 | 126D091B | 01-53 | 146D061A |
| 01-17 | 126D091B | 01-54 | 146D061A |
| 01-18 | 126D104A | 01-55 | 146D061A |
| 01-19 | 126D104A | 01-56 | 146D061A |
| 01-20 | 126D104A | 01-57 | 146D061A |
| 01-21 | not applied | 01-58 | not applied |
| 01-22 | 126D091B | 01-59 | 146D091A |
| 01-23 | 126D119A | 01-60 | 136D107A |
| 01-24 | 126D091B | 01-61 | not applied |
| 01-25 | 126D091B | 01-62 | 146D006A |
| 01-26 | 136D016A | 01-63 | not applied |
| 01-27 | 136D014A | 01-64 | 156D061A |
| 01-28 | 136D014A | 01-65 | 146D007A |
| 01-29 | 136D014A | 01-66 | 146D007A |
| 01-30 | 136D014A | 01-67 | 146D007A |
| 01-31 | 136D014A | 01-68 | 156D016A |
| 01-32 | 136D062A | 01-69 | 146D007A |
| 01-33 | 136D062A | 01-70 | 156D052A |

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|---|---|---|---|
| 01-34 | 136D066A | 01-71 | 156D052A |
| 01-35 | 136D066A | 01-72 | 156D036A |
| 01-36 | not applied | 01-73 | 156D052A |
| 01-37 | 136D069A | | |

**Criteria for evaluation:**

**Efficacy:**

**Primary target variables**

All images will be evaluated for technical adequacy by one 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. On site, the MR perfusion source data will be analyzed in a standardized way using Siemens "MRPerf" software. Furthermore, a global bolus plot is calculated , showing the exact time course of the T2* signal change. CE-MRA will be reconstructed on site as rotating maximum intensity projection (MIP). 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. Hereby, 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 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

**Secundary target variables**

CE-MRA-derived absolute signal-to-noise ratio (SNR) will be measured for 23 supraaortic vessel segments:

- Aortic arch
- Brachiocephalic artery
- Right and left subclavian artery
- Right and left common carotid artery
- Right and left external carotis artery
- Right and left internal carotid artery (each with the extracranial segment, petrous, lacerum and cavernous segment)
- Right and left vertebral artery (each with preforaminal and foraminal segment and C1 loop)

As DSC-MRP parameters highly depend on the current circulation status of the patient, no quantitative assessment will be performed.

**Safety:**

AEs will be listed only along with intensity, relationship, and seriousness. Separate listings will be generated for serious AEs.

**Statistical methods:**

Descriptive statistics will be calculated for quantitative variables; frequency counts by category will be given for qualitative variables. Confidence intervals will be given where appropriate. These intervalls will be two-sided and provide 95% confidence.

The primary and secondary efficacy analyses will be performed on a modified ITT population, for which images of both MRI examinations and readers assessments are available. The primary efficacy endpoint is the overall assessments of contrast enhancement on a three-point scale in a matched-pairs assessment from MR imaging examinations of all MR images

after Gadobutrol and after Gadoterate administration. No subgroup analysis is planned.

Descriptive statistics will be performed on demographic data. Medical and surgical history will be listed only. Baseline data will be listed and summarized descriptively where appropriate.

**SUMMARY - CONCLUSION**

**EFFICACY RESULTS**

To our knowledge this is the first study that quantitatively compared equimolar doses of Gadobutrol and Gadoterate in patients with neurovascular disease for cervical and intracranial CE-MRA.

We could demonstrate, compared to Gadoterate, the use of Gadobutrol resulted in a significantly higher SNR and CNR in cervical and cerebral CE-MRA leading to a better delineation of the intracranial vasculature. This underlines the potential of Gadobutrol for improved CE-MRA assessment of challenging vasculature in patients with cervical and intracranial vessel diseases.

**SAFETY RESULTS**

Safety data were presented for the safety population, which included all patients who had been randomized to receive the study medications. The contrast agents were well tolerated. No adverse event was reported at the visit of Gadovist® injection. One adverse event was reported at the visit of Dotarem® injection.

Hence, overall 1(1.4%) subjects experienced AEs related to system organ class - Nervous system disorders. The event was headache. It was considered not to be related to study drug. No deaths, other SAEs and other significant AE(s) were reported in this study.

**CONCLUSION**

We could demonstrate that the SNR and CNR of Gadobutrol is significantly higher compared to Gadoterate in respect to the total of all measured arteries. This is reflected by a significant better image of the intracerebral vasculature. Further studies are needed to evaluate the clinical impact of improved enhancement on the assessment of cervical and intracranial vessel diseases.

Date of the report:

02/03/2020