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Name and Address of Company: Bracco Imaging Deutschland GmbH Max-Stromeyer-Str. 116 78467 Konstanz, Germany	**(For Bracco Regulatory Affairs Use Only)** **Volume** **Page** **Item #:**	**(For National Authority Use only)**
Name of Finished Product: MultiHance®	**Item #:**	
Name of Active Ingredient: Gadobenate dimeglumine	**Item #:**	

Title of Study:
Intraindividual Cross-over Study to Compare MultiHance® and Omniscan® at a Dose of 0.1 mmol/kg_{bw} in the Differential Diagnosis of Disc Herniation vs. Scar

Investigators/Study Center(s):

[redacted]

Publication (reference, if any): None

Study Period: First subject enrolled: 05 September 2007 Last subject completed: 07 January 2010 Off-site assessment: Not applicable	**Phase of Development:** IV

Objectives:
To compare the contrasting behavior of MultiHance® and Omniscan® with regard to:

- Signal intensity enhancement in disk, herniated disk, scar and other soft tissue;
- The contrast between the different tissue types;
- The qualitative assessment of delineation between scar and herniated tissue;
- The qualitative assessment of the confidence in differential diagnosis between scar and herniated tissue.

Study Design:
Exploratory phase IV, double-blind, randomized, multi-center, intraindividual cross-over study conducted in 5 European centers. During the study, patients were to undergo 2 MRI examinations. At least 72 hours, but no more than 14 days, were to be kept between the 2 exams (14-day limit of interval between exams was stipulated in Amendment No. 2 to the Study Protocol). The sequence of contrast agents was randomized:

Sequence group A: MultiHance® (1st exam) - Ominiscan® (2nd exam)
Sequence group B: Omniscan® (1st exam) - MultiHance® (2nd exam)

A Drug Dispensing Person was in charge of the administration procedure to achieve a blinding of the Investigator.

Postcontrast scans were performed 2, 7, 12 and 17 minutes after the contrast agent administration. All efficacy assessments were performed on-site by the blinded Investigator.

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Subject Population:
Number of Subjects Planned: 20 evaluable subjects (10 per sequence group)
Number of Subjects Enrolled: 31
Number of Subjects Randomized: 31
Number of Subjects Dosed: 31 (MultiHance®: 30, Omniscan®: 28, both agents: 27)
Number of Subjects Evaluated for Efficacy: 26
Number of Subjects Evaluated for Safety: 31

Diagnosis and Main Criteria for Inclusion:
Adult patient (age: ≥18 years) who had a disk surgery at the lumbosacral spine (between 3 weeks and 12 months before enrolment into this study), suffers from clinical symptoms suggesting recurrent symptoms, and is scheduled for Magnetic resonance Imaging (MRI) for differential diagnosis between herniated disk and scar (soft tissue)

Dose and Mode of Administration, Batch Number of Test Agent:
MultiHance® (0.5 M, gadobenate dimeglumine 10.58 g/20 mL; batch no. [redacted]) was administered intravenously using a power injector at an injection rate of 2 mL/s. The injection volume was dependent on the body weight (bw): 0.1 mmol/kg_{bw}, equivalent to 0.2 mL/kg_{bw}. After contrast agent administration, 20 mL saline flush were injected.

Dose and Mode of Administration of Comparative Agent:
Omniscan® (0.5 M, gadodiamid 287 mg/mL; batch no. [redacted]) was administered intravenously using a power injector at an injection rate of 2 mL/s. The injection volume was dependent on the body weight (bw): 0.1 mmol/kg_{bw}, equivalent to 0.2 mL/kg_{bw}. After contrast agent administration, 20 mL saline flush were injected.

Duration of Treatment:
For each patient, the minimum duration of the study was 3 days (minimum interval of 72 hours between MR sessions). The study-related time of each MR session was approximately 35 minutes. Close safety monitoring within the radiological department was performed from the time of signing the Informed Consent until 60 minutes after the first contrast agent injection, and again from just before the 2nd contrast agent administration until 60 minutes after the injection. An active follow-up was performed 24 hours after each contrast agent administration.

