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.

Clinical Trial Results Synopsis

Date of report	30 JAN 2014
Study title:	Multicenter, open-label study to evaluate the safety and efficacy (by blinded reading) of Gadobutrol-enhanced magnetic resonance angiography (MRA) after a single injection of 0.1 mmol/kg of Gadobutrol in subjects with known or suspected renal artery disease.
Sponsor's study number	91759
NCT number	National Clinical Trial number: NCT 01344460
EudraCT number:	2010-023002-13
Sponsor	Bayer Pharmaceuticals Inc.
Clinical phase:	III
Study objectives:	The primary objective of this study was to evaluate the efficacy of gadobutrol-enhanced magnetic resonance angiography (MRA) over two dimensional-Time of Flight (2D-ToF) MRA in subjects with known or suspected renal artery disease, as verified by: • Superiority for structural delineation, • Non-inferiority for the detection of clinically significant vascular disease, • Non-inferiority for the exclusion of clinically significant vascular disease, • Minimum performance for gadobutrol detection of clinically significant vascular disease, and • Minimum performance for gadobutrol exclusion of clinically significant vascular disease; using computed tomographic angiography (CTA) as the standard of reference (SoR) excluding the first objective, structural delineation. A further objective of this study was to confirm the safety profile of gadobutrol for this indication.
Test drug (INN):	Gadobutrol (Gadavist/Gadovist, BAY no. 86-4875)
Name of active ingredient:	Gadobutrol, 1.0 molar
Dose:	0.1 mmol/kg body weight (BW)
Route of administration:	Single intravenous (I.V.) bolus injection
Duration of treatment:	Single dose
Reference drug:	Not applicable

Indication:	Gadobutrol injection is indicated for MRA of adults with known or suspected vascular disease for visualization and diagnosis of clinically significant disease involving the renal arteries.
Diagnosis and main criteria for inclusion:	Male or female subjects, age ≥ 18 years with known or suspected renal artery disease based on any of the following: • referred for evaluation of the renal arteries for clinically significant stenosis • follow-up for a metallic stent in a renal artery • prior imaging study (CTA) showing ≥ 50% renal artery stenosis (within 60 days prior to consent)
Study design:	This was a multicenter, open-label study to evaluate the safety and efficacy of Gadobutrol-enhanced MRA of the renal arteries using a power injector. The evaluations involved blinded reading of all images.
Methodology:	During the course of the study, two sets of magnetic resonance (MR) images were obtained from each subject: non-contrast axial (2D-ToF) sequence MRA before the administration of gadobutrol and contrast-enhanced MRA after the injection of gadobutrol. All MRA images (non-contrast and gadobutrol-enhanced) were evaluated by the clinical investigators and by 3 independent blinded readers. Safety was assessed using data from physical exam, vital signs, laboratory values, and monitoring of adverse events (AEs) between the execution of the informed consent (IC) and follow-up approximately 72 hours after study drug administration or until the CTA, if performed after the MRA as part of the study).
Type of control:	Non-contrast MRA (performed immediately prior to the gadobutrol-enhanced MRA).
Standard of reference:	The diagnostic performance of gadobutrol was assessed by establishing the clinically significant vascular disease (50 to 99% stenosis, excluding occlusions) for each arterial segment as an independent SoR based on a blinded read of a CTA by 3 independent blinded readers who were independent of the MRA blinded readers and the clinical investigators.
Investigators:	Number of study centers: 55 active study centers in 13 countries
Study centers:	3 sites in Argentina, 2 sites in Austria, 4 sites in Brazil, 4 sites in Switzerland, 4 sites in Colombia, 3 sites in the Czech Republic, 5 sites in Germany, 4 sites in France, 5 sites in South Korea, 3 sites in Poland, 4 Sites in Turkey, 2 sites in Taiwan, and 12 sites in the United States.
Publication based on the study:	Not applicable
Study period:	**First subject, first visit:** 16 MAY 2011 **Last subject, last visit:** 06 JUL 2012

