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 AG	
Study Number:	91463	NCT00296855
Study Phase:	IIIb	
Official Study Title:	Intra-individual open-label multicenter comparison study of magnetic resonance angiography (MRA) with the blood pool contrast agent Vasovist and a conventional extracellular contrast agent with intra-arterial digital subtraction angiography (i.a. DSA) in patients with peripheral artery disease.	
Therapeutic Area:	Diagnostic Imaging	
Test Product		
Name of Test Product:	Gadofosveset trisodium (Vasovist, BAY86-5283, MS-325)	
Name of Active Ingredient:	Gadofosveset trisodium	
Dose and Mode of Administration:	Test product: 0.03 mmol/kg body weight (BW) injected as a single bolus, intravenously.	
Reference Therapy/Placebo		
Reference Therapy:	Conventional 0.5 molar extra cellular contrast medium (ECCM)	
Dose and Mode of Administration:	Total dose of 0.2 mmol/kg body weight. A single administration given as a biphasic bolus injection was recommended.	
Duration of Treatment:	Test product: Single intravenous (IV) administration of Vasovist with a follow-up-period of 24 (±4) hours. Reference therapy: One single IV bolus injection.	
Studied period:	Date of first subjects' first visit:	17 FEB 2006
	Date of last subjects' last visit:	17 FEB 2007
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	Amendment no. 1 (dated 02 MAY 2006) specified the following changes: • The recruitment phase was postponed from NOV 2005 - JUN 2006 to JAN 2006 - DEC 2006. • Intra-arterial DSA imaging requirements were changed to reduce the volume of contrast agent and the radiation exposure of the subjects. • Vital signs (blood pressure, heart rate) were measured at different time-points during the study in order to better evaluate the safety of Vasovist. Amendment no. 2 (dated 08 FEB 2007) specified the following changes: • The end of the recruitment phase was postponed from DEC 2006 to MAR 2007. • The number of recruitment sites was increased from 4 to 27.	

	• The 21 target vessel segments were classified to allow further sub-analysis (pelvis, thigh, knee, and calf). • The quantitative measurement of stenosis was restricted to arteries 1 to 15. Stenoses were only measured if they appeared to be above 35%. Stenosis categories were modified to ≤50%, >50% -<100%, 100%. • Three more analysis variables (sensitivity, specificity, and accuracy) were included to improve the comparability of results with other studies. • Signal Intensity (SI) measurements were performed for one leg only (preferably the left leg). • Severity score was replaced by single item evaluation named "qualitative assessment of disease". • The assessment of plaque morphology was assessed for all vessel segments. • Venous enhancement and plaque morphology assessments were excluded from the study. The diagnostic potential of venous enhancement was only assessed for the combined first pass (FP) and steady state (SS) images. Amendment no. 3 (dated 01 JUN 2007) specified the following changes: • For contrast measurements, regions of interest (ROIs) were located at two extravascular regions (muscle tissue and fatty tissue). • Change in signal intensity between pre-injection and post-injection during FP was calculated. The SI measurements were done using the FP and SS raw data sets of Vasovist MRA and ECCM MRA.
Study Centre(s):	The study was conducted at 22 centers in 6 countries: Argentina (4), Austria (3), Brazil (3), Germany (8), Mexico (2), and Switzerland (2).
Methodology:	This is an intra-individual, open-label, multi-center comparison study. Subjects were included in the study if MRA with a conventional 0.5 molar extracellular contrast agent had been performed prior to the study. Thus conventional extracellular MR contrast agent procedure was performed outside the study. MRA examination using the contrast agent Vasovist was compared to that using a conventional extracellular MR contrast agent intra-individually by means of an independent blinded off-site evaluation. For all subjects included into the study electronic datasets for an intra-arterial DSA examination and an MRA examination using a conventional ECCM were made available. Intra-arterial DSA and both MRA examinations (ECCM and Vasovist) displayed all imaging stations from the infrarenal aorta to the calves. Vasovist-enhanced MRA imaging was performed using the same MR system as was used for ECCM-enhanced. Imaging was performed both before (non-enhanced baseline 3D image data sets for FP and and all field of views (FOVs) were obtained for producing subtracted images) and after (images for FP MRA and SS MRA (all FOVs) were taken) the injection of Vasovist. The safety follow-up period was 24 (± 4) hours post-injection (p.i.) of Vasovist and included the assessment of adverse events (AEs) as well as the assessment of physical examinations and vital signs.
Indication/ Main Inclusion Criteria:	Indication: Contrast-enhanced MRA (CE-MRA)

