Report Synopsis of Study:

EudraCT-Nr.: 2010 – 021526-36

Vorlage-Nr.: 4036906

1) **Name of Sponsor/Company:** Klinikum der Ludwig-Maximilians Universität München	4) **Individual Study Table Referring to Part of the Dossier:** not applicable[1] Volume: not applicable Page: not applicable	*(For National Authority Use only)*
2) **Name of Finished Product:** Gadovist, Dotarem, Multihance		
3) **Name of Active Substance:** Gadobutrol**,** Gadoteric Acid, Gadobenic Acid		

5) **Title of Study[2]:**

Dynamic and high-resolution MR angiography of the supraaortic vessels at 3 Tesla: Performance of Gadobutrol (Gadovist) in comparison to Gedobenate Dimeglumine (Multihance) and Gadoterate Meglumine (Dotarem) at equimolar dose (0.1 mmol/kg BW) in volunteers and patients with carotid artery stenosis

Protocol Amendment:

Protocol Amendment 21.02.2011, Protocol Version 1.1: Clarification of sample size, clarification of exclusion criteria regarding renal disease, no reduction provision for insurance added, clarification of financial aspect, minimum gap of MRI examination was extended from 12h to 48h

6) **Principal Investigator(s):** Prof. Konstantin Nikolaou

7) **Study centre(s):** Klinikum der Ludwig-Maximilians Universität München, Institut für klinische Radiologie, Marchioninistr. 15, 81377 München

8) **Publication (reference):** Invest Radiol. 2013 Mar;48(3):121-8. doi: 10.1097/RLI.0b013e31827752b4

9) **Studied period (years)[3]:** Date of first enrolment: 06/2011 Date of last completed: 08/2011	10) **Phase of development:** Phase IV

11) **Objectives:**

Primary Objectives: To compare the performance of 1 molar gadobutrol in dynamic and static high resolution supraaortic MR angiography with two different 0.5 molar Gd-chelates exhibiting weak (gadobenate dimeglumine) or no (gadoterate meglumine) protein binding at 3 Tesla using equimolar-doses.
Primary objective of the volunteer study is to provide estimates of the overall assessment of contrast enhancement of the three contrast agents as the basis for the sample size calculation of the subsequent patient study.

Remark: Patient study was not conducted, due to much too high figures of the calculation power, based on the data of the volunteer study. Patient study could have not been realized in a reasonable timeframe.

Secondary Objectives:

- to compare vessel signal-to-noise (SNR) and contrast-to-noise (CNR) in high resolution MR angiography at the carotid bifurcation and at the intracranial internal carotid artery at the level of carotid T

[1] This information is only required in connection with filing of a dossier for marketing authorization.

[2] The latest protocol version must be clearly stated, this means including all amendments – the amendments are to be declared and identified.

[3] Here also study suspensions and premature terminations of a trial/premature conclusion of a trial should be listed, including the reasons for that.

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• to compare vessel signal-to-noise (SNR) and contrast-to-noise (CNR) in dynamic MR angiography at the carotid bifurcation and at the intracranial internal carotid artery at the level of carotid T

• to document safety data for the three compounds

12) **Methodology:** Single blind, prospective, controlled intra-individual comparison study with central reading of patient image data by two independent and blinded readers.

Volunteer part: 20 Volunteers without evidence of significant supraaortic vessel disease will receive 3 contrast-enhanced MR angiography (MRA) studies. Each volunteer will receive all three tested MR contrast agents in random order (1 contrast agent per MRA examination), the interval between three MRA studies will be between 48 hours and 30 days. The investigator in an interim analysis will analyze image data from the volunteers. Based on the results of the interim analysis, the sample size for the patient part of this study will be determined.

Patient part: The exact number of patients required for this study part will be determined after completion of the analysis of the volunteer part. Patients with suspected or proven carotid artery disease will receive 2 MRA examinations with either gadobutrol and gadobenate dimeglumine (group 1) or gadobu- trol and gadoterate meglumine (group 2). The minimum interval between the 2 MRA examinations will be between 48 hours and 30 days. Image data from the patient studies will be analyzed in a centralized analysis by three independent andblinded readers.