Evaluation Parameters:
Efficacy
Imaging procedures:
MRI was performed using 1.5 Tesla imaging systems. Each patient was to undergo the following MRI scans:

Precontrast scans:

- T2-weighted images sagittal;
- T2-weighted images axial:
- T1-weighted images axial;
- T1-weighted images sagittal.

Postcontrast scans:

- T1-weighted images axial, 2 minutes after contrast agent;
- T1-weighted images axial, 7 minutes after contrast agent;
- T1-weighted images sagittal, 12 minutes after contrast agent;
- T1-weighted images axial, 17 minutes after contrast agent.

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Evaluation Parameters (continued):

Efficacy (continued)

The following assessments were separately performed for images obtained from the 1st and 2nd MR examination.

Technical quality

The Investigator stated whether all T1 images were of sufficient technical quality to allow clinical evaluation. In case of insufficient technical quality the reason was to be described and the evaluation was to be stopped. Patients with insufficient technical quality were to be replaced.

Presence of Recurrent Disk Herniation

The Investigator stated whether there was a recurrent disk herniation present. In case there was no herniated disk tissue present, the evaluation was to be stopped and the patient was to be discontinued from the study. Discontinued patients were to be replaced.

Qualitative Assessments

Qualitative assessments were performed by direct comparison of the combined T1-weighted postcontrast images of the 1st and the 2nd MR examination (matched pair assessment). If there was multiple herniated disk tissue present, the herniated disk tissue next to the scar was to be measured.

Quality of delineation between scar and herniated disk tissue

The quality of delineation between herniated disk tissue and scar was assessed in a matched pair comparison between 1st and 2nd MR examination on a scale from 0 (= 1st examination much better than 2nd examination) over 9 (both images are equal) to 18 (= 2nd examination much better than 1st examination). In case there was a difference between the examinations, it was stated whether this difference contributed to a difference in final diagnosis.

Confidence in differential diagnosis scar - herniated disk tissue

The confidence in differentiating scar and herniated disk tissue was assessed in a matched pair comparison between 1st and 2nd MR examination on a scale from 0 (= from 1st examination much better confidence in the differential diagnosis than 2nd examination) over 9 (both images are equal) to 18 (= 2nd examination much better confidence in the differential diagnosis than 1st examination).

Quantitative Assessments

Quantitative assessments were only to be performed after conclusion of qualitative assessments. If there was multiple herniated disk tissue present, the herniated disk tissue next to the scar was to be measured. Signal intensity (SI) measurements were performed:

- in the normal intervertebral disk tissue;
- in herniated disk tissue;
- in the scar;
- in other surrounding soft tissue (muscle tissue and fat);
- and in the air (noise).

The following images/time points were used:

Precontrast scans

- T1-weighted images axial;
- T1-weighted images sagittal.

Postcontrast scans:

- T1-weighted images axial, 2 minutes after contrast agent;
- T1-weighted images axial, 7 minutes after contrast agent;
- T1-weighted images sagittal, 12 minutes after contrast agent;
- T1-weighted images axial, 17 minutes after contrast agent.

The size of the region of interest (ROI), mean SI of the ROI and the standard deviation (SD) of the ROI were recorded. ROIs were to be as large as possible covering homogeneous areas of the respective tissues. The same tissue portion had to be measured on comparable pre- and postcontrast images of the 1st and 2nd MR examination.

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Evaluation Parameters (continued):

Safety

Patients were monitored for any untoward medical occurrence from the time of signed Informed Consent on. Only postdose events occurring between administration of contrast agent and 24 hours after each administration were classified as adverse events through data analysis.

Statistical Methods:

Demographics and Baseline Characteristics:

Summary tables were provided for the number of subjects who had been enrolled, randomized, dosed, and completed according to the protocol guidelines. Summary tables were provided for demographic and baseline characteristics, including age, sex, race, height, and weight. Frequency distribution tables (number [N], %) were produced for categorical data and summary statistics (N, mean, SD, median, minimum, maximum) for continuous data. The demographic and baseline characteristics were summarized by sequence group and inferential statistics were provided to compare the 2 sequences.