	Main Inclusion criteria: Subjects who had an indication for the evaluation of the complete run-off arteries (i.e., infrarenal aorta from level of renal arteries to calf arteries excluding foot), and had to undergo intra-arterial DSA within a timeframe of 1-30 days after study MRA and had already undergone ECCM MRA within 7 days to 24 hours prior to the administration of study drug with no interventional or surgical procedure in between all imaging procedures.
Study Objectives:	Overall: To demonstrate non-inferiority of the diagnostic potential of Vasovist-enhanced MRA as compared to an ECCM for detection of infrarenal aorta and/or peripheral artery diseases using intra-arterial DSA as SOR. To demonstrate safety of Vasovist-enhanced MRA.
Evaluation Criteria:	Efficacy (Primary): Difference in diagnostic accuracy between combined FP and SS Vasovist MRA and FP ECCM MRA averaged over three blinded readers (for vessel segments 1 to 15, excluding vessel segments 16 to 21 of the lower calf). Per reader the diagnostic accuracy was defined as the agreement between the stenosis measurements for FP ECCM MRA and SOR, or combined FP and SS Vasovist MRA and SOR (i.e., same stenosis categories ≤50%, >50% - <100%, and 100%, or difference not greater than 20%). Efficacy (Secondary): • Diagnostic accuracy • Quantitative and qualitative assessment of the stenosis categories • Sensitivity, specificity and accuracy • Signal enhancement • Qualitative assessment of disease and plaque morphology • Quality of depiction of vascular anatomy • Delineation of vessel wall • Diagnostic potential of venous enhancement Safety: Adverse event reports, vital signs, and physical examination
Statistical Methods:	Efficacy (Primary): Test of non-inferiority of Vasovist compared to ECCM using intra-arterial DSA as SOR. Combined FP and SS Vasovist MRA was defined as non-inferior to FP ECCM MRA, if the lower limit of the 95% confidence interval (CI) of the difference of the averaged diagnostic accuracies was above – 10%. Efficacy (Secondary): Descriptive statistics were calculated for each quantitative variable. Absolute and relative frequencies were given for categorical data. Two-sided confidence interval were also calculated.

	Safety: Continuous safety variables were presented by descriptive statistics. Frequency tables were given for categorical data. For variables with classifications shift tables were made.
Number of Subjects:	Planned: minimum of 180 efficacy evaluable subjects. Analyzed: 261 subjects in the safety population and 211 subjects in the per-protocol set (PPS).

Study Results

Results Summary — Subject Disposition and Baseline

In total, 264 subjects had been enrolled in this study. Three dropouts were not included in the safety population, as no study medication was administered to them. The safety population (SAF) encompassed 261 subjects. Of the 261 subjects, 4 subjects discontinued the study prematurely. Thus, 257 subjects participated in the study for the entire time as planned in the study protocol. A total of 50 subjects of the SAF were not included in the PPS which included 211 subjects.

The mean age of the 261 subjects in the safety population was 64.8 years (range: 32 to 86). Their body mass index was on average 26.7 kg/m^2 (range: 16.8 to 43.4).

Of the 261 subjects, 171 subjects (65.5%) were males and 90 subjects (34.5%) were females. Subjects were either Caucasians (44.4%) or Hispanics (46.7%). For 8.8% as ethnic group "other" was ticked and "South-American" was documented.

