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

Title of Study:

Intra-individual, randomized multicentric comparison of the MRI contrast agents Gadovist® 1.0 versus Dotarem® in patients with Multiple Sclerosis at 3T

Investigator(s): Prof. Dr. Arnd Dörfler, Prof. Dr. Martin Bendszus, Prof. Dr. Michael Knauth, Prof. Dr. Olav Jansen, Prof. Dr. Norbert Hosten, Prof. Dr. Massimo Filippi

Study centre(s):

01-Erlangen	04-Kiel
02-Heidelberg	05-Greifswald
03-Göttingen	06-Milano

Publication:

Saake M, Langner S, Schwenke C, Weibart M, Jansen O, Hosten N, Doerfler A. MRI in multiple sclerosis: an intra-individual, randomized and multicentric comparison of gadobutrol with gadoterate meglumine at 3 T. Eur Radiol. 2016 Mar;26(3):820-8. doi: 10.1007/s00330-015-3889-7. Epub 2015 Jun 30. PubMed PMID: 26123410.

Study period:	**Phase of development:**
From: 01. Jan 2010 **To:** 01. Jan 2011	**IV**

Objectives:

Primary Objective

The primary objective of the study was to prove, that Gadovist® 1.0 provides superior contrast enhancement characteristics of MS lesions as compared to Dotarem® using a qualitative three-point scale (better, equal, worse), thereby providing superior information for further diagnostic and / or therapeutic decisions.

Secondary Objective

The secondary objective of the study was the quantitative assessment of the degree/difference in gadobutrol and gadoterate in regard to: lesion delineation from surrounding tissue and oedema, signal intensity of the lesions, lesion-to-brain contrast and number of enhancing lesions.

Methodology:

Enrolled patients will receive two MRI examinations of the brain in random order, one with the contrast agent Gadovist®, the other one with the contrast agent Dotarem®. The resulting images will be compared with regard to the contrast enhancement and personal preference of the images.

Number of patients: 74 enrolled Patients

Diagnosis and main criteria for inclusion:

Subjects with suspected or known MS lesions

1. Adult patients, age 18-85 years

2. With clinically define MS or a clinically isolated episode of CNS involvement and disease dissemination in space, according to MCDonald's criteria
3. Known or suspected active MS lesion(s) of brain or spine
4. Planned MR examination of the brain with 0.1 mmol Gd per kg bw
5. No contraindication for MRI or gadolinium-containing contrast media application
6. Had not received any gadolinium-containing contrast media within the last 24 hours
7. Written inform consent

Test product, dose and mode of administration:

Gadobutrol 1mmol/ml Injection Bayer Healthcare

Patient ID	Gadovist Batch	Patient ID	Gadovist Batch
01-01	925338	01-38	94033D
01-02	93519A	01-39	94033D
01-03	93519A	01-40	94033D
01-04	not applied	01-41	94033D
01-05	94520A	01-42	94033D
01-06	94520A	01-43	02773A
01-07	94520A	01-44	02773A
01-08	94520A	01-45	117784 F
01-09	94537G	01-46	not applied
01-10	94537G	01-47	not applied
01-11	not applied	01-48	117784F
01-12	94537G	01-49	117784F
01-13	not applied	01-50	117784F
01-14	01522SA	01-51	11778L
01-15	03524C	01-52	11778L
01-16	03524C	01-53	11778L
01-17	01522A	01-54	11778L
01-18	03545A	01-55	13782E
01-19	not applied	01-56	13782E
01-20	04548F	01-57	13782E
01-21	11526D	01-58	13782E
01-22	11551C	01-59	21064C
01-23	11551C	01-60	11778LL
01-24	not applied	01-61	21064C
01-25	not applied	01-62	not applied
01-26	11551C	01-63	22788G
01-27	14534C	01-64	22788G
01-28	11551C	01-65	22788G
01-29	91768D	01-66	22788G
01-30	94032A	01-67	not applied
01-31	94032A	01-68	13782E
01-32	94032A	01-69	13782E
01-33	94032A	01-70	13782E
01-34	94771A	01-71	21064C
01-35	not applied	01-72	21064C
01-36	94771A	01-73	21064C
01-37	not applied	01-74	not applied

Duration of treatment:

Duration of treatment is the intervall between the two MR examinations. Only when a contrast-enhancing lesion was present in the first MR examination, a second MR examination was scheduled. If no contrast-enhancing lesion was present, the duration of treatment was approximately 30 minutes. If a second MR examination was performed, the duration of treatment was between 12 hours up to a maximum of 4 days.

