Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Bayer HealthCare

Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer HealthCare Pharmaceuticals Inc.	
Study Number:	91681	NCT00709852
Study Phase:	III	
Official Study Title:	A multicenter, randomized, double-blind, crossover, phase 3 study to determine the safety and efficacy of gadobutrol 1.0 molar (Gadovist®) in patients referred for contrast-enhanced MRI of the central nervous system (CNS)	
Therapeutic Area:	Diagnostic Imaging	
Test Product		
Name of Test Product:	Gadobutrol (Gadovist, BAY86-4875)	
Name of Active Ingredient:	Gadobutrol	
Dose and Mode of Administration:	0.1 mmol/kg body weight (bw); i.v.	
Reference Therapy/Placebo		
Reference Therapy:	ProHance® (gadoteridol) 0.5 molar	
Dose and Mode of Administration:	0.1 mmol/kg body weight (bw); i.v.	
Duration of Treatment:	Single dose, each of test product and reference therapy	
Studied period:	Date of first subjects' first visit:	11 JUN 2008
	Date of last subjects' last visit:	03 APR 2009
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	Amendment No. 1, dated 24 JUL 2008, (serial number 110) specified the following modifications: • "Known long QT syndrome" was added an example to exclusion criterion defining severe cardiovascular disease • The specification that the statistical analysis of the visualization parameters will be performed using data from evaluations of normal structures and evaluations from lesions was added Amendment No. 2, dated 08 JAN 2009, applied to Japan only with the following modification: The original protocol stated that the maximum number of subjects that could be enrolled at each center was approximately 20. To allow a larger proportion of Japanese subjects to be included in a possible Japanese registration, this number was increased to 30 subjects for Japan only, with a limit of 110 total subjects enrolled. Amendments and supplements to the statistical analysis plan (SAP): Although formal comparisons of unenhanced versus combined	

	unenhanced/gadoteridol-enhanced were not specified in the protocol or SAP, they were performed for the primary and secondary efficacy variables. The statistical methods used for these tests were the same as those used for the unenhanced versus combined unenhanced/gadobutrol-enhanced comparison. The reason for these additions was that the demonstration of gadoteridol superiority over unenhanced would validate the choice as an active comparator and would provide more support for the noninferiority comparison with gadobutrol. Though a non-parametric test was not specified in the protocol or statistical analysis plan for primary analysis of primary variables, it was performed for number of lesions as supplementary analysis following the secondary analysis, for which non-parametric test was prespecified, and using non-inferiority margin of -10% specified for categorical secondary variables. The reason for the addition was that non-parametric analysis was considered appropriate based on the observed data.
Study Centre(s):	This study was conducted at 13 sites in the United States, 15 sites in Germany, 12 sites in Japan, 2 sites in Australia, 2 sites in Austria, 3 sites in Colombia, and 4 sites in Switzerland.
Methodology:	In this study, subjects received 2 contrast agents, gadobutrol and gadoteridol (as an active comparator) separated by at least 24 hours, but by not more than 15 days. Unenhanced MR images (T1-weighted [T1w], T2-weighted [T2w], and Fluid Attenuated Inversion Recovery/Short Time Inversion Recovery [FLAIR/STIR] sequences) were obtained from each subject before the administration of each of the contrast enhancement agents. Enhanced T1w MR images were obtained after the administration of contrast enhancement agents. The clinical investigators and blinded readers evaluated these unenhanced and enhanced MR images.
Indication/ Main Inclusion Criteria:	Indication Contrast-enhancement in MRI of the central nervous system (CNS) for the detection/visualization of areas with normal and disrupted blood brain barrier (BBB) and/or abnormal vascularity. Main inclusion criteria • Male and female subjects at least 18 years of age referred for contrast-enhanced MRI of the CNS based on current clinical symptoms or on a previous imaging procedure • Estimated glomerular filtration rate (eGFR) value ≥60 mL/min/1.73m^2 (derived from a serum creatinine result) within 2 weeks prior to study enrollment
Study Objectives:	<u>Overall:</u> Not applicable <u>Primary:</u> • The superiority of combined unenhanced and gadobutrol-enhanced MRI compared to unenhanced MRI based on the evaluation of following visualization parameters: ▪ Degree of contrast enhancement ▪ Assessment of border delineation