Results Summary — Efficacy

Primary efficacy variables

Primary efficacy variable was the diagnostic accuracy, based on the average reader score, for combined FP and SS Vasovist MRA and FP ECCM MRA. To determine diagnostic accuracy of both MRA methods, intra-arterial DSA served as SOR for each of the 15 pre-specified vessel segments.

The result of the primary efficacy analysis demonstrated that the difference in the diagnostic accuracy of combined Vasovist MRA and FP ECCM MRA for the average reader was –0.80%. The corresponding 95% CI was -2.83% to 1.22%. Based on the prospective plan, non-inferiority of Vasovist compared to ECCM was proven, as the lower bound of the 95% CI was greater than -10%.

Using the same analysis and success criteria, which were applied to the average reader results, for each of the individual blinded reader results, non-inferiority was observed for all 3 blinded readers. These individual blinded reader results were in line with the average reader results.

The result of the primary efficacy analysis was calculated for the PPS, i.e., for the set of 15 upper vessel segments of each of the 211 subjects without major protocol violations, for which an assessment by the SOR intra-arterial DSA was available.

Secondary efficacy variables

Quantitative assessment of vessel segments with a relevant stenosis

For vessels with a clinically relevant stenosis measurement of >50% as determined by intra-arterial DSA, the corresponding MRA stenosis measurements were analyzed. The highest number of clinically relevant stenoses were identified in the superficial femoral artery. When compared to intra-arterial DSA, differences in the average stenosis measurements were less than 8 percentage points for all MRA assessments, i.e., Vasovist (FP), Vasovist (combined), ECCM (FP), and ECCM (combined).

For the popliteal artery, which according to intra-arterial DSA also presented with a high number of vessel segments with a relevant stenosis, differences in the average stenosis measurements were more pronounced. All MRA average assessments substantially underestimated the degree of stenosis compared to intra-arterial DSA.

In case of infrarenal aorta, common iliac artery, external iliac artery, common femoral artery, deep femoral artery, and tibiofibular trunk the number of vessel segments with a relevant stenosis was smaller. Differences in the determined stenosis degree between intra-arterial DSA and MRA were greatest for the deep femoral artery.

Overall, with the used imaging protocol both MRA examination methods were comparable. Advantages due to a prolonged imaging window in case of Vasovist (combined) compared to Vasovist (FP) could not be inferred from these data. Results following ECCM (FP) and ECCM (combined) were comparable too.

Qualitative assessment of vessel segments: Diagnostic accuracy and further indices (sensitivity, specificity and accuracy)

The diagnostic accuracy was defined as the agreement between the stenosis measurement obtained following the MRA examination and the result of the intra-arterial DSA examination based on the stenosis categories ≤ 50%, >50% - <100%, 100% and taking into account the 20% rule.

Diagnostic accuracies were calculated for Vasovist (combined) and ECCM (FP) (i.e., the MRA examination methods used for the primary efficacy analysis) as well as for Vasovist (FP) and ECCM (combined) for each of the 15 pre-specified vessel segments. Diagnostic accuracies were in the range of 82.5% (Vasovist [FP]) to 86.7% (ECCM [combined]). This confirmed the comparable performance of both types of contrast agents.

Diagnostic accuracies calculated in vessel segments representative for pelvis, thigh, knee and calf showed expected results: Diagnostic accuracy was highest for pelvis and decreased distally as the caliper of the vessel segments became smaller. Similar results were obtained for the individual vessel segments. Obvious differences between Vasovist and ECCM were not observed. Non-inferiority of Vasovist compared to ECCM could be shown for all comparisons when using the same stipulation given for the primary variable (i.e., the lower bound of the 95% confidence interval >−10%).

