Single Dose Gadobutrol in comparison to single dose Gadobenate Dimeglumine for Magnetic Resonance Imaging of Chronic Myocardial Infarction at 3 Tesla GADOVIT

Test product: **Gadobutrol**

Study Code: GAD-1140-WIL-0020-I

Eudra-CT Number: 2010-022570-13

First Patient First Visit: 31.08.2012– Last Patient Last Visit: 20.05.2013

Sponsor
Technische Universität München (TUM), Fakultät für Medizin
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Synopsis

Name of Sponsor: Technische Universität München Fakultät für Medizin	
Name of Finished. Product: Gadobutrol	
Name of Active Ingredient: Gadobenate Dimeglumine	
Title of Study: Single Dose Gadobutrol in comparison to single dose Gadobenate Dimeglumine for Magnetic Resonance Imaging of Chronic Myocardial Infarction at 3 Tesla	
Investigators: PD. Dr. med. Armin Huber Dr. med. Moritz Wildgruber	
Study centre(s): Single Centre	
Publication (reference): Bauner KJ, Reiser MF, Huber AM (2009). Invest Radiol; 44: 95-104 FDA alert (6-2006, updated 12-2006): FDA Information for Healthcare Professionals: Development of Serious, Sometimes Fatal Nephrogenic Systemic Fibrosis/Nephrogenic Fibrosing Dermopathy following exposure to Gadolinium-based Contrast Agents. Grobner T (2006). Nephrol Dial Transplant; 21: 1104-8 Huber AM, Schoenberg SO, Spannagl B et al (2004). Radiologe; 44: 146-51 Hunt CH, Hartman RP, Hesley GK (2009). Am J Roentgenol; 193:1124-7 Kim HW, Farzaneh-Far, Kim RJ (2010). JACC; 55: 1-16 Thygesen K, Alpert JS, White HD et al. On behalf of the joint ESC/ACCF/AHA/WHF Task force Redefinition of Myocardial Infarction (2007). Circulation; 116:2634-2653 Theisen D, Wintersberger BJ, Huber AM et al. (2007). Invest Radiol; 42: 499-506	
Studied period: one year **first patient in: 31.08.2012** **last patient out: 20.05.2013** **Approvals:** After submission to Bundesinstitut für Arzneimittel und Medizinprodukt (BfArM) 21.09.2010 and subsequent approval 25.07.2012 documents were submitted to Ethics Committee (EC) 21.09.2010 and consecutively approved 20.07.2012 No amendment was requested. CSR: Final Version 1.0 from 12.08.2010 Knowledge of a non-substantial change Finale version 1.1 from 25.06.2012	**Phase: II**

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Objectives:
Primary Objective
Comparison of contrast to noise ratio (CNR) after 0.1mmol/kg gadobutrol compared to 0.1mmol/kg gadobenate dimeglumine between infarcted and remote myocardium as between infarcted myocardium and blood pool.
Secondary Objectives
Comparison of signal to noise ratio (SNR) after 0.1mmol/kg gadobutrol compared to 0.1mmol/kg gadobenate dimeglumine in infarcted and remote myocardium as well as within the blood pool

Methodology:
Overall Study Design and Plan
Single-center, prospective randomized study, cross-over design, patients with chronic myocardial infarction
Application of two different gadolinium-based contrast agents within 28 days

Number of patients (planned and analyzed):
Planned sample size: 20 patients.
Randomized: 20 patients.
Analyzed: 20 patients (12 male, 8 female).

Test product, close and mode of administration, batch number:
Treatment:
Test product : Gadobutrol (Gadovist®, Bayer Schering Pharma AG)
Chargen-number: 13034C, 13034B, 22042E, 21039 A and 21041D
Reference product: Gadobenate dimeglumin (Multihance®, Bracco Imaging GmbH)
Chargen-number: S2P274C
Specify total dose (number and unit): 0,1 mmol/kgKG
Route of administration: Intravenous use

Duration of treatment:
28 days

Criteria for evaluation:
Safety:
Adverse events were to be recorded, classified and listed.

Two sample cohorts were defined: Safety Set (SAF) and Full-Analysis Set (FAS):
1. The Safety Set (SAF) incorporates all patients enrolled in the study (written informed consent) who completed one of the two MRI sessions (1st visit).
2. Patients who did not complete both MRI sessions were excluded from the final data analysis. The Analysis Set (FAS) contains all patients that completed both MRI sessions (visit 1 and 2).
As all patients completed each visit, the SAF is identical with the FAS. Therefore only this report refers only to one dataset.
Due to the limited number of 20 patients no further subgroups were defined.
Adverse events
Safety assessments for the study were defined as followed:

- Frequency of serious adverse events (SAE)
- Frequency of adverse events (AE)
- Frequency of AE categorized according to the cause related to the AE
- Frequency of AE classified according to the severity of the AE

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Statistical methods:
Confirmatory analysis of the primary endpoints using two-sample t-tests on a two-sided 2.5% level of significance (two tests, Bonferroni correction).
Exploratory Analysis of the interaction between treatment and period using two-sided, two-sample t-tests.
Descriptive statistics given by arithmetic means and standard deviations.
Analysis set: Per-Protocol-Population consisting of 20 patients who completed both MRI sessions.
Efficacy Measurements
Primary endpoints: Contrast to noise ratio (CNR) after 0.1mmol/kg gadobutrol compared to 0.1mmol/kg gadobenate dimeglumine between infarcted and remote myocardium as between infarcted myocardium and blood pool: $CNR = (SI_{infarct} - SI_{myokardium}) / SD_{noise}$ *and* $CNR = (SI_{infarct} - SI_{blood}) / SD_{noise}$.
Secondary endpoints: Signal to noise ratio (SNR) after 0.1mmol/kg gadobutrol compared to 0.1mmol/kg gadobenate dimeglumine in infarcted and remote myocardium as well as within the blood pool: $SNR = SI_{infarct}/SI_{noise}$ and $SNR = SI_{myocardiumt}/SI_{noise}$ and $SNR = SI_{blood}/SI_{noise}$.

