Clinical trial results:
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

Summary

EudraCT number	2010-023002-13
Trial protocol	CZ DE AT
Global end of trial date	06 July 2012

Results information

Result version number	v3 (current)
This version publication date	07 September 2016
First version publication date	09 November 2014
Version creation reason	• New data added to full data set • Correction of full data set Bayer sponsor contact information to be updated
Summary attachment (see zip file)	Bayer Study Synopsis (91759_Study Synopsis_CTP.pdf)

Trial information

Trial identification

Sponsor protocol code	BAY 86-4875/91759

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01344460
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 July 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 July 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects and/or their legally authorized representative. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 May 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Poland: 35
Country: Number of subjects enrolled	Czech Republic: 15
Country: Number of subjects enrolled	France: 31
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Argentina: 37
Country: Number of subjects enrolled	Brazil: 31
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	Colombia: 15

Country: Number of subjects enrolled	Korea, Republic of: 58
Country: Number of subjects enrolled	Turkey: 13
Country: Number of subjects enrolled	Taiwan: 7
Country: Number of subjects enrolled	United States: 52
Worldwide total number of subjects	315
EEA total number of subjects	98

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	203
From 65 to 84 years	109
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 55 study centers in 13 countries, between 16 May 2011 (first subject first visit) and 06 July 2012 (last subject last visit).

Pre-assignment

Screening details:

A total of 338 subjects were screened, of which 317 were enrolled and 315 received the study drug. The 23 subjects who did not receive the study drug included 9 screen failures and 12 premature discontinuations (10 subjects withdrew consent and 2 subjects for other reasons) and 2 subjects never received the study drug.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Gadobutrol (Gadavist, BAY 86-4875)

Arm description:

Gadobutrol was administered to all subjects receiving study drug at the standard dose of 0.1 millimole per kilogram (mmol/kg) body weight (BW) by single intravenous (IV) bolus injection. During the course of the study, non-contrast MRA images were obtained before the administration of gadobutrol, and gadobutrol-enhanced MRA images were obtained after injection.

Arm type	Experimental
Investigational medicinal product name	Gadobutrol
Investigational medicinal product code	BAY 86-4875
Other name	Gadovist, Gadavist
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Gadobutrol was administered to all subjects receiving study drug at the standard dose of 0.1 mmol/kg BW by single IV bolus injection.

Number of subjects in period 1	Gadobutrol (Gadavist, BAY 86-4875)
Started	315
Completed	312
Not completed	3
Consent withdrawn by subject	1
Lost to follow-up	2

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description:

Gadobutrol was administered to all subjects receiving study drug at the standard dose of 0.1 mmol/kg BW by single IV bolus injection. During the course of the study, non-contrast MRA images were obtained before the administration of gadobutrol, and Gadobutrol-enhanced MRA images were obtained after injection.

Reporting group values	Overall Trial	Total	
Number of subjects	315	315	
Age categorical Units: Subjects			
< 45 years	92	92	
45 - 64 years	111	111	
>= 65 years	112	112	
Age continuous Units: years			
arithmetic mean	54.9		
standard deviation	± 16.9	-	
Gender categorical Units: Subjects			
Female	145	145	
Male	170	170	
Baseline Weight Units: kilogram(s)			
arithmetic mean	77.5		
standard deviation	± 16.9	-	

End points

End points reporting groups

Reporting group title	Gadobutrol (Gadavist, BAY 86-4875)

Reporting group description:

Gadobutrol was administered to all subjects receiving study drug at the standard dose of 0.1 millimole per kilogram (mmol/kg) body weight (BW) by single intravenous (IV) bolus injection. During the course of the study, non-contrast MRA images were obtained before the administration of gadobutrol, and gadobutrol-enhanced MRA images were obtained after injection.

Subject analysis set title	Gadobutrol-Enhanced MRA set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Gadobutrol-Enhanced MRA set included those subjects in Full analysis set (FAS) who showed only Gadobutrol enhanced MRA image sets.

Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis

Subject analysis set description:

SAF included all subjects administered gadobutrol, including any subjects used for blinded reader training.

Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

FAS included all subjects who have both gadobutrol-enhanced and non-contrast (unenhanced) MRA image sets, and the SoR diagnosis were available (CTA was required to be interpretable and without technical problems). FAS excluded those subjects for who images were used for blinded reader training.