Efficacy Analysis:

Data were presented by contrast agent: frequency distribution tables for categorical data and summary statistics (N, mean, SD, median, minimum, maximum) for continuous data. Statistical tests were 2-sided with a level of significance of 0.05.

Quantitative Assessments

For all postcontrast time points, the percent contrast enhancement (CE) were calculated for all tissues measured according to the following formula:

$$CE = (SI_{Post} - SI_{Pre}) \times 100 / SI_{Pre}$$

The contrast between tissues was analyzed by calculating the contrast ratio (CR):

$$CR = (SI_{Tissue\ 1} - SI_{Tissue\ 2}) / SI_{Tissue\ 2}$$

The following pairs of tissues were analyzed:

Tissue 1		**Tissue 2**
Scar	-	Herniated disk tissue
Scar	-	Normal intervertebral disk tissue
Scar	-	Surrounding soft tissue (muscle tissue)
Herniated soft tissue	-	Normal intervertebral disk tissue

The CR was displayed for all precontrast and postcontrast time points.Differences between the contrast agents in quantitative variables were explored by WILCOXON signed rank test.

Qualitative Assessments

Matched pairs qualitative assessments were summarized by frequency distribution tables. Differences between the contrast agents were explored by WILCOXON signed rank test.

Safety Analysis:

Safety data were summarized for all patients dosed with contrast agent (SAF population). Safety analysis was based on the analysis of adverse events.

Adverse events were summarized separately for both contrast agents by primary Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term, by intensity, and by causal relationship to the investigational product.

Concomitant medication data were presented in data listings and summarized by frequency counts according to anatomical and therapeutic area (drug reference list of the World Health Organization) for all patients dosed.

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Summary and Conclusions:

Demographics:
The mean age of the 31 SAF patients was 46.6 ± 13.1 years and the mean age of the 26 EFF patients was 47.2 ± 13.4 years. The SAF comprised 16 male and 15 female patients; the EFF comprised 13 male and 13 female patients. All study patients were white. There were no statistically significant differences between the 2 sequence groups with regard to the demographic characteristics (age, sex, weight, and height) in the SAF or EFF ($p \geq 0.5495$).

Exposure to Investigational Product and/or Comparator Product:
For patients who underwent both MRI examinations, the body-weight dependent volumes of injected contrast agent (either 0.5 M MultiHance® or 0.5 M Omniscan®) were equal at both examinations. For both contrast agents, the mean dose was 0.1 mmol/kg in the EFF (N = 26), which was in accordance with the protocol, and 0.099 mmol/kg in the SAF (N = 31). A total of 4 patients received slightly lower doses of both contrast agents (lowest dose: 0.08 mmol/kg), but the doses were considered sufficient for diagnosis.

Efficacy:

Technical Quality of T1-weighted Images
The technical quality of all T1-weighted images was sufficient to allow for clinical evaluations

Matched Pairs Qualitative Assessments
Quality of delineation between scar and herniated disk
The qualitative assessment of matched image pairs from the 1st and the 2nd MRI examination showed that there was a tendency towards better quality of delineation between scar and herniated disk tissue when MultiHance® was used for contrast enhancement. Investigators assessed quality of delineation as being better with MultiHance® in 38.5% of the patients (N = 10) and as being better with Omniscan® in 15.4% of the patients (N = 4). The contrast agents were assessed as being equal with regard to quality of delineation in 46.2% of the patients. The difference between the contrast agents was not statistically significant (p = 0.1609, Wilcoxon signed rank test based on the 18-point scale).