Early termination	No
Number of subjects per treatment group:	Planned: 336; Enrolled: 317; Analyzed: 315 Subjects who received drug (safety analysis set)
Criteria for evaluation **Efficacy:**	The primary efficacy evaluation was based on three variables which were calculated for both gadobutrol-enhanced MRA and non-contrast MRA: Assessability, Sensitivity and Specificity. These were used to evaluate five co-primary endpoints: • Superior structural delineation with gadobutrol-enhanced MRA compared to non-contrast MRA based on the number of assessable vascular segments with 6 possible vascular segments per subject (3 segments in the right renal artery and 3 segments in the left renal artery) and up to 9 segments in subjects with renal transplant (4 subjects). • Non-inferior detection of clinically significant disease based on the sensitivity for clinically significant disease [50 to 99% stenosis] on a segmental basis • Non-inferior exclusion of clinically significant disease based on the specificity for clinically significant disease [50 to 99% stenosis] on a segmental basis • The two minimum gadobutrol performance criteria based on the sensitivity for clinically significant disease > 50% (chance) and based on the specificity for clinically significant disease > 50% (chance). The secondary efficacy evaluations included the following: • Length of the right and left renal arteries • Narrowest diameter of a segment • Location of stenoses in the proximal segments: Proximal segment divided into ≤ 5 mm from the aorta or ≥ 5 mm from the aorta (or iliac artery in the case of a transplant kidney) • Artifacts by type (segmental) • Accessory (duplicate) renal arteries • Aneurysmal dilatation (segmental) • Diagnosis (subject): FMD vs. arteriosclerosis • Diagnostic confidence (segmental) • Additional imaging studies recommended (subject)
Safety:	The safety of the subjects was assessed using data from vital signs, physical checks, laboratory values, and monitoring of adverse events (AEs). Safety was assessed from the time the consent was signed until the 72 (± 6) hour follow-up after the study MRA, and continued until the end of the study (either at the 72 hour follow-up or the CTA, if performed after the MRA).
Other:	Not applicable to this study.

Statistical methods:	The primary analysis included point estimation and statistical comparisons (hypothesis testing) of the arterial segment assessability, and the segment sensitivity and specificity for gadobutrol-enhanced versus non-contrast MRA in the detection of clinically significant disease (50 to 99% stenosis). The two-sided 95% confidence intervals (CIs) for the differences between gadobutrol-enhanced and unenhanced MRA in assessability, and the one-sided 95% CIs for the differences in sensitivity, and specificity were used to assess superiority for assessability, and non-inferiority for specificity and sensitivity (using a 7.5% non-inferiority margin). If the lower limit of the one-sided 95% CI (for gadobutrol-enhanced MRA *minus* unenhanced MRA) was > -7.5%, then non-inferiority was demonstrated. If the lower limit of the CI was > 0, then superiority was demonstrated. Minimum gadobutrol performance was assessed by requiring the lower limit of the one-sided 95% CI for both the sensitivity and specificity for gadobutrol-enhanced MRA to be > 50%. For all five co-primary variables, the majority reader assessment of the complete analysis set was considered the primary assessment. The majority reader was defined as the outcome determined by at least two of the three blinded readers.
Premature Study Suspension/Termination	Not applicable
Substantial protocol changes	Local protocol amendment applicable to German study centers. • Clarification on the inclusion of subjects in Germany to only those who either had a prior computed tomographic angiography (CTA) or were referred by the physician to have a CTA. In Germany, only subjects who had undergone a CTA within 60 days prior to consent or subjects who clinically required a CTA which was ordered by the referring physician as part of the standard clinical routine were included.to meet the local guidelines and obtain a separate approval from the local German Radiation Protection Authority. • The German regulatory authority (BfArM) requested excluding subjects with hypokalaemia and medications that prolonged repolarization like Class III anti-arrhythmics. This was addressed by advising the investigators to adhere to the local package insert which included the respective warnings.

Study subjects

The study enrolled 317 subjects at 55 study centers in 13 countries, of which a total of 315 subjects received approximately 0.1 mmol/kg (0.1 mL/kg) gadobutrol as a single bolus

injection. The mean age of the subjects in the study was 54.9 years (range: 18-88). The majority of subjects in the study were White (68.3%) and there were 170 (54.0%) males and 145 (46.0%) females.

All subjects who were administered study drug were included in the safety analysis set (315 subjects). The efficacy analysis sets included the full analysis set (292 subjects) and the per-protocol set (265 subjects). A total of 235 subjects had protocol deviations categorized as major or minor.