Subject analysis set title	Unenhanced MRA
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Unenhanced MRA set included those subjects in FAS who showed only unenhanced MRA image sets.

Subject analysis set title	Computed Tomographic Angiography (CTA)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

CTA included those subjects in FAS who showed only CTA scan image sets.

Subject analysis set title	CTA minus gadobutrol-enhanced MRA for blinded reading
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects with CTA scan images minus gadobutrol-enhanced MRA images for blinded reading included in this set.

Subject analysis set title	CTA minus Unenhanced MRA for blinded reading
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects with CTA scan images minus unenhanced MRA images for blinded reading included in this set.

Primary: Percentage of Assessable Vascular Segments Using Gadobutrol-Enhanced MRA and Unenhanced MRA

End point title	Percentage of Assessable Vascular Segments Using Gadobutrol-Enhanced MRA and Unenhanced MRA[1]

End point description:

Each vascular segment was visualized using unenhanced MRA and gadobutrol-enhanced MRA, characterized by the on-site investigators, three independent blinded readers (reader 1, 2 and 3) and majority readers (the outcome determined by at least two of the blinded readers). The segments were predefined to standardize the blinded reader evaluations.
A segment was assessable if it was visualized along its entire length and if any region of stenosis, was measured reliably. There were 6 segments assessed 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.

In below table, "n/n" signifies the number of subjects/segments that were evaluable in specified category of each group.

End point type	Primary

End point timeframe:

Images were taken pre-injection and post-injection

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: EudraCT format does auto-adding of number of subjects analysed while reporting an explorative analysis of two treatment groups. Due to this format constrains, we have uploaded charts with the accurate details of statistical analyses for this endpoint. Please find the statistical analyses in the attachment below.

End point values	Gadobutrol-Enhanced MRA set	Unenhanced MRA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	292[2]	292[3]		
Units: Percentage of segments				
number (not applicable)				
Majority reader (n=292/1752)	95.9	77.6		
Blinded reader 1 (n=292/1746)	98.1	81.7		
Blinded reader 2 (n=292/1752)	95.5	71.5		
Blinded reader 3 (n=292/1734)	95.5	78.1		
Clinical investigators (n=292/1764)	94.4	68.9		

Notes:

[2] - FAS

[3] - FAS

Attachments (see zip file)	91759_Statistical Analyses_Primary OM_Assessability.docx

Statistical analyses

No statistical analyses for this end point

Primary: Sensitivity for Detection of Clinically Significant Disease Using Gadobutrol-Enhanced MRA and Unenhanced MRA

End point title	Sensitivity for Detection of Clinically Significant Disease Using Gadobutrol-Enhanced MRA and Unenhanced MRA[4]

End point description:

Clinically significant disease was defined as 50 to 99 percent (%) stenosis of a segment, but not occluded as assessed by the SoR. For each segment, the most severe stenosis/narrowing was identified and considered for the evaluation of clinically significant disease. In the below table, "n" signifies subjects who were evaluable for the specified parameter for each arm, respectively.
In below table, "n/n" signifies the number of subjects/segments that were evaluable in specified category of each group

End point type	Primary

End point timeframe:

Images were taken pre-injection and post-injection

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: EudraCT format does auto-adding of number of subjects analysed while reporting an explorative analysis of two treatment groups. Due to this format constrains, we have uploaded charts with the accurate details of statistical analyses for this endpoint. Please find the statistical analyses in the attachment below.

End point values	Gadobutrol-Enhanced MRA set	Unenhanced MRA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	292[5]	292[6]		
Units: percentage of Sensitivity				
number (not applicable)				
Majority reader (n=93/133)	53.4	46.6		
Blinded reader 1 (n=93/133)	51.9	51.1		
Blinded reader 2 (n=93/133)	54.1	39.1		
Blinded reader 3 (n=93/133)	52.6	50.4		
Clinical investigators (n=113/140)	69.3	50		

Notes:

[5] - FAS

[6] - FAS

Attachments (see zip file)	91759_Statistical Analysis_Primary OM_Sensitivity.docx

Statistical analyses

No statistical analyses for this end point

Primary: Specificity for Exclusion of Clinically Significant Disease Using Gadobutrol-Enhanced MRA and Unenhanced MRA

End point title	Specificity for Exclusion of Clinically Significant Disease Using Gadobutrol-Enhanced MRA and Unenhanced MRA[7]

End point description:

Clinically significant disease (stenosis) was defined as 50 to 99 percent (%) stenosis of a segment, but not occluded as assessed by the SoR. For each segment, the most severe stenosis/narrowing was identified and considered for the evaluation of clinically significant disease.
Specificity = percentage of subjects for which the imaging modalities (unenhanced or gadobutrol-enhanced) in the detection and exclusion of clinically significant stenosis.
In below table, "n/n" signifies the number of subjects/segments that were evaluable in specified category of each group.