Confidence in differential diagnosis of scar vs. herniated disk
The qualitative assessment of matched image pairs from the 2 MRI examinations showed that there was a tendency towards higher confidence in the differential diagnosis of scar vs. herniated disk tissue when MultiHance® was used for contrast enhancement. The proportion of patients for whom investigators had a higher confidence in differential diagnosis was higher with MultiHance® (26.9%, N = 7) than with Omniscan® (11.5%, N = 3). In 61.5% of the patients, Investigators had equal confidence in the differential diagnosis of scar vs. herniated disk with both contrast agents. The difference between the contrast agents was not statistically significant (p = 0.1406, Wilcoxon signed rank test based on the 18-point scale).

Quantitative Assessments
Signal Intensity Measurements
There were significant differences between the precontrast measurements before administration of contrast agent, i.e., SI values derived from T1-weighted axial images were higher before administration of MultiHance® than before administration of Omniscan® in normal disk tissue (p = 0.0310) and in herniated disk tissue (p = 0.0002). In contrast, mean SI values derived from precontrast T1-weighted sagittal images were comparable prior to administration of the 2 contrast agents within the same type of tissue. However, the mean sagittal precontrast SI values were distinctly lower than the mean axial precontrast SI values in normal disk tissue, herniated disk tissue, and scar, and slightly lower in muscle tissue.

At 12 minutes postcontrast, axial scans instead of sagittal scans were performed in 5 EFF patients. As in normal disk, herniated disk, and scar, mean postcontrast SI values (combined analysis of axial and sagittal images) were distinctly lower at 12 minutes than at 2, 7, and 17 minutes and measurement errors could not be excluded, the description of SI analysis results (i.e., CE and CR) was limited to the values obtained from axial images at 2, 7, and 17 minutes postcontrast.

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Summary and Conclusions (continued):

Efficacy (continued):

Contrast Enhancement (CE)

The comparison of SI values between precontrast and postcontrast T1-weighted axial images showed that with MultiHance® as well as with Omniscan® the highest percent CE was reached in scar tissue and the lowest CE was obtained in normal disk tissue, followed by herniated disk tissue. Interindividual variability of the percent CE values was high, especially for the measurements in herniated and normal disk tissue at all measured time points.

In herniated disk tissue, the mean CE was similar with both contrast agents at 2 and 7 minutes postcontrast: 35.6 ± 40.3% and 39.1 ± 46.3% with MultiHance®, 36.9 ± 34.0% and 39.0 ± 39.1% with Omniscan®. At 17 minutes postcontrast, the percent CE with MultiHance® was further increased to 41.8 ± 40.6%, whereas the CE with Omniscan® was slightly decreased to 36.5 ± 36.9%. There were no statistically significant differences between the contrast agents with regard to percent CE in herniated disk tissue.

In scar tissue, the mean CE after administration of MultiHance® was 101.2 ± 32.8% at 2 minutes postcontrast and increased further over time to 118.5 ± 37.6% at 7 minutes and 120.5± 33.7% at 17 minutes. The increase of the mean CE in scar tissue after administration of Omniscan® was less pronounced; the CE was 90.3 ± 41.7% at 2 minutes and increased to 103.2 ± 46.8% at 7 minutes; at 17 minutes, the mean CE was 102.4 ± 48.9%. The differences between the 2 contrast agents with regard to percent CE were statistically significant at 7 minutes ($p = 0.0249$) and at 17 minutes ($p = 0.0198$).

Contrast Ratios (CRs) Between Different Tissues

The comparison of SI measurements from pre- and postcontrast T1-weighted images between different tissues showed that with MultiHance® as well as with Omniscan® the highest postcontrast CRs were reached between scar and normal disk tissue (e.g., mean CR at 17 minutes: 1.71 and 1.43), followed by scar vs. herniated disk tissue (e.g., mean CR at 17 minutes: 1.08 and 1.11).