Summery –Results- Conclusions:
Concomitant medications/non-drug therapy: none
Efficacy:
A statistically significant result was observed for the primary endpoint given by the CNR of infarct and left ventricular blood. All other endpoints did not reach statistical significance. All tests could be performed as there was no evidence of a treatment time period interaction. Results are summarized by Table 1.
Safety: No AE, SAE, SARs or SUSAR occurred during the entire study period.
Adverse Events of Special Interest (AESI)
There were no specific signs, symptoms or diagnoses preceding SAE (AESI) identified during the course of the study.
Efficacy Conclusions and Safety Conclusions
In the current study, we compared two high-relaxivity contrast agents, gadobutrol and gadobenate dimeglumine for late-gadolinium enhancement of chronic myocardial infarction at 3 T. A field strength of 3 T is becoming more commonly used for clinical MRI examinations, as the SNR increases proportionally to B_0 in theory with subsequent higher SNR and CNR values. The determination of the correct TI is important to obtain a high contrast between the bright infarcted and the remote myocardium on magnitude images. A failure in choosing the correct TI can lead to a severe loss of contrast and image artifacts. Therefore, Kellman et al implemented a phase-sensitive inversion recovery (PSIR) technique for LGE imaging. It has been shown that PSIR imaging provides a high and stable CNR between infarct and normal myocardium, even when short default inversion times are used. Thus, the need to determine the correct TI can be avoided and a more consistent image quality can be achieved. We chose a segmented 2D PSIR gradient echo sequence for LGE imaging in our study protocol. However, we used an individual adaptation of the inversion time in order to make images, acquired after the application of the two different contrast agents, as comparable as possible. Our results demonstrate that gadobutrol and gadobenate dimeglumine administered at a dose of 0.1 mmol/kg are similarly effective in determining the size of the infarcted myocardium. The infarct area determined on a selected slice, the entire infarct volume and the transmural extent showed high concordance for LGE imaging with gadobutrol and gadobenate dimeglumine. Gadobutrol provided a higher contrast between infarcted myocardium and the left ventricular blood compared to gadobenate dimeglumine. According to previous observations, the signal intensity in the left ventricular cavity is still high, when images are acquired 10 minutes after the application of gadobenate dimeglumine. The

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protein binding properties of gadobenate dimeglumine are considered to be responsible for this observation. In a previous study, Secchi et al. detected only a minor contrast between left ventricular cavity and adjacent infarcted myocardium at 1.5 T. A delay of at least 10 minutes seems to be necessary to allow for a certain clearing of gadobenate dimeglumine from the blood with subsequently improved contrast between infarct and blood. When using gadobutrol at a dose of 0.1 mmol/kg, LGE imaging seems to be possible already at 10 minutes post contrast injection with high CNR between infarcted and remote myocardium as well as between infarcted myocardium and blood. The blood half-life of gadobenate dimeglumine and gadobutrol in healthy subjects is reported in a similar range of 1.5 hours, which however increases dramatically in case of decreased renal function[18]. As all patients included in our study had similarly normal renal function, a significant impact of renal clearance on the blood pool contrast is considered as unlikely. In conclusion, both gadobutrol and gadobenate dimeglumine allow for successful LGE imaging at a reduced dose of 0.1 mmol/kg at 3 T. Ten minutes after injection gadobutrol is superior compared to gadobenate dimeglumine concerning the contrast between infarct and the left ventricular cavity, which may be advantageous for the detection of small subendocardial infarctions. Contrast between infarct and myocardium, infarct areas, volumes and transmurality are similar for both contrast agents. No adverse events (AE) or serious adverse events (SAE) occurred during the entire study period. Therefore cardiac MRI with both contrast agents at the applied dose can be regarded as acceptable in terms of patient safety and tolerability.
Datum des Berichts: 28.05.2014

Table1:

The mean ± standard deviation of SNR and CNR are given in Table 1. Mean SNR values of infarct, remote myocardium and blood showed only minimal differences between gadobutrol and gadobenate dimeglumine. The comparison of the mean CNRinfarct/myocardium values between the two contrast agents showed similar high contrast between the infarct and the remote myocardium (p=0.619). The mean CNRinfarct/blood of infarct and left ventricular blood, however, was significantly higher on gadobutrol enhanced images compared to gadobenate dimeglumine (p=0.016).

Table 1:

		Gadobutrol 0.1mmol/kg	Gadobenate dimeglumine 0.1mmol/kg	p-value	p-value treatment times period interaction
Secondary endpoints	SNR infarct	18.6 ± 6.5	18.8 ± 8.8	0.940	0.280
	SNR myocardium	4.1 ± 3.7	4.9 ± 4.5	0.485	0.097
	SNR Blood Pool	14.6 ± 7.5	17.8 ± 10.1	0.123	0.514
Primary endpoints	CNR (infarct-myocardium)	14.5 ± 5.6	13.9 ± 6.9	0.619	0.806
	CNR (infarct-bloodpool)	4.0 ± 4.4	1.0 ± 4.4	0.016	0.605