BRACCO ALTANA PHARMA

Clinical Study Report

Title Page

Study Report No.: 192/ 2006 (version 1.1)

(Shaded areas contain information for internal use only)		
Project No.: Not applicable	Compound No.: Not applicable	Batch No.: PL822-55
Report archived on:	No. of pages: 87	Documentation code: CLB1
Study title: Intraindividual cross-over study to compare 1.5-tesla and 3.0-tesla MRI with 0.05+0.05 mmol/ kg_{BW} MultiHance® in patients with myocardial infarction		Name of test drug: MultiHance® Protocol/ Study No.: MultiH/ BRA/ 900 Development phase: III
Study initiation date: 20.07.2005	Study completion date: 03.02.2006	Date of early termination: Not applicable.
Indication studied: MRI of patients with myocardial infarction		Report date: 31.10.2006
Name and affiliation of principal Investigator: [redacted]		
Name of Sponsor's responsible medical officer: Astrid Seeberg, PhD, Bracco ALTANA Pharma GmbH, Max-Stromeyer-Str. 116, 78467 Konstanz, Germany		
Person responsible for study report: [redacted]		
Sponsor contact persons: Please refer to letter of application for name, telephone and fax number.		
Statement of GCP compliance: This study was performed in accordance with Good Clinical Practice regulations as set out in the ICH consolidated guideline E6.		
Archiving responsibility for essential documents: [redacted]		

2. Synopsis

Name of Sponsor / Company: Bracco ALTANA Pharma GmbH **Name of Finished Product:** MultiHance® **Name of Active Substance:** Gadobenate dimeglumine	**TABULATED STUDY REPORT** **ref. to Part IV of the Dossier** Volume: Page: Report No.: 192/ 2006 Report date:	*(For National Authority Use only)*
Title of study:	Intraindividual cross-over study to compare 1.5-tesla and 3.0-tesla MRI with 0.05+0.05 mmol/ kg_{BW} MultiHance® in patients with myocardial infarction.	
Investigator:	[redacted]	
Study center:	[redacted]	
Publication (reference):	Not applicable.	
Study period:	July 2005 - February 2006	
Objectives:	Primary objective of the present study is to prove the superiority of MultiHance® enhanced 3.0-tesla MRI compared to 1.5-tesla MRI in the contrast-to-noise ratio during the late enhancement of myocardial infarctions. Secondary objectives: • To compare MultiHance® enhanced 3.0-tesla and 1.5-tesla late MRI with regard to: - Presence and localization of the infarction; - Extent of the infarction; - Signal intensity measurements; - Qualitative matched pairs assessments. • To compare MultiHance® enhanced 3.0-tesla and 1.5-tesla MR perfusion images with regard to presence and localization of the perfusion defects. To evaluate safety of MultiHance® application in patients with confirmed chronic myocardial infarction.	
Methodology:	Open-label, single-center, intra-individual cross-over study. Blinded and randomized off-site assessment of MRI images by the Co-Investigator and two additional independent readers.	
Number of subjects: (total and for each treatment group)	Planned: 20 evaluable patients (1 study center) Recruited: 21 Safety analysis: 21 Efficacy analysis: 20	
Diagnosis and main criteria for inclusion:	Patients with confirmed chronic myocardial infarction, first diagnosis at least 3 months ago.	
Test product: dose: mode of administration: batch number:	MultiHance® (Gadobenate dimeglumine 0.5 M, 10.58 g/ 20 ml) 0.05 + 0.05 mmol/ kg_{bw} (equivalent to 0.1 + 0.1 ml/ kg_{bw}) Intravenous bolus injections with automatic power injector First dose: 4 ml/ sec, followed by 20 ml saline flush at the same rate. Second dose: 1 ml/ sec, followed by 20 ml saline flush at the same rate. [redacted]	