	▪ Internal morphology of lesions • Noninferiority of combined unenhanced and gadobutrol-enhanced MRI compared to unenhanced MRI based on the evaluation of the total number of detected lesions <u>Secondary:</u> • To demonstrate noninferiority of gadobutrol compared to gadoteridol for the 4 visualization parameters (degree of contrast enhancement, border delineation, internal morphology of lesions, and total number of detected lesions) • To demonstrate improvement of gadobutrol-enhanced MRI to unenhanced MRI and noninferiority to gadoteridol-enhanced MRI for: ▪ Exact match of the MR diagnoses with the final clinical diagnosis ▪ Sensitivity and specificity for normal/abnormal brain tissue based on the comparison of the T1w contrast-enhanced and T1w unenhanced MR images ▪ Sensitivity and specificity for the detection of malignant CNS lesions ▪ Confidence in diagnosis • To compare gadobutrol to gadoteridol for: ▪ T1w MRI image quality in a paired comparison ▪ The number of contrast-enhanced lesions ▪ Quantitative parameters based on signal intensity (SI) measurements • To assess the safety profile of gadobutrol and gadoteridol after i.v. administration
Evaluation Criteria:	The evaluation of the unenhanced MRI, combined unenhanced and gadobutrol enhanced MRI, and combined unenhanced and gadoteridol-enhanced MRI were done by the clinical study investigators and 3 independent blinded readers. <u>Efficacy (Primary):</u> The visual assessment scores of MR images of lesions or normal structures in the CNS were given by the individual blinded readers for the following variables: • Contrast enhancement: Scale of 1 to 4, in which 1 = no enhancement and 4 = excellent enhancement • Border delineation: Scale of 1 to 4 in which 1 = no or unclear delineation and 4 = excellent delineation • Internal morphology of lesions: Scale of 1 to 3, in which 1 = poor visibility and 3 = good visibility • Total number of detected lesions: Count of detectable lesions <u>Efficacy (Secondary):</u> • The visual assessment scores of MR images of lesions or normal structures in the CNS were given by the clinical investigators for the aforementioned primary efficacy variables • Signal intensity measurement: Quantitative measurements to evaluate the percentage of lesion enhancement in the T1w sequence

	• Number of contrast-enhanced lesions: An independent blinded evaluation for identifying differences in the numbers of lesions enhanced by gadobutrol compared to gadoteridol • Detection of normal/abnormal brain tissue: The blinded readers provided their assessments of whether the T1w images were normal or abnormal • Detection of malignant lesions: The presence or absence of malignant lesions was derived from the diagnoses given by the investigators and blinded readers on the evaluation of the unenhanced image set and the combined unenhanced and gadobutrol-enhanced image sets • Diagnosis/confidence in diagnosis: Diagnostic confidence was evaluated to determine the level of certainty that the investigator/ blinded readers assigned to a diagnosis. The degree of confidence was rated on an ordinal scale of 1 to 4 (1 = not confident and 4 = very confident) • Standard of truth (final clinical diagnosis): A final clinical diagnosis was determined by an independent truth committee following evaluation of findings from referral through a 3-month follow-up period, not including the study-specific MR image sets (both unenhanced and enhanced). • Exact Match Diagnosis: A comparison of the final clinical diagnosis to the diagnoses made by the blinded readers and clinical investigators for each image set • Image quality: The blinded readers evaluated the relative image quality of the gadobutrol-enhanced T1w MR images and the gadoteridol-enhanced T1w MR images Safety: Vital signs, physical examinations, clinical laboratory parameters (blood and urine), and monitoring of adverse events (AEs) up to 72 hours following study period 2 were done for safety evaluation.
	Pharmacokinetics: Not applicable Other: Not applicable
Statistical Methods:	Efficacy (Primary): The primary efficacy analysis was based on the data from the blinded readers' evaluation of the following visualization parameters, which were evaluated in unenhanced and combined unenhanced and enhanced MR image sets: • Contrast enhancement (measured on an ordinal 4-point scale) • Border delineation (measured on an ordinal 4-point scale) • Internal morphology (measured on an ordinal 3-point scale) • Number of lesions detected The primary objective was to demonstrate the superiority for the combined gadobutrol and unenhanced MRI to unenhanced MRI for contrast enhancement, border delineation, and internal morphology, and noninferiority for the number of lesions detected.

The analysis for each of these parameters was performed on the mean of the values for the 3 blinded readers (blinded reader average). For each of the first 3 parameters, this analysis was performed on the dataset including the subject average ratings for both lesions and normal structures.

Degree of contrast enhancement, border delineation, and internal morphology were tested for the superiority of gadobutrol-enhanced MRI versus unenhanced MRI using paired t-tests. The null and alternative hypotheses follow:

H_0: combined unenhanced and gadobutrol mean = unenhanced MRI mean versus

H_1: combined unenhanced and gadobutrol mean ≠ unenhanced MRI mean

Where "mean" was the mean of the blinded reader averages.