End point type	Primary

End point timeframe:

Images were taken pre-injection and post-injection

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: EudraCT format does auto-adding of number of subjects analysed while reporting an explorative analysis of two treatment groups. Due to this format constrains, we have uploaded charts with the accurate details of statistical analyses for this endpoint. Please find the statistical analyses in the attachment below.

End point values	Gadobutrol-Enhanced MRA set	Unenhanced MRA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	292[8]	292[9]		
Units: Percentage of Specificity				
number (not applicable)				
Majority reader (n=292/1605)	94.8	85.7		
Blinded reader 1 (n=292/1605)	94.4	83.1		
Blinded reader 2 (n=292/1605)	94.8	85		
Blinded reader 3 (n=292/1605)	94	80.7		

Clinical investigators (n=292/1598)	96.5	83.5		

Notes:

[8] - Evaluable subjects in FAS

[9] - Evaluable subjects in FAS

Attachments (see zip file)	91759_Statistical Analysis_Primary OM_Specificity.docx

Statistical analyses

No statistical analyses for this end point

Primary: Minimum Gadobutrol Performance for Sensitivity: Sensitivity > 50%

End point title	Minimum Gadobutrol Performance for Sensitivity: Sensitivity > 50%[10]

End point description:

Clinically significant disease was defined as >50% stenosis of a segment, but not occluded as assessed by the SoR. For each segment, the most severe stenosis/narrowing was identified and considered for the evaluation of clinically significant disease. Gadobutrol minimum performance criteria was based on a stenosis of 50% calculated from the native vessel diameter. In the below table, "n" signifies subjects who were evaluable for the specified parameter for each arm, respectively.
In below table, "n/n" signifies the number of subjects/segments that were evaluable in specified category.

End point type	Primary

End point timeframe:

Images were taken pre-injection and post-injection

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: EudraCT format does auto-adding of number of subjects analysed while reporting an explorative analysis of two treatment groups. Due to this format constrains, we have uploaded charts with the accurate details of statistical analyses for this endpoint. Please find the statistical analyses in the attachment below.

End point values	Gadobutrol-Enhanced MRA set			
Subject group type	Subject analysis set			
Number of subjects analysed	292[11]			
Units: Percentage of sensitivity				
number (not applicable)				
Majority reader (n=84/119)	54.6			
Blinded reader 1 (n=91/128)	51.6			
Blinded reader 2 (n=82/114)	54.4			
Blinded reader 3 (n=83/118)	53.4			
Clinical investigators (n=108/129)	71.3			

Notes:

[11] - FAS

Attachments (see zip file)	91759_Statistical Analysis_Primary OM_Sensitivity_50.docx

Statistical analyses

No statistical analyses for this end point

Primary: Minimum Gadobutrol Performance for Specificity: Specificity > 50%

End point title	Minimum Gadobutrol Performance for Specificity: Specificity > 50%[12]

End point description:

Clinically significant disease (stenosis) was defined as >50% stenosis of a segment, but not occluded as assessed by the SoR. For each segment, the most severe stenosis/narrowing was identified and considered for the evaluation of clinically significant disease. Gadobutrol minimum performance criteria was based on a stenosis of 50% calculated from the native vessel diameter.
In the below table, "n" signifies subjects who were evaluable for the specified parameter for each arm, respectively.
In below table, "n/n" signifies the number of subjects/segments that were evaluable in specified category.

End point type	Primary

End point timeframe:

Images were taken pre-injection and post-injection

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: EudraCT format does auto-adding of number of subjects analysed while reporting an explorative analysis of two treatment groups. Due to this format constrains, we have uploaded charts with the accurate details of statistical analyses for this endpoint. Please find the statistical analyses in the attachment below.