13) **Number of patients (planned and analyzed):** 20

14) **Diagnosis and main criteria for inclusion:**

Inclusion criteria:

Volunteer part:

1. age: at least 18 years

2. no history of cardiovascular disease

3. willing to undergo all study procedures

4. has voluntarily signed and dated the informed consent form

Women of childbearing potential:

5. a negative pregnancy test (urine test) on the day of contrast agent administration

6. use of a highly effective method of birth control during the duration of the study (e.g. implants, injectables, combined oral contraceptives, some intrauterine devices, sexual abstinence or vasectomised partner)

Patient part**:**

1. age: at least 18 years

2. suspicion or proven carotid artery stenosis / stenoses

3. willing to undergo all study procedures

4. has voluntarily signed and dated the informed consent form

Women of childbearing potential:

5. a negative pregnancy test (urine test) on the day of contrast agent administration

6. use of a highly effective method of birth control during the duration of the study (e.g. implants, injectables, combined oral contraceptives, some intrauterine devices, sexual abstinence or vasectomised partner

15) **Test product, dose and mode of administration, batch number:**

Gadobutrol, at single dose (1mmol/kg body-weight). Injection via antecubital vein @ 2ml/sec injection rate.

Volunteer part:

Gadobutrol (Gadovist)

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BatchNr. 11778F: Patient Nr. 01-19

BatchNr. 12870D: Patient Nr. 20

Patient part: was not conducted

16) **Duration of treatment:** 3 visits, each visit approx. 90min. All visits within 90 days.

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

Gadoteric Acid, Gadobenic Acid– all administered at single dose (0,5 mmol/kg body-weight). Injection via antecubital vein @ 2ml/sec injection rate.

Volunteer part:

Gadoteric Acid (Dotarem):

BatchNr. 11GD003A: PatientNr. 01-09,11-14, 17

BatchNr. 11GD007B: PatientNr 10,16,18,19

BatchNr. 11GD025B: PatientNr 15, 20

Gadobenic Acid (Multihance):

BatchNr. S1P254E: PatientNr. 01-19

BatchNr. S1P252D: PatientNr. 20

Patient part: was not conducted

18) **Criteria for evaluation:**

Efficacy:

Qualitative image quality of all static MRA data sets was assessed independently by two radiologists with each more than 10 years of experience in MRA using pairwise comparisons with grading the following categories: better, equal or worse than the comparator. Both observers were blinded to any information in regard to the used contrast agent. Quantitative analysis of both, static and dynamic MRA datasets was performed based on the assessment of signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) at the level of the proximal internal carotid artery (ICA) next to the carotid bifurcation and at the distal ICA just proximal to the carotid T at the level of the skull base. Since static and dynamic MRA acquisitions employed parallel imaging techniques, SNR and CNR evaluations were performed applying the difference method as previously described by Dietrich et al.. Hence two consecutive unenhanced datasets were acquired prior to contrast agent application and subtracted from each other. The standard deviation within a region-of-interest (ROI) positioned in the subtracted dataset at identical position than the signal measurement in the enhanced data set was defined as image noise for that specific location. For calculation of contrast between the vessel signal and the surrounding tissues a ROI was positioned within the masseter muscle. In addition to SNR and CNR evaluation a semi-automated quantitative evaluation of the vessel edge sharpness (VS) was performed using an in-house developed MATLAB® (MathWorks, Natick, MA, USA) based tool. After user-based identification of the center of the vessel of interest on an axial reformatted slice the tool automatically generated six equally spaced radial spokes in 30º intervals. Each of the six spokes provided a line profile and two vessel edges for a total of twelve vessel edges. VS (mm) was defined as the distance between the 20% and 80% of the maximum signal intensity on each side of the line profile

Safety: Following each exam hemodynamic parameters were reassessed and subjects monitored for the occurrence of adverse events. No adverse events were observed.

19) **Statistical methods:**

For assessment of contrast agent superiority via qualitative pair-wise preference comparisons a Wilcoxon signed rank test as well as Cohen's kappa for assessment of inter-reader agreement were used. For assessment of quantitative parameters like SNR, CNR and VS

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linear mixed effects models, 6 Kruskal-Wallis tests as well as Wilcoxon rank-sum test were used. P < 0.05 (twosided) was considered as statistically significant. Computations were done using measurements of all volunteers; given values are mean values. Given standard deviations are mean values of measured standard deviations. All computations were done in R for Windows, version 2.12.1 (R Development Core Team, 2009).