2. Synopsis

Comparator:	Not applicable.
Duration of treatment:	2 MR sessions of 45 minutes each. Minimum study duration: 5 days including both MR examinations and AE follow-up. Maximum study duration: 23 days.
Criteria for evaluation: - Efficacy:	Primary criterion: Contrast-to-noise ratio; contrast is the difference in signal intensity between infarcted and normal myocardium Secondary criteria: • Contrast enhanced late MRI, quantitative assessments: - SI of infarcted myocardium, - SI of normal myocardium, - Contrast infarcted myocardium minus normal myocardium, - Ratio normal myocardium / skeleton muscle; • Contrast enhanced late MRI, qualitative assessments: - Image quality, - Presence of infarction, - Localization of infarction, - Extent of infarction, - Confidence in diagnosis, - Matched pairs assessment of image quality, ability to localize infarction, ability to determine extent of infarction, and confidence in diagnosis; • Perfusion images: - Image quality, - Detection of perfusion defects, - Localization of perfusion defect(s).
- Safety:	Monitoring of adverse events from inclusion (Informed Consent) up to 48 hours after the last contrast-agent administration.
Statistical methods:	Primary criterion: Null Hypothesis: There is no difference in contrast-to-noise ratio (CNR) between MultiHance® enhanced 1.5- tesla and 3.0-tesla MRI during late enhancement of the myocardium. The null hypothesis had to be rejected if $p \leq 0.05$ (paired t-test). The difference in CNR between 1.5 T and 3.0 T MRI was computed together with its two-sided 95% confidence intervals. The contrast-to-noise ratio during late enhancement was calculated according to the following formula: $CNR = (SI_{Infarcted\ myocardium} - SI_{Normal\ myocardium}) / SD_{Noise}$ Where: CNR = Contrast-to-noise ratio, SI = Signal intensity (= 90% percentile of the pooled ROIs) SD = Standard deviation of the ROI pixels It was planned to measure signal intensity in all slices that include infarcted tissue. All ROIs measured for a certain tissue of a patient were pooled. The 90% percentile of pooled ROI pixels were obtained. This was to minimize the influence of nonenhanced tissue included in the ROI on SI analysis. All analyses of signal intensities were based on 90% percentiles. Signal intensities were normalized to the mean signal intensity values of the skeleton muscle. In order to maintain the original magnitude of SI values, the normalization factor contained the mean value of all patients

	measured with the same field strength: $SI_k = SI \cdot \frac{k}{\overline{SI_N}}$ Where: SI_k = normalized signal intensity SI = signal intensity as measured k = mean of all signal intensity values of the skeleton muscle of all patients measured with the same field strength $\overline{SI_N}$ = mean of signal intensity of all skeleton muscle ROIs of a patient Since skeletal muscle could not always be measured, it was decided at the DRM to produce a second set of tables (14.2.2.3/ 4) without normalization, in order not to loose information. <u>Secondary criteria:</u> Frequency distribution tables (N, %) were produced for categorical data and summary statistics (n, mean, standard deviation, median, Q1, Q3, minimum, maximum) for continuous data. Paired t-tests were applied to explore differences between 1.5 T and 3.0 T assessments concerning continuous data. For the matched pairs assessments, WILCOXON signed rank tests were performed. 95% confidence intervals for the mean of the differences were computed. In addition to the analysis of 90% percentiles, all quantitative analyses were also performed on the basis of means of the ROIs.
Summary - Conclusion: - Efficacy results:	<u>Primary criterion</u> The primary criterion of this study was to prove the superiority of MultiHance® enhanced 3.0-tesla MRI compared to 1.5-tesla MRI in the normalized contrast-to-noise ratio during the late enhancement of myocardial infarctions. Basis were the 90% percentiles from conventional MRI (T1 IR images). Mean CNR for 1.5 T was 14.5 ± 4.7 (range 6.2 to 19.3), compared to a 3.0 T mean of 27.3 ± 14.8 (range 8.7 to 57.7) for the Co-Investigator. The difference between 3.0 T and 1.5 T was 12.8. This was statistically significant (p-value of paired t-test: 0.0007). For Reader 1 mean CNR (1.5 T vs. 3.0 T) was 14.0 ± 6.8 (range 3.3 to 30.7) vs. 24.7 ± 15.4 (range 6.8 to 57.1). The difference between 3.0 T and 1.5 T was 10.6, which was also statistically significant (p = 0.0069). Mean CNR for Reader 2 was 13.7 ± 5.9 (range 5.8 to 23.9) vs. 22.1 ± 13.4 (range 10.0 to 53.3). The difference of 8.4 in favour of 3.0 T was marginally significant (p-value of paired t-test = 0.0536). Using the original (i.e., not normalized) signal intensities allowed including the patients with missing signal intensity measurements of skeletal muscle (N = 10) in the analysis. The overall data did not change considerably with original signal intensities. However, all p-values concerning the primary criterion were lower compared to normalized signal intensities, making the difference between 3.0 T and 1.5 T statistically significant for Reader 2 as well (p = 0.0007). Thus, data from all off-site evaluators agree that the contrast-to-noise ratio at 3.0 T field strength is superior in patients with myocardial infarctions during late enhancement MRI compared to 1.5 T. This is mainly due to the lower noise at 3.0 T field strength compared to 1.5 T. The difference was statistically significant for 2 evaluators (p < 0.05),

and marginally significant for 1 evaluator (p = 0.0536), so that the null hypothesis ('no difference in contrast-to-noise ratio') can be rejected.

Secondary criteria

Perfusion imaging: Image quality, Detection and Localization of perfusion defects

The on-site Investigator rated 18 out of 19 perfusion images (94.7%) taken at a field strength of 3.0 T to be of excellent quality, but only 12 out of 19 (63.2%) perfusion images taken at 1.5 T. WILCOXON signed rank test showed the advantage for 3.0 T to be statistically relevant (p-value of 0.0313).