Noninferiority of the number of lesions detected was assessed using confidence intervals based on the t-distribution, using a noninferiority margin of 0.35. This means that a 95% 2-sided confidence interval for the mean difference combined gadobutrol and unenhanced score – unenhanced score must have excluded the value -0.35 for noninferiority to be achieved (that is, the lower limit of the confidence interval must be greater than -0.35). If the lower limit of the confidence interval was greater than zero, superiority was achieved. A one-sided test conducted at the 0.025 level of significance would be a statistically equivalent procedure. The null and alternative hypotheses for noninferiority are:

H_0: combined unenhanced and gadobutrol mean – unenhanced mean < -0.35, versus

H_1: combined unenhanced and gadobutrol mean – unenhanced mean ≥ -0.35.

"Mean" was the mean of the blinded reader averages.

No type I error adjustment for multiple comparisons was needed because tests on all 4 variables must have been significant to demonstrate primary efficacy.

As a secondary analysis, for each of the 4 visualization parameters, the noninferiority of gadobutrol versus gadoteridol was also evaluated using confidence intervals based on the t-distribution. A noninferiority margin of 0.35 was used in each case.

Efficacy (Secondary):

For the secondary efficacy variables accuracy of exact match diagnosis, and sensitivity, specificity, and accuracy of detection of malignant lesions and T1w abnormal brain tissue, proportions of blinded reader assessments consistent with the standard of truth assessments were calculated for gadobutrol and gadoteridol and unenhanced MRI, and McNemar's test for the difference in these proportions was used. Signal intensity measurements were summarized by MRI modality using descriptive statistics and confidence intervals.

	Safety: Asymptotic confidence intervals were used to assess the significance of the differences in AE incidence rates between gadobutrol and gadoteridol.
	Pharmacokinetics: Not applicable Other: Not applicable
Number of Subjects:	Planned subjects (a maximum of 110 subjects in Japan): 350 Subjects analyzed for: • Safety :402 • Efficacy by Full Analysis Set (FAS): 336 • Efficacy by Per Protocol Set (PPS): 316

Study Results

Results Summary — Subject Disposition and Baseline

A total of 419 subjects were screened for inclusion into the study; 17 subjects prematurely discontinued from the study prior to receiving any study drug. A total of 402 subjects received study drug; 228 subjects were in the gadobutrol:gadoteridol treatment sequence and 174 subjects were in the gadoteridol:gadobutrol treatment sequence. (Note: With the exception of the 54 sample subjects (gadobutrol:gadoteridol treatment sequence), randomization was 1:1. Images from sample subjects were not included in the efficacy evaluation; their safety data were included in the safety analyses).

Of the 402 treated subjects, 399 subjects received gadobutrol, 393 subjects received gadoteridol, and 390 subjects received both gadobutrol and gadoteridol. A total of 380 completed the study; 211 subjects in the gadobutrol:gadoteridol treatment sequence and 169 subjects in the gadoteridol:gadobutrol treatment sequence. Twenty-two subjects prematurely discontinued the study.

Most of the subjects in the safety analysis set were Caucasians (58.5%), followed by Asians (27.9%) and Hispanics (7.7%). More than one-half (56.5%) of the subjects were female. Most of the subjects were <65 years of age (76.6%), with a mean age of 50.8 years. Approximately one-third of all subjects were enrolled at study centers in the United States (30.6%) and one-quarter each at study centers in Japan (27.1%) and Germany (26.6%); the remaining subjects were divided among centers in Colombia, Switzerland, Australia, and Austria. The mean age of the subjects was 50.8 years (range 18 to 84), mean height was 166.9 cm (range 138 to 200), and the mean weight was 72.6 kg (range 31 to 145).

The most commonly reported main referral lesion types were "other" (36.3% of subjects), multiple sclerosis (15.9% of subjects), metastasis (14.9% of subjects), and meningioma (10.9% of subjects). Of the 60 subjects considered to have metastasis, the primary tumor sites were the lungs in 35 subjects, breasts in 11 subjects, "other" in 9 subjects, kidney in 2 subjects, and the stomach, colon, and unknown in 1 subject each.

Results Summary — Efficacy

Efficacy analyses were performed for the FAS and the PPS for the 4 primary efficacy variables for both the blinded readers and clinical investigators, and for the exact match diagnosis, normal/abnormal brain tissue, and malignant lesions for the blinded readers. As there was only a difference of 20 subjects between the FAS (N=336) and the PPS (N=316), the results

for the PPS are extremely similar to the results from the FAS. There were no differences in conclusions in the PPS from the conclusions in the FAS for any of the primary efficacy variables. Results for the secondary efficacy variables were also very similar to the results for the same variables in the FAS, which are presented herein.