The diagnostic accuracy was also calculated stratified by the spatial resolution used for the acquisition of the MR data (0-1.0 mm^3, 0-0.5 mm^3, >0.5 mm^3-1.0 mm^3, and >1.0 mm^3). Using a spatial resolution of >0.5 to 1 mm^3 led to diagnostic accuracy rates which were about 5 percentage points higher than those of vessel segments measured with a spatial resolution below 0.5 mm^3 or above 1 mm^3, indicating that the choice of a suitable spatial resolution can significantly improve the result. For the spatial resolution of 0-0.5 mm^3 only limited data was available so no conclusions could be drawn. This analysis was only performed for Vasovist (combined) and ECCM (FP) (i.e., the methods which formed the basis for calculation of the primary efficacy analysis).

Besides diagnostic accuracy, sensitivity, specificity, and accuracy were calculated for all vessel segments. Again, intra-arterial DSA was used as the standard of truth.

Sensitivities, i.e., the probability that a vessel segment which actually is diseased was correctly diagnosed, for Vasovist (combined) and ECCM (FP) were quite low, 57.7% and 56.6% respectively, but comparable between both MR examination methods. Specificities, defined as the probability that a vessel segment without a relevant stenosis was correctly diagnosed as not being diseased, for both Vasovist (combined) and ECCM (FP) were good, 89.0% and 89.7% respectively. Accuracy, i.e., the rate of all vessel segments correctly diagnosed as diseased or non-diseased based on the cut-off point 50%, was dominated by the high specificity, and was 80.6% for Vasovist (combined) and 80.7% for ECCM (FP). Thus, in this subject population with a low prevalence of diseased vessel segments, both MR examination methods were comparable, which confirmed the result of the primary efficacy analysis.

Signal enhancement

Signal intensities were measured in four arteries of different luminal sizes (common iliac artery, superficial femoral artery, popliteal artery, and one of the calf arteries). Relevant differences due to the imaging technique were neither expected not detected.

Vasovist and ECCM showed comparable results for FP. Signal enhancement from pre-injection to post-injection showed a clear increase (762% for Vasovist [FP] and 860% for ECCM [FP]), whereas in the adjacent muscle region the signal stayed almost unchanged (14% both for Vasovist [FP] and ECCM [FP]).

As expected, the imaging window was prolonged by Vasovist during steady state, demonstrating a sufficient vascular signal over a longer time period, whereas contrast was found relevantly reduced for ECCM (SS). A direct determination of SI enhancement from pre-injection to post-injection for Vasovist (SS) or ECCM (SS) was not possible due to technical reasons.

Qualitative assessment of disease and plaque morphology

By the results of the qualitative assessment of the disease and of the plaque morphology relevant differences between Vasovist (FP), Vasovist (combined), ECCM (FP), and ECCM (combined) were not shown. Here, the differences between the individual blinded readers were most obvious.

Quality of depiction of vascular anatomy

With the use of Vasovist (combined) results were comparable to results following ECCM (combined). Vasovist (FP) showed for 50.6% to 72.3% of all vessel segments the same results as ECCM (FP). The number of vessels, for which Vasovist (FP) was judged to be superior to ECCM (FP) was slightly lower than vice versa (7.8% to 15.4% compared to 16.9% to 31.2%).

Delineation of vessel wall

From the results obtained for the delineation of vessel walls, a slight advantage for Vasovist (combined) might be inferred. Already for the FP, Vasovist was assessed to be equal to or better than ECCM (FP) for 70.4% to 90.4% of all vessel segments. Following the combined assessment, Vasovist was equal to or better than ECCM in about 90% of all assessments. For 2 of the 3 blinded readers use of Vasovist (combined) had slightly improved the outcome compared to the sole FP evaluation.

Diagnostic potential of venous enhancement

For Vasovist (combined) and ECCM (combined) the 3 blinded readers recorded whether there was a potential to give additional diagnostic information about venous pathologies due to the presence of venous enhancement.

Overall, despite considerable differences in the assessments between the individual blinded readers, an advantage for Vasovist was indicated. Already the number of subjects whose data showed no further potential for additional diagnostic information, was higher following ECCM (combined) (22.7% to 57.8%) than following Vasovist (combined) (6.2% to 10.8%).