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

Intravenous gadolinium-containing contrast media administration was performed identically in both examinations. A dose of 0.1 mmol Gd/kg bodyweight (i.e. 0.1 ml/kg for gadobutrol and 0.2 ml/kg for gadoterate meglumine) was injected into an antecubital veinby manual or power

injection, followed by a saline flush of20 ml.

Patient ID	Dotarem Batch	Patient ID	Dotarem Batch
01-01	not applied	01-38	10GD001A
01-02	096D072B	01-39	not applied
01-03	096D072B	01-40	10GD001A
01-04	096D072B	01-41	10GD001A
01-05	not applied	01-42	10GD030A
01-06	10GD001A	01-43	10GD030A
01-07	10GD001A	01-44	10GD030A
01-08	10GD001A	01-45	10GD030A
01-09	not applied	01-46	not applied
01-10	10GD001A	01-47	10GD030A
01-11	10GD001A	01-48	10GD030A
01-12	10GD030A	01-49	10GD030A
01-13	10GD030A	01-50	10GD030A
01-14	10GD030A	01-51	10GD030A
01-15	10GD049A	01-52	10GD030A
01-16	10GD049A	01-53	10GD030A
01-17	10GD049A	01-54	9GF046B
01-18	10GD049A	01-55	9GF046B
01-19	10GD049A	01-56	9GF046B
01-20	10GD049A	01-57	9GF046B
01-21	10GD049A	01-58	not applied
01-22	10GD049A	01-59	9GF046B
01-23	not applied	01-60	9GF046B
01-24	10GD049A	01-61	10GD049A
01-25	11GD025B	01-62	10GD049A
01-26	11GD025B	01-63	10GD049A
01-27	11GD025B	01-64	11GD025B
01-28	12GD025A	01-65	11GD025B
01-29	9GD046B	01-66	11GD025B
01-30	not applied	01-67	11GD025B
01-31	9GD046B	01-68	11GD025B
01-32	9GD046B	01-69	11GD025B
01-33	9GD046B	01-70	11GD025B
01-34	10GD046B	01-71	12GD012B
01-35	10GD001A	01-72	12GD012B
01-36	10GD001A	01-73	12GD012B
01-37	10GD001A	01-74	12GD012B

Criteria for evaluation:

Efficacy:

All efficacy variables will be analysed on the PP population.

Visual (qualitative) assessment of the degree/ difference in:

- Lesion delineation from surrounding tissue and oedema

An overall assessment will be provided on a three-point scale (better, equal, worse). Summary statistics will be provided for the visual assessment of the combined assessments of the readers and for each reader's assessment separately. The variability among the readers will be evaluated by the weighted kappa coefficient.

Technical (quantitative) assessment of the change of:

- Signal intensity of the lesions
- Lesion-to-brain contrast
- Number of enhancing lesions

Summary statistics will be provided for the technical assessments per time point. The time

courses of signal intensity and lesion-to-brain contrast of both treatment groups will be evaluated graphically and by descriptive statistics.

Safety:

As Dotarem and Gadovist have established safety profiles, safety measures are confined to the documentation of AEs.

Statistical methods:

The primary efficacy variable is the overall assessment of contrast enhancement on a three-point scale (better, equal, worse) in a matched-pairs assessment from MR imaging examinations of all post-contrast T1-weighted images comparing MR images after Gadovist® 1.0 and after Dotarem® administration.
The primary efficacy variable will be tested by a one-sided sign test with a level of significance of 2.5%.

The test will be performed for a combination of the single assessments of the two blinded readers as described below (primary analysis). In addition, the analysis will be done descriptively for each blinded reader's assessments separately.

SUMMARY CONCLUSIONS:

EFFICACY RESULTS

Seventy-four patients (male, 26; mean age, 35 years) were enrolled in three centres. In 45 patients enhancing lesions were found. Number of enhancing lesions increased over time for both contrast agents without significant difference (median 2 for both). Lesions signal intensity was significantly higher for gadobutrol ($p<0.05$ at time points 3, 6 and 9 min). Subjective preference rating showed non-significant tendency in favour of gadobutrol.

SAFETY RESULTS

For gadobutrol and gadoterate meglumine, no adverse events were reported during the study period for any patient.

CONCLUSION

Both gadobutrol and gadoterate meglumine can be used for imaging of acute inflammatory MS lesions. However, gadobutrol generates higher lesion SI.

DATE OF THE REPORT:

02/03/2020