20) **Summary – Conclusions:**

Efficacy results:

Qualitative analysis

In none of the volunteers circulatory parameters in terms of blood pressure and heart rate differed significantly from each other between the three different exams. No significant differences were observed between pre- and post-exam measurements. Additionally, since the investigated cohort consists of healthy, relatively young men, no significantly different circulatory parameters occurred interindividually. Combined results of the pair-wise comparison of static MRA datasets acquired with Gadobutrol, Gadobenate dimeglumine and Gadoterate meglumine showed Gadobutrol superior to Gadobenate dimeglumine in 10 (50%) cases and to Gadoterate meglumine in 17 (85%) cases. It was rated as equal to the comparator in 7 and 2 cases (35/10%) when compared to Gadobenate dimeglumine and Gadoterate meglumine, respectively. Gadobutrol was judged as inferior compared to Gadobenate dimeglumine and Gadoterate meglumine in 3 and 1 case (15/5%) respectively. Gadobenate dimeglumine was judged as superior, equal or inferior as compared to Gadoterate meglumine in 10, 5 and 5 cases (50/25/25%, figure 2, table 3). Wilcoxon rank test reavealed Gadobutrol to be insignificantly different compared to Gadobenate dimeglumine (p 0.057) but significantly superior as compared to Gadoterate meglumine (p < 0.005). Gadobenate dimeglumine was rated as not significantly different from Gadoterate meglumine (p 0.208). The inter-reader agreement for this qualitative pair-wise evaluation was good to excellent with Cohen's kappa values of 0.66 to 0.83 for the comparison of Gadobutrol with Gadobenate dimeglumine (k=0.656) and Gadoterate meglumine (k=0.830) as well as Gadobenate dimeglumine and Gadoterate meglumine (k=0.663).

Quantitative analysis

Static MRA

Gadobutrol featured significantly higher SNR at the level of the proximal ICA as compared to Gadobenate dimeglumine (p=0.045) and Gadoterate meglumine (p=0.033) with values of 87.39±4.22, 47.82±3.99 and 44.87±3.45 (55% and 51% of SNR achieved with Gadobutrol) respectively. In the distal ICA at the level of the skull base SNR was not significantly different between all agents with values of 81.72±5.62, 58.41±7.07 (71%) and 51.95±5.83 (64%) for Gadobutrol, Gadobenate dimeglumine and Gadoterate meglumine respectively. CNR in MRA datasets acquired with Gadobutrol again was superior as compared to Gadobenate dimeglumine (p=0.134) and significantly better than Gadoterate meglumine (p=0.03) with values of 71.13±3.8, 36.94±3.92 (52%) and 30.52±3.47 (43%) respectively. Calculation of vessel sharpness revealed no significant different results for all three agents with values of 1.172±0.239mm, 1.051±0.177mm and 1.114±0.266mm for Gadobutrol, Gadobenate dimeglumine and Gadoterate meglumine, respectively.

Dynamic MRA

The absence of significant inter- and intraindividual differences in terms of hemodynamic parameters is reflected by the finding that the average maximal SNR is reached within a range of 3 timeframes (18.5 – 21 sec p.i. in the proximal ICA, 20 – 22 sec p.i. at the level of the skull base) in all exams. Dynamic MRA like static MRA showed higher SNR of Gadobutrol as compared to both comparators at the two investigated levels in the proximal ICA as well as at the level of the skull base (proximal ICA p 0.022 and 0.002, distal ICA p 0.04 and 0.012). At the level of the proximal ICA Gadobutrol, Gadobenate dimeglumine and Gadoterate meglumine reached a maximal SNR of 76.73, 59.41 (77%) and 43.99 (57%) respectively. At the level of the skull base agents reached a maximal SNR of 117.77, 83.77 (71%) and 71.22 (60%) respectively.

Safety results: Following each exam hemodynamic parameters were reassessed and subjects monitored for the occurrence of adverse events. No adverse events were observed.

Conclusion:

This study indicates that in static and dynamic MRA of the carotid arteries a contrast agent that features a higher Gd-concentration shows higher qualitative image quality as well as higher SNR and CNR as compared to 0.5 molar agents, no matter if they feature protein interaction / binding or not. Since we could not confirm the finding that contrast agents with an at least temporary binding to blood components are beneficial for morphologic imaging for MRA applications, it appears that the high relaxivity of these agents due to concentration differences of contrast agent molecules and human albumin in the first pass bolus is reached after some time of interaction with blood components but not directly after injection. However, these agents might be superior due to higher relaxivity in later phase imaging. Our results reflect findings in carotid MRA and the evaluated characteristics might be different in other vascular territories that are imaged with an extended delay after injection. Using a highly concentrated GBCA enables comprehensive static and dynamic MRA imaging of the head and neck arteries without the need to exceed the recommended dosage of 0.1mmol/kg bw.

21) **Date of the report: 02.09.2020; rev.: 16.11.2020**