End point values	Gadobutrol-Enhanced MRA set			
Subject group type	Subject analysis set			
Number of subjects analysed	292[13]			
Units: Percentage of specifity				
number (not applicable)				
Majority reader (n=291/1555)	95.9			
Blinded reader 1 (n=292/1585)	95			
Blinded reader 2 (n=291/1554)	96.2			
Blinded reader 3 (n=290/1544)	95.8			
Clinical investigators (n=289/1535)	98.4			

Notes:

[13] - FAS

Attachments (see zip file)	91759_Statistical Analysis_Primary OM_Specificity_50.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Length of the right and left renal arteries assessed by gadobutrol-enhanced MRA and unenhanced MRA - Blinded reader

End point title	Length of the right and left renal arteries assessed by gadobutrol-enhanced MRA and unenhanced MRA - Blinded reader

End point description:

The length of the left and right renal arteries were measured from the origin at the aorta to the bifurcation into the upper and lower pole arteries or the most distal point of the renal artery which could be visualized. This distal margin was the point where the diameter was still assessable. If there were more than 2 distal branches then the first large branch that was the dominant supply to a renal pole was

used as the distal point.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection

End point values	Gadobutrol-Enhanced MRA set	Unenhanced MRA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	292[14]	292[15]		
Units: millimeter(s) (mm)				
arithmetic mean (standard deviation)				
Left renal artery- Blind reader 1	35.07 (± 11.76)	32.25 (± 11.32)		
Right renal artery - Blind reader 1	46.23 (± 14.01)	43.05 (± 14.34)		
Left renal artery- Blind reader 2	35.07 (± 11.76)	32.15 (± 11.35)		
Right renal artery - Blind reader 2	46.27 (± 14.01)	42.95 (± 14.42)		
Left renal artery- Blind reader 3	35.07 (± 11.76)	32.64 (± 12.74)		
Right renal artery - Blind reader 3	46.23 (± 14)	43.05 (± 14.34)		

Notes:

[14] - Evaluable subjects in FAS

[15] - Evaluable subjects in FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Length of the right and left renal arteries assessed by computed tomographic angiography (CTA) - blinded reader

End point title	Length of the right and left renal arteries assessed by computed tomographic angiography (CTA) - blinded reader

End point description:

The length of the left and right renal arteries were measured from the origin at the aorta to the bifurcation into the upper and lower pole arteries or the most distal point of the renal artery which could be visualized. This distal margin was the point where the diameter was still assessable. If there were more than 2 distal branches then the first large branch that was the dominant supply to a renal pole was used as the distal point.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection

End point values	Computed Tomographic Angiography (CTA)			
Subject group type	Subject analysis set			
Number of subjects analysed	292[16]			
Units: millimeter(s) (mm)				
arithmetic mean (standard deviation)				
Left renal artery- CTA Blind reader 4	36.59 (± 12.14)			
Right renal artery - CTA Blind reader 4	48.44 (± 14.51)			
Left renal artery- CTA Blind reader 5	36.59 (± 12.14)			
Right renal artery - CTA Blind reader 5	48.44 (± 14.5)			
Left renal artery- CTA Blind reader 6	36.59 (± 12.14)			
Right renal artery - CTA Blind reader 6	48.45 (± 14.5)			

Notes:

[16] - Evaluable subjects in FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Difference in Vessel Diameter (millimeter [mm]) at Normal and Narrowest point assessed by gadobutrol-enhanced MRA and unenhanced MRA compared to CTA

End point title	Mean Difference in Vessel Diameter (millimeter [mm]) at Normal and Narrowest point assessed by gadobutrol-enhanced MRA and unenhanced MRA compared to CTA

End point description:

The segment evaluated to have a reduction in diameter of greater than 10% was considered abnormal and measured. The diameter of each of these abnormal segments was measured using electronic calipers (perpendicular to the long axis of the vessel) at the point of most severe stenosis within each segment. The mean of vessel diameters was calculated by segment across readers separately for CTA and MRA readers.
In below table, "n" signifies the number of segments that were evaluable in specified category.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection

End point values	CTA minus gadobutrol-enhanced MRA for blinded reading	CTA minus Unenhanced MRA for blinded reading		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	292[17]	292[18]		
Units: millimeter				
arithmetic mean (standard deviation)				
Vessel DIA at normal point: BRs (n=298; 320)	-0.09 (± 1.14)	0.17 (± 1.28)		
Vessel DIA at narrowest point: BRs (n=298; 320)	-0.15 (± 1.01)	0.41 (± 1.15)		