The mean precontrast CR between scar and herniated disk derived from images obtained prior to administration of MultiHance® was statistically significantly ($p = 0.0467$) lower than the mean precontrast CR derived from images obtained prior to administration of Omniscan® (0.26 ± 0.43 vs. 0.33 ± 0.47). With regard to the mean postcontrast CRs between scar and herniated disk, there was no statistically significant difference between the 2 contrast agents. With MultiHance®, the mean CR was 0.97 ± 0.79 at 2 minutes, 1.12 ± 0.85 at 7 minutes and 1.08 ± 0.90 at 17 minutes. With Omniscan®, the mean CR increased from 0.92 ± 0.84 at 2 minutes to 1.04 ± 0.91 at 7 minutes and 1.11 ± 1.05 at 17 minutes.

Prior to contrast agent administration, the mean CR between scar and muscle obtained from the MultiHance® MRI examination was very small and similar to the mean CR obtained from the Omniscan® MRI examination (0.03 ± 0.25 vs. 0.02 ± 0.26). The postcontrast comparison of scar vs. muscle tissue showed that after contrast agent administration, the mean CR between scar and muscle increased more pronounced with MultiHance® than with Omniscan® (2 minutes: 0.54 ± 0.39 vs. 0.50 ± 0.43; 7 minutes: 0.70 ± 0.40 vs. 0.62 ± 0.42; 17 minutes: 0.81 ± 0.45 vs. 0.68 ± 0.46 at 17 minutes). The differences between the contrast agents with regard to the CR between scar and muscle were statistically significant at 7 minutes ($p = 0.0467$) and at 17 minutes ($p = 0.0006$).

Safety:

Two non-serious adverse events in 2 patients (6.7%) were reported after the injection of MultiHance®. Both adverse events (nausea) were of mild intensity and were assessed by the Investigators as probably related to the administration of the investigational product. The patients recovered after a few minutes. One patient discontinued the study because of the adverse event.

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Conclusions:

The following conclusions can be drawn from this exploratory, double-blind, randomized, multi-center, intraindividual cross-over study comparing the contrasting behavior of MultiHance® with Omniscan® in MRI for differential diagnosis of tissues in 31 patients with previous disk surgery at the lumbosacral spine and anew onset of back pain:

- The qualitative assessments of matched image pairs from 1st and 2nd MRI examinations showed that there was a tendency towards better quality of delineation between scar and herniated disk with MultiHance®. Investigators assessed delineation as being better with MultiHance® in 38.5% and with Omniscan® in 15.4% of the 26 efficacy analyzable patients.
- The qualitative assessments of matched image pairs also showed that the proportion of patients for whom Investigators had a higher confidence in differential diagnosis was numerically higher with MultiHance® than with Omniscan® (26.9% vs. 11.5%).
- CE was highest in scar tissue and lowest in normal disk tissue with both contrast agents. CE in herniated disk tissue was similar with both contrast agents. Statistically significantly ($p \leq 0.0437$) higher CE was obtained with MultiHance® than with Omniscan® in scar tissue at 7 and 17 minutes postcontrast and in muscle tissue at all postcontrast time points.
- Postcontrast CRs were highest between scar vs. normal disk, followed by scar vs. herniated disk. With regard to the comparisons of scar vs. herniated disk, there were no statistically significant differences between the contrast agents at any postcontrast time point. However, the CRs between scar and muscle tissue were statistically significantly ($p \leq 0.0467$) higher with MultiHance® than with Omniscan® at 7 and 17 minutes postcontrast, indicating towards better enhancement of scar tissue with MultiHance®.
- Two non-serious adverse events (nausea) in 2 patients (6.7%) were reported after the injection of MultiHance®. The symptoms were mild and resolved quickly. No previously unknown risks of MultiHance® were detected.

Overall, the results of this exploratory study showed that MultiHance® is a suitable contrast agent for the differential diagnosis of scar vs. herniated disk tissue in MRI. In comparison to Omniscan®, MultiHance® achieved a qualitatively better delineation between scar and herniated disk in a higher proportion of patients and a quantitatively better enhancement of scar tissue. Quantitative assessments did not confirm better contrast between scar and herniated disk with MultiHance®.

Both MultiHance® and Omniscan® were safe and well tolerated at a dose of 0.1 mmol/kg_{bw}.

Date of Report: 15 February 2011 (Final)