Perfusion defects were detected in 12 patients (63.2%) at 1.5 T and in 14 patients (73.7%) at 3.0 T field strength. Localization of the perfusion defect was completely identical between 1.5 and 3.0 T in 5 cases (35.7%), identical in at least one segment, but not in all segments in 7 cases (50%), and not detected at one field strength in 2 cases (14.3%)

The overall better quality of perfusion images at 3.0 T compared to 1.5 T could be responsible for the slightly higher rate of detection of perfusion defects (14 detections versus 12 detections).

Conventional MRI: separate qualitative assessments

Secondary criteria for separate qualitative assessments were image quality, presence/ localization/ extend of infarction, and confidence in diagnosis.

Although there was no statistic difference between the field strengths concerning image quality, all evaluators had consistently more namings for 1.5 T than for 3.0 T in their highest image-quality category ('excellent' for the Co-Investigator and Reader 2, 'good' for Reader 1). The proportion in the highest image-quality category (1.5 T vs. 3.0 T) was 10:6 for the Co-Investigator, 15:10 for Reader 1, and 10:5 for Reader 2.

No relevant differences could be observed concerning the extent and localization of the detected infarctions between 1.5 and 3.0 T.

No explicit difference could be detected for confidence in diagnosis between the two field strengths for the Co-Investigator and Reader 2 (p > 0.4, WILCOXON signed rank tests). However, there is a statistical trend towards an advantage for 1.5 T over 3.0 T for Reader 1 (p = 0.1211), who stated to have 'good' confidence in 15 diagnoses made at 1.5 T vs. 10 diagnoses made at 3.0 T.

Conventional MRI: matched-pairs qualitative assessments

Secondary criteria for matched-pairs qualitative assessments were image quality, ability to localize and to determine the extent of infarction, and confidence in diagnosis.

Evaluating the image quality, Reader 1 preferred 1.5 T over 3.0 T images, with 1.5 T being judged as better in 13 out of 20 evaluations in each of the 4 qualitative criteria, and 3.0 T being judged as better in 4 cases (20%; p-value < 0.05, WILCOXON signed rank test).

Reader 2 did not prefer one field strength over the other (p-values > 0.2), except for a trend in favor of 1.5 T in the category 'ability to localize infarction' (p = 0.1406), with 6 (30%) namings as '1.5 T better', and 1 naming (5.0%) as '3.0 T better'.

The Co-Investigator generally preferred 3.0 T images over 1.5 T images. In all 4 categories, only 3 image sets each (15%) were rated as better for 1.5 T and 13 (65%) to 16 (80%) were found to be better for 3.0 T. Except for 'ability to determine extend of infarction', where only a strong statistic trend could be seen (p = 0.0609), p-values of all other categories were statistically relevant (p < 0.05).

2. Synopsis

	Thus, the three evaluators disagreed about the better field strength when images were shown as matched pairs. The Co-Investigator preferred 3.0 T, Reader 1 preferred 1.5 T, and Reader 2 was undecided. In summary, quantitative data of conventional MRI (late enhancement) such as the signal intensity in infarcted myocardium, the noise, and the contrast-to-noise ratio (primary criterion) showed an advantage for 3.0 T over 1.5 T, which was statistically significant in 2 out of 3 evaluators for the CNR. There were also more perfusion images of excellent quality at 3.0 T compared to 1.5 T. The difference was statistically relevant. Separate qualitative assessments, however, display a statistical trend in favor of 1.5 T, and matched pairs qualitative assessments show mixed results for the three off-site evaluators.
- Safety results:	No adverse events were reported during the course of the study, confirming MultiHance® as a safe and well tolerated intravenous MR contrast agent.
- Conclusions:	The following conclusion can be drawn from this intra-individual cross-over study on MultiHance® in 1.5 T and 3.0 T MRI in patients with myocardial infarction: • In MultiHance® enhanced conventional MRI, examinations at 3.0 T consistently showed better contrast-to-noise ratios during late enhancement than imaging at 1.5 T ($p < 0.05$ for 2 evaluators, $p = 0.0536$ for 1 evaluator, paired t-test). • In MultiHance® enhanced perfusion imaging, more images were of excellent quality for 3.0 T compared to 1.5 T ($p < 0.05$, WILCOXON signed rank test). • No consistent differences between 1.5 T and 3.0 T could be found in qualitative matched-pairs comparisons of conventional MRI. The Investigator favoured 3.0 T images (3 out of 4 categories with statistically relevant difference), Reader 1 favoured 1.5 T images (statistically relevant difference in all 4 categories), and Reader 2 was undecided (no statistical difference in any category). • For the image quality and the confidence in diagnosis in qualitative separate assessments of conventional MRI, all evaluators had consistently more namings in their highest image-quality/ confidence categories at 1.5 T compared to 3.0 T, although the differences between field strengths were not statistically relevant ($p > 0.05$). • Thus, better technical values for the 3.0 T system did not automatically translate into better diagnosability of conventional MR images. • MultiHance® was confirmed again to be a safe and well tolerated intravenous MR contrast agent. No adverse events occurred.