Notes:

[17] - Evaluable subjects in FAS

[18] - Evaluable subjects in FAS

Statistical analyses

No statistical analyses for this end point

Secondary: The Percentage of Location of Stenosis >= 50% (Within and Beyond 5 millimeter From the Aorta) in the Proximal Segments Assessed by Gadobutrol-Enhanced MRA and Unenhanced MRA

End point title	The Percentage of Location of Stenosis >= 50% (Within and Beyond 5 millimeter From the Aorta) in the Proximal Segments Assessed by Gadobutrol-Enhanced MRA and Unenhanced MRA

End point description:

Location within the right and left proximal segment was based on the point of greatest stenosis and was recorded for stenosis >=50% as:
- Within 5 mm of the aorta (or occlusion proximal to the origin of the segment)
- Beyond 5 mm from the aorta.
In below table, "n" signifies the number of segments that were evaluable in specified category of each group.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection

End point values	Gadobutrol-Enhanced MRA set	Unenhanced MRA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	292[19]	292[20]		
Units: Percentage of location				
number (not applicable)				
Within 5 mm of the aorta BR 1 (n=105; 110)	26.4	22.9		
Within 5 mm of the aorta BR 2 (n=39; 83)	73.5	71.8		
Within 5 mm of the aorta BR 3 (n=87; 83)	25.3	21.8		
Beyond 5 mm from the aorta BR 1 (n=105; 110)	73.6	77.1		
Beyond 5 mm from the aorta BR 2 (n=39; 83)	26.5	28.2		
Beyond 5 mm from the aorta BR 3 (n=87; 83)	74.7	78.2		

Notes:

[19] - Evaluable subjects in FAS

[20] - Evaluable subjects in FAS

Statistical analyses

No statistical analyses for this end point

Secondary: The Percentage of Segments With Artifacts Presence

End point title	The Percentage of Segments With Artifacts Presence

End point description:

Artifacts were collected for the MRA images on a segmental basis. In the below table, "n" signifies number of subjects that were evaluable for the specified category.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection

End point values	Gadobutrol-Enhanced MRA set	Unenhanced MRA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	292[21]	292[22]		
Units: percentage of subjects				
number (not applicable)				
Blinded Reader 1	97.4	92.3		
Blinded Reader 2	22.1	80.4		
Blinded Reader 3	41.5	97.4		

Notes:

[21] - Evaluable subjects in FAS

[22] - Evaluable subjects in FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Types of Artifacts Assessed by Gadobutrol-enhanced MRA and Unenhanced MRA by Blinded Reader 1

End point title	Types of Artifacts Assessed by Gadobutrol-enhanced MRA and Unenhanced MRA by Blinded Reader 1

End point description:

The following types of artifacts were considered: Motion artifact (including pulsatility, breathing, swallowing), venous opacification, saturation artifact (for example [eg], in-plane flow, turbulence, dephasing, saturation band), susceptibility artifacts (including devices, eg, stents), ringing artifact (eg, bands), bolus timing error, and other (artifact not specified above or no artifact).

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection

End point values	Gadobutrol-Enhanced MRA set	Unenhanced MRA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	292[23]	292[24]		
Units: Percentage of segments				
number (not applicable)				
Motion artifact	17.5	81.4		
Venous opacification	4.8	15.1		

Saturation artifact	0.2	0.4		
Susceptibility artifacts	0	0.1		
Other	5	7.2		

Notes:

[23] - Subjects in FAS with artifacts presence.

[24] - Subjects in FAS with artifacts presence.

Statistical analyses

No statistical analyses for this end point

Secondary: Types of Artifacts Assessed by Gadobutrol-Enhanced MRA and Unenhanced MRA by Blinded Reader 2

End point title	Types of Artifacts Assessed by Gadobutrol-Enhanced MRA and Unenhanced MRA by Blinded Reader 2

End point description:

The following types of artifacts were considered: Motion artifact (including pulsatility, breathing, swallowing), venous opacification, saturation artifact (eg, in-plane flow, turbulence, dephasing, saturation band), susceptibility artifacts (including devices, eg, stents), ringing artifact (eg, bands), bolus timing error, and other (artifact not specified above or no artifact).