Almost all subjects (314 / 315) in the study had at least one medical history finding. The most frequent risk factor in this study was hypertension, recorded in the medical history of 300 subjects (95.2%).

Efficacy evaluation

The primary efficacy evaluations were based on the five co-primary endpoints: assessability, non-inferior sensitivity and specificity, and minimum performance sensitivity and specificity.

The endpoint of assessability is achieved, since the majority reader assessment of gadobutrol-enhanced MRA demonstrated a statistically significantly higher assessability rate than unenhanced MRA, 95.9% vs 77.6%, $P < 0.0001$.

For sensitivity and specificity, two sets of hypotheses were tested:

For the first set, comparisons of gadobutrol-enhanced MRA vs unenhanced MRA were performed, to determine if gadobutrol-enhanced MRA was non-inferior to unenhanced MRA, using a pre-specified non-inferiority margin of -7.5%. For the non-inferiority test of sensitivity, gadobutrol-enhanced MRA had a sensitivity of 53.4%, and unenhanced MRA had a sensitivity of 46.6%. The lower limit of the one-sided 95% CI for this difference was -2.2%. Since this value was greater than -7.5%, non-inferiority was demonstrated. For the non-inferiority test of specificity, gadobutrol-enhanced MRA had a specificity of 94.8%, and unenhanced MRA had a specificity of 85.7%. The lower limit of the one-sided 95% CI for this difference was 7.0%. Since this value was greater than -7.5%, non-inferiority was demonstrated. A statistical superiority of gadobutrol-enhanced MRA was concluded since the lower limit was greater than 0.

For the second set of hypotheses, the sensitivity and specificity values for gadobutrol-enhanced MRA were also compared to the value of 50%. In these analyses, segments considered unassessable, and therefore unavailable for calculations of sensitivity and specificity were excluded. For this objective, the sensitivity for gadobutrol-enhanced MRA was 54.6%. The lower limit of the one-sided 95% CI for this value was 46.2%. Therefore, although the point estimate for sensitivity did exceed the pre-specified value of 50%, the lower limit of the CI did not. Thus, formally this objective was not met. The specificity for gadobutrol-enhanced MRA for this primary objective was 95.9%. The objective of demonstrating greater than 50% specificity was achieved since the lower limit of the one-sided 95% CI for this value was 94.9%.

Results for the five co-primary endpoints for the per protocol set were similar to the results from the full analysis set.

The objectives for all five co-primary endpoints were achieved for the clinical investigators. Statistical superiority of gadobutrol-enhanced MRA vs unenhanced MRA was demonstrated for assessability, sensitivity, and specificity. For assessability, the rates were 94.4% for gadobutrol-enhanced MRA vs. 68.9% for unenhanced MRA ($P < 0.0001$). The sensitivity values for the clinical investigators were 69.3% for gadobutrol-enhanced MRA and 50.0% for unenhanced MRA, and the lower limit of the one-sided 95% CI was 11.7%. Since this value was greater than 0, statistical superiority of gadobutrol-enhanced MRA can be concluded. The specificity values for the clinical investigators were 96.5% for gadobutrol-enhanced MRA and 83.5% for unenhanced MRA, and the lower limit of the one-sided 95% CI was 11.0%. Since this value was greater than 0, statistical superiority of gadobutrol-enhanced MRA can be concluded.

The sensitivity and specificity values for gadobutrol-enhanced MRA for the comparison to the value of 50% were very similar to the values for the non-inferiority comparisons, 71.3% for sensitivity and 98.4% for specificity. The lower limits of the one-sided 95% CIs were 64.7% for sensitivity and 97.8% for specificity. Therefore, the objectives of demonstrating greater than 50% sensitivity and specificity were achieved.

Inter-reader variability measures show a complete reader agreement for 84.8% of the segments (all 3 blinded readers either matched or did not match the standard of reference), and the overall kappa value of 0.51 is suggestive of a moderate level of agreement. Intra-reader agreement measured for about 5% of subjects had a kappa value of 0.59, again demonstrating a moderate level of agreement by the individual reader.

Evaluations of the secondary efficacy variables by the blinded readers and/or the investigator include measurements of the renal artery length (right and left), location of stenosis, normal and narrowest vessel diameter, the presence of artifacts in MRA images, diagnostic differentiation of disease (arteriosclerotic disease, fibromuscular dysplasia or aneurysmal dilatation), diagnostic confidence, and additional recommended imaging studies.