In case of Vasovist (combined) the potential to give additional diagnostic information about venous pathologies was sufficient for the majority of all subjects and was always higher than recorded for ECCM (combined).

Results Summary — Safety

The safety population encompassed 261 subjects. All 261 subjects received a single injection of Vasovist in a dosage of 0.03 mmol/kg body weight. For 28 subjects the actual dosage was even higher. In case of 2 subjects the applied dose was considerably higher, which was recorded as a major protocol deviation (0.046 and 0.048 mmol/kg BW).

A total of 51 AEs were reported in 39 of the 261 subjects (14.9%). Nine (9) of these subjects received a specific drug treatment and 1 subject received a non-drug treatment for AEs.

No death was reported and no serious adverse event (SAE) was recorded.

Of the 51 AEs, 2 events were of severe intensity. According to the investigator for both events (pain in the extremity and polyuria) there was no causal relationship to the study drug. A total of 16 AEs were recorded to be moderate, 32 AEs to be mild and for 1 AE (polymenorrhoea) a recording of the intensity was not applicable.

By SOC (system organ class) code, most often gastrointestinal disorders were recorded, with 12 events in 11 (4.2%) of the 261 subjects, followed by nervous system disorders (10 events in 9 subjects) and reproductive system/breast disorders (8 events in 7 subjects).

Of the 51 recorded AEs, 33 AEs were assessed by the investigator to have a possible or a probable causal relationship to the study drug, i.e., to be related AEs. No AE was assessed to be definitely drug-related.

With 11 AEs, burning sensation (genital/vaginal or general) was the AE recorded most often to be a related event. For 7 of these 11 related AEs the intensity was recorded to be moderate.

All 8 AEs of pruritus (genital, ani, or general) were assessed by the investigators to be related events; 1 AE was of moderate intensity and 7 AEs were of mild intensity.

Of the 7 AEs of nausea, 5 AEs were assessed to be related to the study drug; all events were mild.

Besides a burning sensation, pruritus, and nausea, cough, disorientation, dyspnoea, headache, pain/pain in extremity, blurred vision, visual disturbance and vomiting were

described as probably or possibly related to the study drug. Overall the AE profile observed in this study corresponds with the known safety profile of Vasovist.

The majority of AEs (35 AEs) started within 2 hours post-injection, 6 AEs started several hours post-injection and for 10 AEs the exact onset time was not documented. Of the 25 AEs that started within 5 minutes post-injection, 22 AEs were assessed to be related to the injection of Vasovist. The duration of 23 of these 25 AEs was a few seconds up to 5 minutes; for 1 AE the duration was 1 hour and for another AE the duration was missing.

The 2 AEs of severe intensity (pain in extremity and polyuria) were assessed to have no causal relationship to the injection of Vasovist.

The vital signs showed no relevant trends or changes over time after injection of the study drug.

Conclusion(s)

In this study, non-inferiority of diagnostic accuracy of combined first pass and steady state Vasovist MRA at a dose of 0.03 mmol/kg body weight versus first pass ECCM MRA at a total dose of 0.2 mmol/kg body weight was proven. High accuracy and high specificity were given in this subject population with low prevalence of disease.

Vasovist provides adequate imaging during the first pass and offers a prolonged imaging window during the steady state.

Secondary efficacy variables confirmed the result obtained for the primary efficacy variable and indicated advantages for Vasovist regarding vessel wall delineation and venous imaging. In addition, using the combined assessment with Vasovist, the number of assessable segments were increased especially as regards the smaller vessel segments compared to an assessment using first pass Vasovist or first pass ECCM only.

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Investigational Site List

Marketing Authorization Holder in Germany	
Name	
Postal Address	
Sponsor in Germany	
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	Centro de Diagnóstico Dr. Enrique Rossi	Arenales 2777, Buenos Aires Argentina	C1425BEE	Buenos Aires	ARGENTINA
2	Fundacion Cientifica del Sur	Av. Hipolito Yrigoyen 8680	B1832BQS	Lornas de Zamora	ARGENTINA
3	Investigaciones Médicas	Viamonte 1871	C1082ACA	Buenos Aires	ARGENTINA
4	TCba Salguero	Centro Diagnostico J. Salguero 560 C1177AEJ - Buenos Aires Argentina		Buenos Aires	ARGENTINA
5	A. ö. Krankenhaus St. Pölten	Medizinische Radiologie-Diagnostik und Intervention Probst-Fuehrer Strasse 4 3100 St Poelten A-3100 Niederoesterreich	A-3100	St Poelten	AUSTRIA

6	Krankenhaus der Barmherzigen Brüder	Abteilung fuer Radiologie und Department fuer Nuklearmedizin Grosse Mohrengasse 9 1020 Wien	1020	Wien	AUSTRIA
7	Medizinische Universität Graz	Universitaetsklinik Graz Gemeinsame Einrichtung MR Auenbrugger Platz 9 A 8036 Graz	8036	Graz	AUSTRIA
8	Hospital das Clínicas da Faculdade de Medicina da USP	Av Dr Eneas de Carvalho de Aguiar, 255-3	05403-900	Sao Paulo	BRAZIL
9	Hospital das Clínicas da Faculdade de Medicina da USP	Ambulatório Bloco II Sala de Pesquisa Clínica Av. Dr. Éneas de Carvalho Aguiar, 44	05443000	Sao Paulo	BRAZIL
10	Hospital das Clinicas da Universidade Federal do Paraná	Rua General Carneiro, 181 CEP 80060-900 Curitiba	80060-900	Curitiba	BRAZIL
11	Bethanien Krankenhaus	Im Pruefling 23	60389	Frankfurt	GERMANY
12	Charité Campus Virchow-Klinikum (CVK)	Universitaetsklinikum Charite Campus Virchow-Klinikum der Humboldt Universitaet Augustenburger Platz 1 13353 Berlin	13353	Berlin	GERMANY

13	Johannes-Gutenberg-Universität Mainz	Klinikum Johannes-Gutenberg-Universitaet Mainz III. Medizinische Klinik und Poliklinik Langebeckstrasse 1 55131 Mainz	55131	Mainz	GERMANY
14	Klinikum der Johann Wolfgang Goethe Universität Frankfurt	Klinikum der Johann-Wolfgang-Goethe-Universitaet Frankfurt M Theodor-Stern-Kai 7 60590 Frankfurt a. M.	60590	Frankfurt a. M.	GERMANY
15	Medizinische Einrichtungen der Universität Bonn	Universitaetsklinikum Bonn Radiologische Klinik MR Gebaeude Sigmund-Freud-Strasse 25 53127 Bonn	53105	Bonn	GERMANY
16	Universitätsklinikum Essen	Hufelandstrasse 55 45122 Essen	45122	Essen	GERMANY
17	Universitätsklinikum Hamburg Eppendorf (UKE)	Universitätsklinikum Hamburg-Eppendorf Falkenried 88 20251 Hamburg	20251	Hamburg	GERMANY

18	Universitätsklinikum Hamburg Eppendorf (UKE)	Universitaetsklinikum Hamburg-Eppendorf Klinik und Poliklinik für diagnostische und Interventionelle Radiologie Martinistrasse 52 20246 Hamburg	20246	Hamburg	GERMANY
19	Hospital Ángeles Metropolitano	Tlacotalpan No. 59 Col. Roma Sur	06760	Mexico D. F.	MEXICO
20	Hospital Universitario "José Eleuterio González"	Departamento de Radiologia e Imagen Diagnostica Avenida Francisco I. Madero Pte. y Avenida Gonzalitos Col. Mitras Centro CP Monterrey	64460	Monterrey / Nuevo Leon	MEXICO
21	Kantonsspital Baden	Radiologisches Institut Kantonspital Baden	5404	Baden	SWITZERLAND
22	Universitätsspital Basel	Petersgraben 4	4031	Basel	SWITZERLAND