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection

End point values	Gadobutrol-Enhanced MRA set	Unenhanced MRA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	292[25]	292[26]		
Units: Percentage of segments				
number (not applicable)				
Motion artifact	5.4	57.1		
Venous opacification	12	9.6		
Saturation artifact	0.2	24.4		
Susceptibility artifacts	3.6	6		
Ringing artifact	0.6	1.4		
Bolus timing error	1.7	1.4		
Other	1.7	6.5		

Notes:

[25] - Subjects in FAS with artifacts presence.

[26] - Subjects in FAS with artifacts presence.

Statistical analyses

No statistical analyses for this end point

Secondary: Types of Artifacts Assessed by Gadobutrol-Enhanced MRA and Unenhanced MRA by Blinded Reader 3

End point title	Types of Artifacts Assessed by Gadobutrol-Enhanced MRA and Unenhanced MRA by Blinded Reader 3

End point description:

The following types of artifacts were considered: Motion artifact (including pulsatility, breathing,

swallowing), venous opacification, saturation artifact (eg, in-plane flow, turbulence, dephasing, saturation band), susceptibility artifacts (including devices, eg, stents), ringing artifact (eg, bands), bolus timing error, and other (artifact not specified above or no artifact).

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection

End point values	Gadobutrol-Enhanced MRA set	Unenhanced MRA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	292[27]	292[28]		
Units: Percentage of segments				
number (not applicable)				
Motion artifact	32.8	96.2		
Venous opacification	14.2	34.5		
Saturation artifact	3	56		
Susceptibility artifacts	4	7		
Ringing artifact	6.7	7		
Bolus timing error	0.3	1.5		
Other	0.7	0.2		

Notes:

[27] - Subjects in FAS with artifacts presence.

[28] - Subjects in FAS with artifacts presence.

Statistical analyses

No statistical analyses for this end point

Secondary: The Percentage of Accessory (Non-dominant) Renal Artery Presence Assessed by Gadobutrol-Enhanced MRA and Unenhanced MRA

End point title	The Percentage of Accessory (Non-dominant) Renal Artery Presence Assessed by Gadobutrol-Enhanced MRA and Unenhanced MRA

End point description:

An accessory renal artery was defined as an additional, non-dominant, renal artery typically emanating from the aorta and anastomosing distal to the proximal third, segment of that renal artery. It was recorded only as present or absent on the right and left, regardless of how many accessory renal arteries were present.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection

End point values	Gadobutrol-Enhanced MRA set	Unenhanced MRA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	292[29]	292[30]		
Units: Percentage of accessory				
number (not applicable)				
Left side: Reader 1	7.2	0.7		
Right side: Reader 1	9.2	1.4		
Left side: Reader 2	15.4	2.7		
Right side: Reader 2	17.8	3.1		
Left side: Reader 3	13.4	5.8		
Right side: Reader 3	16.4	4.5		
Left side: Clinical investigators	18.2	11.6		
Right side: Clinical investigators	19.2	12.7		

Notes:

[29] - FAS

[30] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: The Presence of any Aneurysmal Dilatation in Each Segment (Proximal, Mid- and Distal) in the Right and the Left Renal Arteries Assessed by Gadobutrol-Enhanced MRA and Unenhanced MRA

End point title	The Presence of any Aneurysmal Dilatation in Each Segment (Proximal, Mid- and Distal) in the Right and the Left Renal Arteries Assessed by Gadobutrol-Enhanced MRA and Unenhanced MRA

End point description:

Any focal dilatation (aneurysmal dilatation) of a segment was recorded. The diameter at the widest point was measured with the electronic calipers if a dilatation was present in any segment. The number of subjects with an aneurysmal dilatation in each segment (proximal, mid- and distal) in the right and the left renal arteries assessed by gadobutrol-enhanced MRA and unenhanced MRA were reported.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection

End point values	Gadobutrol-Enhanced MRA set	Unenhanced MRA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	292[31]	292[32]		
Units: Percentage of subjects				
number (not applicable)				
Right : Proximal	0.3	0		
Right : Mid	1	0		
Right : Distal	1.4	0		
Left : Proximal	0	0		
Left : Mid	0.3	0.3		
Left : Distal	0.7	0.3		

Notes:

[31] - FAS

[32] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: The Percentage of Subjects With Diagnosis of Fibromuscular Dysplasia and Arteriosclerosis Assessed by Gadobutrol-Enhanced MRA and Unenhanced MRA