An additional measure of structural delineation was the length of the renal arteries. The mean lengths as measured by the 3 blinded readers in the gadobutrol-enhanced images were 3 mm longer than the mean lengths in the unenhanced images (gadobutrol enhanced: right artery 46 mm and left artery 35 mm; unenhanced right 43 mm and left 32 mm; CTA right 48 and left 37 mm), so 6% more of the vessel length was seen on the right and 8% more on the left.

Analysis of the reader measurements for the stenosis and the normal vessel diameters was also performed as a secondary endpoint. Measurement of the diameter directly relates to the percent stenosis and does not introduce an artificial “cut-off” for disease, as is the basis for calculating sensitivity. For the clinical investigator read, the mean diameter was 4.93 mm at the normal vessel point and 2.67 mm at the narrowest point for gadobutrol-enhanced and 4.56 mm (median = 4.60 mm) for the normal point and 2.53 mm (median = 2.50 mm) at the narrowest point for unenhanced. The vessel diameter measurements for the three blinded readers were similar to those of the clinical investigator.

The mean diameters at the normal point for CTA readers 4, 5, and 6, were 4.95 mm, 5.92 mm and 4.67 mm, respectively. The corresponding mean diameters for the three MRA readers were 4.84 mm, 4.63 mm and 4.87 mm, respectively, for the unenhanced, and 5.19 mm, 5.08 mm and 5.17 mm for the gadobutrol-enhanced images. The mean diameter was 5.13 mm for the clinical investigators CTA images; the corresponding means for the clinical investigator MRA images were 4.56 mm for unenhanced and 4.93 mm for gadobutrol-enhanced images.

The mean diameters at the narrow point for CTA readers 4, 5, and 6, were 2.81 mm, 2.52 mm and 2.14 mm, respectively. The corresponding mean diameters for the three MRA readers were 2.17 mm, 2.14 mm, and 2.30 mm, respectively, for the unenhanced images, and 2.61 mm, 2.53 mm, and 2.75 mm for the gadobutrol-enhanced images. The mean diameter was 2.80 mm for the clinical investigators CTA images; the corresponding means for the clinical investigator MRA images were 2.53 mm for unenhanced images and 2.67 mm for gadobutrol-enhanced images.

The location of stenosis ≥ 50% (within and beyond 5 mm from the aorta) for the MRA readers was also assessed. The percentage of stenosis locations, recorded as beyond 5 mm from the aorta were 71.7%, 45.7% and 65.3% for the CTA readers 4, 5, and 6, respectively. For the MRA readers, the percentage of locations recorded as beyond 5 mm from the aorta were 77.1%, 28.2%, and 78.2% for unenhanced images for readers 1, 2, and 3, respectively, and 73.6%, 26.5%, and 74.7% for the gadobutrol-enhanced images. The recorded percentage of locations beyond 5 mm of the aorta for MRA readers 1 and 3 was similar and within the range of the three CTA readers, while the MRA reader 2 recorded a lower percentage of locations beyond 5 mm of the aorta than the other 5 readers.

The frequency of artifacts was much more pronounced in unenhanced MRA images. The blinded readers observed artifacts in the unenhanced MRA images of 94.5% (reader 1), 95.9% (reader 2), and 99.3% (reader 3) subjects. With gadobutrol-enhancement, the 3 blinded readers found artifacts in 28.4% (reader 1), 37.7% (reader 2) and 45.9% (reader 3) subjects.

Accessory renal arteries were more frequently identified in gadobutrol-enhanced MRA images in comparison to the unenhanced MRA images. Each subject was also evaluated for the diagnosis of either arteriosclerotic disease, fibromuscular dysplasia, or neither. The diagnostic differentiation of disease by the 3 blinded readers could be determined much more frequently with gadobutrol-enhanced MRA images vs. unenhanced MRA images. Overall, the diagnosis of fibromuscular dysplasia with unenhanced MRA seemed difficult for almost all readers but was markedly improved with gadobutrol-enhancement.

The diagnostic confidence was measured on a 4-point scale, 4 being “very confident” and 1 being “not confident” at all (or not assessable). Two of the 3 readers assigned a mean diagnostic confidence value of 3.5 and one reader assigned 3.0, showing good confidence level in their diagnosis with gadobutrol-enhanced MRA images and all 3 readers assigned a mean diagnostic confidence value in the range of 1.9 to 2.2 demonstrating little confidence with unenhanced MRA images.

A significant reduction was observed in the number of additional diagnostic imaging studies recommended by the blinded readers and the investigators when gadobutrol-enhanced MRA

images were used in comparison to the unenhanced images. Similar to the blinded readers, the investigator recommended additional imaging studies for 43.5% subjects using unenhanced images and 18.8% subjects using gadobutrol-enhanced images. The highest number of recommendations by blinded reader 2 and the investigators was for contrast-enhanced MRA and for blinded readers 1 and 3 was for CTA, when reviewing unenhanced MRA images.

Safety evaluation

Of the total 315 subjects in the safety population, 64 (20.3%) subjects reported at least one or more AE. By system organ class (SOC), the highest number of AEs were in the nervous system disorders (6.3%), followed by the gastrointestinal disorders (4.4%), general disorders and administration site conditions (3.2%), musculoskeletal and connective tissue disorders (2.5%), investigations / skin and subcutaneous tissue disorders (1.9% each), hepatobiliary disorders (1.6%), and in the neoplasm benign, malignant and unspecified (including cysts and polyps) / vascular disorders SOC (1.3% each). The neoplasms were listed as AEs since they were not reported in the patient history but were unexpected findings on the imaging but were not related to gadobutrol exposure.

The most common AEs (≥ 1.0%) by primary SOC and preferred term (PT) were nausea in 8 (2.5%) subjects in the gastrointestinal disorders SOC, dizziness in 6 (1.9%) subjects and headache in 10 (3.2%) subjects in the nervous system disorders SOC, and urticaria in 4 (1.3%) subjects.

Study drug-related AEs were reported by the investigator in 21 (6.7%) subjects while procedure related (injection procedures) AEs were reported in 5.7% (18 of 315) subjects. The most common reported study drug related AE by PT was nausea in 7 (2.2%) subjects in the gastrointestinal disorders SOC, followed by rash and urticaria in 3 (1.0%) subjects each in the skin and subcutaneous tissue disorders SOC. The frequency of occurrence of the remaining study drug related AEs was only 0.3% (1 subject each).

The majority of AEs were of mild intensity (17.1%) while only 2.2 % AEs were considered moderate and 1.0% (3 AEs) of severe intensity. The severe AEs were: eye tired and eyes stinging, considered to be related to the study drug; shoulder pain, considered to be procedure-related and hypertension, each in one subject.

There were no deaths, SAEs or any discontinuations during the study. Adverse events prior to administration of study drug were in a total of 12 (3.8%) subjects.

Subgroup analysis showed that the older age groups (ie, 45 to 64 and ≥ 65 yrs) reported less frequent AEs in comparison to the age group < 45 yr. In the < 45 yrs age group, the most common AE was in the nervous system disorders SOC (for headache and dizziness) and the gastrointestinal disorders SOC (nausea). Overall, the frequency of AEs was slightly higher in the female (22.8%) subject population when compared with males (18.2%). The two most common AEs were nausea in the gastrointestinal disorders SOC and headache in the nervous

system disorders SOC. In terms of ethnicity, the frequency and type of most common AEs in hispanic and non-hispanic subjects was about the same in either subject groups.

Laboratory abnormalities were mostly associated with creatinine, phosphate, potassium, estimated glomerular filtration rate (eGFR), and blood urea nitrogen (BUN), parameters known to be have abnormal values in subjects suspected of renal disease but no trends or significant changes were noted. There was no change that can be considered of clinical significance in any of the vital sign evaluations (heart rate, respiration rate, body temperature and SBP/DBP).

Overall conclusions

Overall, data from this study demonstrated that the use of gadobutrol-enhanced MRA improved visualization and increased the ability to diagnose stenosis in subjects suspected of renal artery disease in comparison to the traditional 2D-ToF (unenhanced) MRA as a result of much more accurate measurement of the stenosis and vessel diameters, thus, potentially improving clinical care and reducing significant costs resulting from additional diagnostic imaging referrals.

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

Investigational Site List

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