Primary efficacy variables

- Combined unenhanced/gadobutrol-enhanced vs unenhanced

The 4 primary efficacy variables were contrast enhancement, border delineation, internal morphology, and number of lesions, as assessed by the blinded readers. For contrast enhancement, border delineation, and internal morphology, the improvement in scores from unenhanced to combined unenhanced/gadobutrol-enhanced was statistically significant for the average reader, as well as for the 3 individual readers ($P<0.0001$ in all cases).

The mean contrast enhancement average reader score increased from 0.97 unenhanced to 2.26 combined unenhanced/enhanced (using a scale of 1 = no enhancement to 4 = excellent enhancement). The mean differences were very consistent across the 3 readers, with all 3 readers demonstrating increases of between 1.06 and 1.59 units on the 4-unit scale.

The mean border delineation average reader score increased from 1.98 unenhanced to 2.58 combined unenhanced/enhanced (using a scale of 1 = no or unclear delineation to 4 = excellent delineation). The mean differences were consistent across the 3 readers, with all 3 readers demonstrating increases of between 0.43 and 0.72 units on the 4-unit scale.

The mean internal morphology average reader score increased from 1.32 unenhanced to 1.93 combined unenhanced/enhanced (using a scale of 1 = poor visibility to 3 = good visibility). The mean differences for the 3 blinded readers, while all showing statistically significant increases, had some variability across the readers, with mean changes of 0.62, 0.82, and 0.41 for readers 1, 2, and 3 respectively.

For the number of lesions, there was a high level of variability across the 3 readers. In particular, reader 2 had a higher mean number of lesions for both the unenhanced and combined unenhanced/enhanced modalities. Reader 2 also had much more variability within his assessments than there was for readers 1 and 3. As a result, the variability in the average reader change from unenhanced to combined unenhanced/enhanced was higher than anticipated in the protocol. There was a mean increase of 0.17 lesions (95% confidence intervals [-0.439 to 0.780]) from unenhanced to combined unenhanced/gadobutrol-enhanced modality.

The lower limit of this confidence interval, -0.439, was slightly lower than the prespecified noninferiority margin of -0.35. However, this was mainly driven by the high standard deviation from reader 2. For readers 1 and 3, the lower limits of the confidence intervals were above the prespecified value of -0.35.

Based upon the observed data, a supplemental nonparametric analysis was performed where the lesion counts were replaced by a categorical variable. For the average reader, the number of lesions detected was equal for the 2 modalities for 20.8% of the subjects, higher for combined unenhanced/gadobutrol-enhanced in 44.0% of subjects, and higher for unenhanced in 35.1% of the subjects. The difference between combined unenhanced/gadobutrol-enhanced and unenhanced was 8.9% (95% confidence intervals [-0.5% to 18.4%]). Using the noninferiority margin of -10%, which was prespecified as the noninferiority margin for the secondary categorical variables, noninferiority was demonstrated for gadobutrol. Noninferiority was demonstrated for all 3 blinded readers as well.

• Combined unenhanced/gadobutrol-enhanced vs combined unenhanced/gadoteridol enhanced

For the average reader, as well as for all 3 individual readers, the contrast enhancement, border delineation, and internal morphology scores were extremely similar for the 2 agents. The noninferiority of gadobutrol to gadoteridol was proven for each parameter.

For the average reader, as well as for all 3 individual readers, the numbers of lesions seen were very similar for the 2 agents. However, as mentioned previously, the variability for reader 2 was much higher than for the other 2 readers, which resulted in higher than expected variability for the average reader. The lower limit of the 95% confidence intervals (-0.601 to 0.622) for the difference between gadobutrol and gadoteridol was lower than the prespecified noninferiority margin of -0.35.

The results of the nonparametric analysis for the number of lesions showed for the average reader, the difference between gadobutrol and gadoteridol was 8.3% (95% confidence interval [-0.9% to 17.6%]). Using the prespecified noninferiority margin of -10%, noninferiority of gadobutrol to gadoteridol was demonstrated. Noninferiority was demonstrated for all 3 blinded readers as well.

Secondary efficacy variables

The 4 primary efficacy variables were also assessed by the clinical investigators. For border delineation and internal morphology, the mean changes for the clinical investigators from unenhanced to combined unenhanced/enhanced were statistically significant (P<0.0001 for each). For the number of lesions, the change from unenhanced to combined unenhanced/ enhanced for the clinical investigators met the noninferiority criterion. For contrast enhancement, although there was no unenhanced assessment for the clinical investigators, the combined unenhanced/enhanced mean score was 2.67, compared to the combined unenhanced/enhanced average reader mean score of 2.26. Noninferiority of gadobutrol to gadoteridol was also shown for all 4 variables.

The blinded readers and clinical investigators provided their diagnoses of the subjects for all 3 modalities. All 3 blinded readers demonstrated a higher accuracy of diagnosis (an exact match to the standard of truth diagnosis) combined unenhanced/gadobutrol-enhanced as compared to unenhanced, and the improvement was statistically significant for 2 of the 3 readers (P=0.0796 for reader 1, P=0.0422 for reader 2, and P=0.0006 for reader 3). The improvement in accuracy rates ranged from 4.5% for reader 1 to 8.6% for reader 3. The majority reader assessment had a statistically significant improvement in accuracy (P=0.0082), improving by 6.2% from unenhanced to combined unenhanced/enhanced.

The clinical investigators also demonstrated a statistically significant improvement (9.9%; P<0.0001) from unenhanced to combined unenhanced/gadobutrol-enhanced in accuracy (from 69.2% to 79.1%).

All 3 blinded readers demonstrated very similar accuracy of diagnosis for the 2 contrast agents, and using the prespecified noninferiority margin of -10%, noninferiority of gadobutrol to gadoteridol was demonstrated for all 3 readers and the majority reader. The clinical investigators also demonstrated very similar accuracy rates between the 2 contrast agents and noninferiority of gadobutrol to gadoteridol was demonstrated for the clinical investigators as well.

The blinded readers provided their assessment of whether the MRI (T1w) images were

normal or abnormal. These assessments were compared to the standard of truth diagnoses, and sensitivity, specificity, and accuracy measurements were calculated for each reader and the majority reader. For all 3 readers and the majority reader, accuracy and sensitivity were statistically significantly higher with gadobutrol-enhanced than unenhanced. For the specificity analysis, the values increased slightly from unenhanced to gadobutrol-enhanced for readers 1 and 2, and decreased for reader 3. There was no loss in specificity for unenhanced and enhanced for the majority reader.

For all 3 readers and the majority reader, accuracy, sensitivity and specificity rates were very similar between gadobutrol and gadoteridol. For accuracy and sensitivity, noninferiority of gadobutrol to gadoteridol was proven for all 3 readers and the majority reader. For specificity, the lower limits of the 95% confidence intervals for the treatment group differences were slightly below -10% for all 3 readers and the majority reader. Sensitivity, specificity, and accuracy were calculated for the blinded readers, the majority reader, and clinical investigators for the malignant or not malignant diagnoses from the blinded readers, clinical investigators, and standard of truth.

For all 3 readers and the majority reader, there were statistically significant increases in sensitivity from unenhanced to combined unenhanced/gadobutrol-enhanced. There was essentially no loss in specificity values from unenhanced to combined unenhanced/enhanced for all 3 readers and the majority reader. As a result of the large increases in sensitivity but essentially no changes in specificity, the accuracy values increased from unenhanced to combined unenhanced/enhanced, but with increases of less magnitude than the sensitivity increases. The 3 blinded readers and the majority reader all had increases in accuracy, which were all statistically significant.

The clinical investigator values increased from unenhanced to combined unenhanced/gadobutrol-enhanced for all 3 measures. The increases in sensitivity and accuracy were statistically significant.

For all 3 measures, the gadobutrol rates were slightly higher than the gadoteridol rates, and noninferiority of gadobutrol to gadoteridol was proven for all 3 measures for all 3 readers and the majority reader. In addition, gadobutrol demonstrated superiority to gadoteridol for the majority reader for sensitivity and accuracy. Gadobutrol also demonstrated superiority to gadoteridol for sensitivity for reader 2. The clinical investigator values were very similar for gadobutrol and gadoteridol for all 3 measures, and noninferiority of gadobutrol to gadoteridol was proven in each case.

The blinded readers and clinical investigators provided the confidence they had in their unenhanced and combined unenhanced/enhanced diagnoses. For the average reader assessment, the mean improvement in diagnostic confidence from unenhanced to combined unenhanced/gadobutrol-enhanced was statistically significant ($P<0.0001$). Each of the individual readers also demonstrated statistically significant improvements in diagnostic confidence ($P\leq0.0004$ for each). The mean change in diagnostic confidence from unenhanced to combined unenhanced/gadobutrol-enhanced for the clinical investigators was also statistically significant ($P<0.0001$).

The results for the combined unenhanced/gadobutrol-enhanced diagnostic confidence values were very consistent with the results from the combined unenhanced/gadoteridol-enhanced values. The mean difference for the average reader diagnostic confidence between the 2 agents was 0, and the mean differences for the 3 individual readers ranged from -0.03 to 0.02. This consistency between agents was also evident for the clinical investigators, for whom the mean difference between agents in diagnostic confidence was 0.04.

Of the 399 subjects who received gadobutrol, 100 (25.1%) subjects reported at least 1 AE during the study. Of the 393 subjects who received gadoteridol, 96 (24.4%) subjects reported at least 1 AE during the study. Of the 390 subjects who received both gadobutrol and gadoteridol, there was no statistically significant difference between the incidence rate of AEs for gadobutrol (24.62%) and the incidence rate of AEs for gadoteridol (24.36%; 95% CI, -5.09% to 5.60%).

The most commonly reported AEs in both the gadobutrol and gadoteridol groups were headache (3.3% and 2.5% of subjects, respectively) and nausea (2.8% and 4.3% of subjects, respectively). No clinically relevant differences were noticed between subgroups and treatment groups when AEs were analyzed by age, ethnic group, gender, or country.

The proportions of subjects with at least 1 drug-related AE in both treatment groups were similar; 40 (10.0%) subjects in the gadobutrol group and 38 (9.7%) subjects in the gadoteridol group. The most common drug-related AE in both the gadobutrol and gadoteridol treatment groups was nausea (6 [1.5%] and 10 [2.5%] subjects, respectively). All other drug-related AEs were reported by ≤1% of subjects in either treatment group. There were no notable differences between treatment groups in the occurrence of individual drug-related AEs.

Of the 390 subjects who received both gadobutrol and gadoteridol, there was no statistically significant difference between the incident rates of the subjects in each treatment group who experienced drug-related AEs (95% CI, -3.73% to 4.24%). In the gadobutrol group, 6 (1.5%) subjects experienced AEs that were rated as severe in intensity; 2 AEs were considered related to study drug (dysgeusia and hematuria).

In the gadoteridol group, 3 (0.8%) subjects experienced AEs that were rated as severe in intensity; 2 AEs were considered related to study drug (vomiting and an upper abdominal pain).

Two subjects each experienced 1 SAE during the gadobutrol period (100180001- brain metastases and 200030019 - an aggravation of hydrocephalus). One subject experienced 2 SAEs (100080002 - worsening of his general condition and somnolence) during the gadoteridol period. None of the SAEs were considered by the investigators to be related to study drug.

No deaths were reported during this study, although 1 subject (in the gadoteridol: gadobutrol treatment sequence) died after the follow-up period of the study. Subject 100080002 (see above), experienced 2 SAEs after receiving gadoteridol. He then received gadobutrol, and prematurely discontinued the study due to these SAEs and died 8 days later.

Clinical laboratory evaluations were performed at baseline (within 1 hour of study drug administration) and at 24 ± 4 hours postinjection for study periods 1 and 2. Serum creatinine was additionally collected at 72 ± 4 hours postinjection during study period 2. The mean changes from baseline for each parameter were not clinically relevant. Most of the laboratory-related AEs that were reported were considered drug-related. None of AEs caused premature discontinuation for any subject. Only one was considered severe (hematuria, which was noted above).

The mean systolic and diastolic blood pressures showed minimal fluctuations from baseline at each time point during the study. At each postinjection time point, most subjects in both

treatment groups had changes within 20 mmHg from baseline in systolic (≥85%) and diastolic (≥94.9%) blood pressure. Both increases and decreases of a magnitude of >20 mmHg were noted at each postinjection time point in each treatment group. Four subjects had changes in blood pressure during the study that were reported by the investigators as AEs; all were during the gadobutrol period (3 subjects with an increase in blood pressure or hypertension, and 1 subject with hypotension). All were mild in intensity and resolved within one day. Only 1 case of an increase in blood pressure was considered to be related to study drug.

The mean heart rate showed minimal fluctuations from baseline at each postinjection time point. At each postinjection time point, the majority of subjects in both treatment groups (≥86.9%) had heart rate values that were within 15 bpm of the baseline value. Five subjects experienced changes in heart rate that were considered AEs. Bradycardia and irregular heart rate were experienced by 1 subject each in the gadobutrol group, and tachycardia was experienced by 1 subject in the gadobutrol group and 2 subjects in the gadoteridol group. All were considered mild. The irregular heart rate and 2 cases of tachycardia (one in each treatment group) were considered related to the study drug. All of the AEs, except for 1 case of tachycardia in the gadoteridol group where the resolution is unknown, resolved between 4 minutes and 6 days.

The mean respiration rates and body temperature at baseline and at 24 hours postinjection were essentially constant for both treatment groups. None of the individual changes in respiration rate or body temperature was considered by the investigator to be an AE.

Results Summary — Pharmacokinetics
Not applicable
Results Summary — Other
Not applicable

Conclusion(s)

In this study, gadobutrol administered for MR contrast-enhancement of the CNS at a dose of 0.1 mmol/kg via a power injector at a rate of 2 mL/s is a safe and effective contrast agent.

Publication(s):	None		
Date Created or Date Last Updated:	23 JAN 2014	Date of Clinical Study Report:	29 JUL 2013

Investigational Site List

Marketing Authorization Holder in Germany	
Name	Bayer Vital GmbH
Postal Address	D-51368, Leverkusen, Germany
Sponsor in Germany (if applicable)	
Legal Entity Name	Bayer HealthCare AG
Postal Address	D-51368, Leverkusen, Germany

List of Investigational Sites

No	Facility Name	Street	ZIP Code	City	Country
1	Monash Medical Centre	Dept of Neurosciences Monash Medical Centre 246 Clayton Road	3168	Clayton	AUSTRALIA
2	Westmead Hospital	Dept of Radiology/MRI Unit Westmead Hospital Darcy Road	2145	Westmead	AUSTRALIA
3	Allgemeines Krankenhaus der Stadt Wien Universitätskliniken	Universitätsklinik für Radiodiagnostik Währingergürtel 18-20	1090	Wien	AUSTRIA
4	Medizinische Universität Graz	Univ.-Klinik f. Radiologie Klin. Abt. f. Neuroradiologie Auenbruggerplatz 9	8036	Graz	AUSTRIA
5	CENTRO DE DIAGNOSTICO MEDICO	Carrera 43 A No. 34 – 95 Local 115		Medellín	COLOMBIA
6	DIME Clinica Neurocardiovascular S.A.	Av. 5 Norte #20 N-75		Cali	COLOMBIA

7	Fundación Instituto de Alta tecnología médica de Antioquia	Carrera 50 No. 63 -95		Medellín	COLOMBIA
8	Deutsches Krebsforschungszentrum	Radiologie Im Neuenheimer Feld 280	69120	Heidelberg	GERMANY
9	Kliniken der Medizinischen Hochschule Hannover	Institut für Diagnostische und Interventionelle Neuroraiologie Carl-Neuberg-Str. 1	30625	Hannover	GERMANY
10	Klinikum der Christian-Albrechts-Universität	Klinik für Diagnostische Radiologie Arnold-Heller-Str. 9	24105	Kiel	GERMANY
11	Klinikum der Christian-Albrechts-Universität	Institut für Neuroradiologie Schittenhelmstr. 10	24105	Kiel	GERMANY
12	Klinikum Ernst von Bergmann	Radiologie Charlottenstr. 72	14467	Potsdam	GERMANY
13	Klinikum Mannheim gGmbH	Abteilung für Neuroradiologie Theodor-Kutzer-Ufer 1-3	68167	Mannheim	GERMANY
14	Krankenhaus Nordwest	Neuroradiologie Steinbacher Hohl 2-26	60488	Frankfurt	GERMANY
15	Medizinische Fakultät Carl Gustav Carus	Institut und Poliklinik für Radiologische Diagnostik Fetscherstraße 74	01307	Dresden	GERMANY
16	Medizinisches Versorgungszentrum Prof. Dr. D. Uhlenbrock	& Partner Wilhelm-Schmidt-Str. 4	44263	Dortmund	GERMANY

17	Städtisches Klinikum Karlsruhe gGmbH	Zentralinstitut für Bildgebende Diagnostik - Radiologie - Moltkestr. 90	76133	Karlsruhe	GERMANY
18	Universität Erlangen-Nürnberg	Neuroradiologische Abteilung Schwabachanlage 6	91054	Erlangen	GERMANY
19	Universitätskliniken des Saarlandes	Klinik für Diagnostische u. Interventionelle Neuroradiologie Kirrberger Str.	66424	Homburg	GERMANY
20	Universitätsklinikum Charite zu Berlin	Campus Charite Mitte Institut Für Radiologie Chariteplatz 1	10117	Berlin	GERMANY
21	Universitätsklinikum Köln	Institut für Diagnostische Radiologie Kerpener Str. 62	50937	Köln	GERMANY
22	Zentralklinikum Augsburg	Klinik für Diagnostische Radiologie und Neuroradiologie Stenglinstr. 2	865156	Augsburg	GERMANY
23	Himeji Central Hospital	Neurosurgery 2-36 Miyake Shikama-ku	672-8501	Himeji	JAPAN
24	Himeji Medical Center	Radiology 68 Honmachi	670-8520	Himeji	JAPAN
25	Institute of Biomedical Research and Innovation	Department of Translational Research 2-2 Minatojimaminamimachi Chuo-ku	650-0047	Kobe	JAPAN
26	Kishiwada Tokushukai Hospital	Department of Radiology 4-27-1 Kamori-cho	596-8522	Kishiwada	JAPAN

27	Nagoya Kyoritsu Clinic	Roentgenology 1-190 Hokke Nakagawa-ku	454-0933	Nagoya	JAPAN
28	Osaka General Medical Center	Department of Imaging Diagnosis 3-1-56 Bandai-higashi, Sumiyoshi-ku	558-8558	Osaka	JAPAN
29	Osaka Medical Center for Cancer and Cardiovascular Diseases	Department of Radiology 1-3-3, Nakamichi, Higashinari-ku	537-8511	Osaka	JAPAN
30	Osaka National Hospital	Department of Radiology 2-1-14 Hoenzaka, Chuo-ku	540-0006	Osaka	JAPAN
31	Shimonoseki Kosei Hospital	Neurosurgery 3-3-8 Kamishinchi-cho	750-0061	Shimonoseki	JAPAN
32	Shin Suma Hospital	Neurosurgery 4-1-6 Isonare-cho Suma-ku	654-0047	Kobe	JAPAN
33	Social Insurance Chukyo Hospital	Department of Neurosurgery 1-1-10 Sanjo Minami-ku	457-8510	Nagoya	JAPAN
34	Utano National Hospital	Department of Neurosurgery 8 Narutakiondoyama-cho Ukyo-ku	616-8255	Kyoto	JAPAN
35	Hôpital Cantonal Universitaire de Genève	Département de radiologie Division de radiodiagnostic Rue Gabrielle-Perret-Gentil 4	1211	Genève	SWITZERLAND

36	Inselspital Bern	Institut für Diagnostische und Interventionelle Neuroradiologie Freiburgstrasse 4	3010	Bern	SWITZERLAND
37	Luzerner Kantonsspital	Luzerner Kantonsspital Institut für Radiologie Spitalstrasse	6000	Luzern	SWITZERLAND
38	Universitätsspital Basel	Abteilung für diagnostische und interventionelle Neuroradiologie Universitätsspital Basel Petersgraben 4	4031	Basel	SWITZERLAND
39	Achieve Clinical Research, LLC	Black Warrior Medical Center 100 Rice Mine Road Loop Suite 104	35406	Tuscaloosa	UNITED STATES
40	Atchison Hospital	1301 North Second Street	66002	Atchison	UNITED STATES
41	Hoag Memorial Hospital Presbyterian	Neuroscience Center One Hoag Drive	92658-6100	Newport Beach	UNITED STATES
42	Hospital of the University of Pennsylvania	University of Pennsylvania Health System 3400 Spruce Street 2nd Floor Dulles Building Suite 219	19104	Philadelphia	UNITED STATES
43	Kingston Neurological Associates, PC	365 Broadway	12401	Kingston	UNITED STATES

44	Los Gatos MRI	800 Pollard Road Suite B-101	95032	Los Gatos	UNITED STATES
45	Medical University of South Carolina	96 Jonathan Lucas Street	29425	Charleston	UNITED STATES
46	NorthShore University HealthSystem-Evanston Hospital	Evanston Hospital 2650 Ridge Ave Walgreen Building/Room B517	60201	Evanston	UNITED STATES
47	Rhode Island Hospital	Diagnostic Imaging 593 Eddy Street	02903	Providence	UNITED STATES
48	University of Florida - Jacksonville	Shands Jacksonville Med. Center Department of Radiology C-90 655 West 8th Street	32209	Jacksonville	UNITED STATES
49	University of Washington Medical Center	Department of Radiology Box 357115 1959 NE Pacific Street	98195	Seattle	UNITED STATES
50	Washington University School of Medicine	510 South Kings Highway Blvd. Box 8131 Suite 16105	63110	St. Louis	UNITED STATES
51	West Alabama Research, Inc.	2018 Brookwood Medical Center Drive Suite 314	35209	Birmingham	UNITED STATES
49	Hospital Cantonal Universitaire, Departement of Radiolgie, Division of Radiodiagnostic	Rue Gabrielle-Perret-Gentil 4	CH-1211	Genève	Switzerland
50	Universitätsspital Basel Neuroradiologie	Petersgraben4	CH-4031	Basel	Switzerland
51	Institute of Diagnostic and Interventional Neuroradiology University of Bern / Inselspital	Freiburgstrasse 4	CH-3010	Bern	Switzerland

Product Identification Information

Product Type	Drug
US Brand/Trade Name(s)	Gadavist
Brand/Trade Name(s) ex-US	Gadovist
Generic Name	Gadobutrol
Main Product Company Code	BAY86-4875
Other Company Code(s)	ZK 135079
Chemical Description	10–[(1SR,2RS)–2,3–dihydroxy–1–hydroxymethylpropyl]–1,4,7,10–tetraazacyclododecane–1,4,7–triacetic acid, gadolinium complex
Other Product Aliases	

Date of last Update/Change: 28 May 2013