End point title	The Percentage of Subjects With Diagnosis of Fibromuscular Dysplasia and Arteriosclerosis Assessed by Gadobutrol-Enhanced MRA and Unenhanced MRA

End point description:

Any focal dilatation (aneurysmal dilatation) of a segment was recorded. The diameter at the widest point was measured with the electronic calipers if a dilatation was present in any segment. The number of participants with an aneurysmal dilatation in each segment (proximal, mid- and distal) in the right and the left renal arteries assessed by gadobutrol-enhanced MRA and unenhanced MRA were reported.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection

End point values	Gadobutrol-Enhanced MRA set	Unenhanced MRA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	292[33]	292[34]		
Units: Percentage of subjects				
number (not applicable)				
Fibromuscular dysplasia : reader 1	2.7	0.7		
Arteriosclerotic : reader 1	16.4	12		
Fibromuscular dysplasia : reader 2	4.1	0		
Arteriosclerotic : reader 2	38.4	18.8		
Fibromuscular dysplasia : reader 3	6.2	0.7		
Arteriosclerotic : reader 3	41.1	54.5		

Notes:

[33] - FAS

[34] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Diagnostic Confidence by the Blinded Readers Using Gadobutrol-Enhanced MRA and Unenhanced MRA

End point title	Diagnostic Confidence by the Blinded Readers Using Gadobutrol-Enhanced MRA and Unenhanced MRA

End point description:

Diagnostic confidence was evaluated to determine the level of certainty that the blinded readers assigned to a diagnosis for each segment. This was defined as the degree of confidence that the information on the MRA images represented the true and complete clinical picture of a particular segment.
The degree of confidence was rated on a 4-point scale: 1 = Not confident, 2 = Somewhat confident, 3 = Confident, and 4 = Very confident.
In the below table, "n" signifies the number of segments that were evaluable in specified category of each group.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection

End point values	Gadobutrol-Enhanced MRA set	Unenhanced MRA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	292[35]	292[36]		
Units: Units on scale				
arithmetic mean (standard deviation)				
Blinded reader 1 (n=1728, 1745)	3 (± 0.8)	1.9 (± 0.7)		
Blinded reader 2 (n=1729, 1745)	3.5 (± 0.8)	2.1 (± 1)		
Blinded reader 3 (n=1737, 1749)	3.5 (± 0.8)	2.2 (± 0.9)		

Notes:

[35] - Evaluable subjects in FAS

[36] - Evaluable subjects in FAS

Statistical analyses

No statistical analyses for this end point

Secondary: The Percentage of Subjects With Additional Imaging Studies Recommended by the Blinded Readers and the Clinical Investigator After Evaluation of the Gadobutrol-Enhanced and Unenhanced MRA Images

End point title	The Percentage of Subjects With Additional Imaging Studies Recommended by the Blinded Readers and the Clinical Investigator After Evaluation of the Gadobutrol-Enhanced and Unenhanced MRA Images

End point description:

A measure of diagnostic value was the reduction in the number of additional diagnostic imaging studies recommended/ordered. The clinical investigators and the blinded readers were asked if they had recommended an additional imaging study for each subject, and the data were recorded.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection

End point values	Gadobutrol-Enhanced MRA set	Unenhanced MRA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	292[37]	292[38]		
Units: Percentage of subjects				
number (not applicable)				
Reader: 1	41.4	96.6		
Reader: 2	14	77.1		
Reader: 3	8.6	44.9		
Clinical investigators	18.8	43.5		

Notes:

[37] - FAS

[38] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Types of Additional Imaging Studies Recommended by the Blinded Readers After Evaluation of the Gadobutrol-Enhanced and Unenhanced MRA images – Blinded Reader 1

End point title	Types of Additional Imaging Studies Recommended by the Blinded Readers After Evaluation of the Gadobutrol-Enhanced and Unenhanced MRA images – Blinded Reader 1

End point description:

An additional imaging study recommended was specified from the following list: Non-contrast MRA, Contrast-enhanced MRA, CTA, Ultrasound, Digital subtraction catheter angiogram (DSCA), and Nuclear medicine study.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection

End point values	Gadobutrol-Enhanced MRA set	Unenhanced MRA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	121[39]	282[40]		
Units: Subjects				
Non-contrast MRA	0	2		
Contrast-enhanced MRA	1	0		
CTA	120	280		
Ultrasound	0	0		
DSCA	0	0		
Nuclear medicine study	0	0		

Notes:

[39] - FAS with subjects who were recommended for additional imaging studies.

[40] - FAS with subjects who were recommended for additional imaging studies.

Statistical analyses

No statistical analyses for this end point

Secondary: Types of Additional Imaging Studies Recommended by the Blinded Readers After Evaluation of the Gadobutrol-Enhanced and Unenhanced MRA images – Blinded Reader 2

End point title	Types of Additional Imaging Studies Recommended by the Blinded Readers After Evaluation of the Gadobutrol-Enhanced and Unenhanced MRA images – Blinded Reader 2

End point description:

An additional imaging study recommended was specified from the following list: Non-contrast MRA, Contrast-enhanced MRA, CTA, Ultrasound, DSCA, and Nuclear medicine study.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection

End point values	Gadobutrol-Enhanced MRA set	Unenhanced MRA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	41[41]	225[42]		
Units: Subjects				
Non-contrast MRA	0	0		
Contrast-enhanced MRA	0	114		
CTA	39	110		
Ultrasound	1	1		
DSCA	1	0		
Nuclear medicine study	0	0		

Notes:

[41] - FAS with subjects who were recommended for additional imaging studies.

[42] - FAS with subjects who were recommended for additional imaging studies.

Statistical analyses

No statistical analyses for this end point

Secondary: Types of Additional Imaging Studies Recommended by the Blinded Readers After Evaluation of the Gadobutrol-Enhanced and Unenhanced MRA images – Blinded Reader 3

End point title	Types of Additional Imaging Studies Recommended by the Blinded Readers After Evaluation of the Gadobutrol-Enhanced and Unenhanced MRA images – Blinded Reader 3

End point description:

An additional imaging study recommended was specified from the following list: Non-contrast MRA, Contrast-enhanced MRA, CTA, Ultrasound, DSCA, and Nuclear medicine study.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection

End point values	Gadobutrol-Enhanced MRA set	Unenhanced MRA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25[43]	131[44]		
Units: Subjects				
Non-contrast MRA	0	1		
Contrast-enhanced MRA	1	14		
CTA	22	116		
Ultrasound	0	0		
DSCA	2	0		
Nuclear medicine study	0	0		

Notes:

[43] - FAS with subjects who were recommended for additional imaging studies.

[44] - FAS with subjects who were recommended for additional imaging studies.

Statistical analyses

No statistical analyses for this end point

Secondary: Types of Additional Imaging Studies Recommended by the Clinical Investigator After Evaluation of the Unenhanced and Gadobutrol-Enhanced MRA Images

End point title	Types of Additional Imaging Studies Recommended by the Clinical Investigator After Evaluation of the Unenhanced and Gadobutrol-Enhanced MRA Images

End point description:

An additional imaging study recommended was specified from the following list: Non-contrast MRA, Contrast-enhanced MRA, CTA, Ultrasound, DSCA, and Nuclear medicine study.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection

End point values	Gadobutrol-Enhanced MRA set	Unenhanced MRA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55[45]	127[46]		
Units: Subjects				
Non-contrast MRA	0	0		
Contrast-enhanced MRA	2	114		
CTA	50	12		
Ultrasound	0	0		
Nuclear medicine study	3	1		

Notes:

[45] - FAS with subjects who were recommended for additional imaging studies.

[46] - FAS with subjects who were recommended for additional imaging studies.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were assessed from the time the consent was signed until 72 (+/-6) hours follow-up after the study MRA and continued until the end of the study (either the 72 hour follow-up or the CTA, if performed after the MRA as part of the study

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Gadobutrol (Gadavist, BAY 86-4875)

Reporting group description:

Gadobutrol was administered to all subjects receiving study drug at the standard dose of 0.1 mmol/kg BW by single IV bolus injection. During the course of the study, non-contrast MRA images were obtained before the administration of gadobutrol, and Gadobutrol-enhanced MRA images were obtained after injection.

Serious adverse events	Gadobutrol (Gadavist, BAY 86-4875)		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 315 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Gadobutrol (Gadavist, BAY 86-4875)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 315 (4.44%)		
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 315 (2.22%)		
occurrences (all)	7		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	8 / 315 (2.54%)		
occurrences (all)	8		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported