Clinical trial results:
Multicenter, open-label study to evaluate the safety and efficacy (by blinded reading) of contrast-enhanced magnetic resonance angiography (MRA) after a single intravenous injection of 0.1 mmol/kg gadobutrol in subjects with known or suspected vascular disease of the supra-aortic vessels

Summary

EudraCT number	2010-023001-36
Trial protocol	DE CZ SE FR IT PL AT
Global end of trial date	28 May 2014
Results information	
Result version number	v2 (current)
This version publication date	04 September 2016
First version publication date	13 June 2015
Version creation reason	• New data added to full data set • Correction of full data set Bayer sponsor contact information to be updated

Trial information

Trial identification	
Sponsor protocol code	BAY 86-4875/14607
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01344447
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, D-51368, Leverkusen, Germany,
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	28 May 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 May 2014
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 MRA over two dimensional-Time of Flight (2D-ToF) MRA in subjects with known or suspected vascular disease of the supra-aortic arteries, 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 and
- The minimum gadobutrol performance criteria for sensitivity (more than [>] 50 percent [%]) and
- The minimum gadobutrol performance criteria for specificity (> 50%)

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	12 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	Argentina: 17
Country: Number of subjects enrolled	Australia: 19
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	China: 11
Country: Number of subjects enrolled	Korea, Republic of: 60
Country: Number of subjects enrolled	Turkey: 15
Country: Number of subjects enrolled	United States: 89
Country: Number of subjects enrolled	Poland: 117
Country: Number of subjects enrolled	Sweden: 8
Country: Number of subjects enrolled	Austria: 2

Country: Number of subjects enrolled	Czech Republic: 6
Country: Number of subjects enrolled	France: 22
Country: Number of subjects enrolled	Germany: 33
Country: Number of subjects enrolled	Italy: 78
Worldwide total number of subjects	479
EEA total number of subjects	266

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)	164
From 65 to 84 years	302
85 years and over	13

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 56 study centers in 14 countries, between 12 May 2011 (first subject first visit) and 28 May 2014 (last subject last visit).

Pre-assignment

Screening details:

Of 504 subjects screened, 17 did not complete screening; due to screen failure in 6, consent withdrawal in 6 and other reasons in 5 subjects. Of 487 subjects assigned to treatment, 479 received study drug and 8 discontinued prior to medication due to adverse event in 7 subjects, and other reason in 1 subject.

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	479
Completed	471
Not completed	8
Consent withdrawn by subject	1
Physician decision	1
Protocol violation	1
MRA unsuccessful	1
Error of power injector	1
Adverse event	1

Bolus tracking failed	1
The contrast was not seen	1

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	479	479	
Age categorical Units: Subjects			
<45 years	9	9	
45-64 years	155	155	
>=65 years	315	315	
Age continuous Units: years			
arithmetic mean	68.2		
standard deviation	± 10	-	
Gender categorical Units: Subjects			
Female	167	167	
Male	312	312	
Weight Units: kilogram(s)			
arithmetic mean	76		
standard deviation	± 14.5	-	

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

Subject analysis set description:

FAS included all subjects who have both gadobutrol-enhanced and 2D-ToF MRA image sets, and the SoR diagnosis were available (CTA was required to be interpretable and without technical problems).

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

Subject analysis set description:

SAF included all subjects who were administered study drug.

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

Subject analysis set description:

Gadobutrol-Enhanced MRA set included those subjects in FAS who showed only gadobutrol-enhanced MRA image sets.

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 clinical investigators (CI), three independent blinded readers (BR) (BR 1, BR 2 and BR 3) and majority readers (the outcome determined by at least two of the blinded readers). A segment was assessable if it was visualized along its entire length and if any region of stenosis, was measured reliably. There were 21 segments of the supra-aortic arteries assessed per subject. This outcome measure was analyzed on a segment basis, in the below table, "n" signifies segments that were evaluable for the specified category.

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 database does auto-adding of number of subjects analysed while reporting an explorative analysis of two treatment groups. Due to this format constraint, charts have been uploaded 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	Unenhanced MRA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	457[2]	457[3]		
Units: percentage of segments				
number (not applicable)				
Majority reader (n=9597)	95	72.7		
Blinded reader 1 (n=9597)	88.2	24.4		
Blinded reader 2 (n=9597)	94.9	75.3		
Blinded reader 3 (n=9597)	97.4	82.4		
Clinical investigators (n=9597)	97	78.6		

Notes:

[2] - FAS

[3] - FAS

Attachments (see zip file)	14607_Statistical Analysis_Primary

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 70 to 99% stenosis of a segment, but not occluded, as assessed by the SoR (CTA; blinded readers). This was determined using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria. For each segment, the most severe stenosis/narrowing was identified and considered for the evaluation of clinically significant disease. In case of multiple stenosis in any one segment, the most severe stenosis in the segment was recorded. This outcome measure was analyzed on a segment basis, in the below table, "n/n" signifies those subjects/segments that were evaluable for the 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 database does auto-adding of number of subjects analysed while reporting an explorative analysis of two treatment groups. Due to this format constraint, charts have been uploaded 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	Unenhanced MRA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	457[5]	457[6]		
Units: percentage of sensitivity				
number (not applicable)				
Majority reader (n=141/158)	60.1	54.4		
Blinded reader 1 (n=141/158)	59.5	54.4		
Blinded reader 2 (n=141/158)	59.5	54.1		
Blinded reader 3 (n=141/158)	58.2	55.7		
Clinical investigators (n=238/297)	60.9	39.4		

Notes:

[5] - FAS

[6] - FAS

Attachments (see zip file)	14607_Statistical Analysis_Primary

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 was defined as 70 to 99% stenosis of a segment, but not occluded, as assessed by the SoR (CTA; blinded readers). This was determined using the NASCET criteria. For each segment, the most severe stenosis/narrowing was identified and considered for the evaluation of clinically significant disease. In case of multiple stenosis in any one segment, the most severe stenosis in the segment was recorded. This outcome measure was analyzed on a segment basis, in the below table, "n/n" signifies those subjects/segments that were evaluable for the 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 database does auto-adding of number of subjects analysed while reporting an explorative analysis of two treatment groups. Due to this format constraint, charts have been uploaded 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	Unenhanced MRA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	457[8]	457[9]		
Units: percentage of specificity				
number (not applicable)				
Majority reader (n=457/9321)	96.1	87.3		
Blinded reader 1 (n=457/9321)	92	61.7		
Blinded reader 2 (n=457/9321)	94.7	85.1		
Blinded reader 3 (n=457/9321)	96.7	89.1		
Clinical investigators (n=457/9133)	98.1	89.1		

Notes:
[8] - FAS
[9] - FAS

Attachments (see zip file)	14607_Statistical Analysis_Primary

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 70 to 99% stenosis of a segment, but not occluded as assessed by the SoR (CTA; blinded readers). 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. This outcome measure was analyzed on a segment basis, in the below table, "n/n" signifies those subjects/segments that were evaluable for the 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 database does auto-adding of number of subjects analysed while reporting an explorative analysis of two treatment groups. Due to this format constraint, charts have been uploaded 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			
Subject group type	Subject analysis set			
Number of subjects analysed	457[11]			
Units: percentage of sensitivity				
number (not applicable)				
Majority reader (n=135/149)	61.7			
Blinded reader 1 (n=132/146)	60.3			
Blinded reader 2 (n=139/156)	59.6			
Blinded reader 3 (n=140/155)	58.7			
Clinical investigators (n=230 /283)	61.5			

Notes:
[11] - FAS

Attachments (see zip file)	14607_Statistical Analysis_Primary

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 was defined as 70 to 99% stenosis of a segment, but not occluded as assessed by the SoR (CTA; blinded readers). 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. This outcome measure was analyzed on a segment basis, in the below table, "n/n" signifies those subjects/segments that were evaluable for the 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 database does auto-adding of number of subjects analysed while reporting an explorative analysis of two treatment groups. Due to this format constraint, charts have been uploaded 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			
Subject group type	Subject analysis set			
Number of subjects analysed	457[13]			
Units: percentage of specificity				
number (not applicable)				
Majority reader (n=457/8805)	98			
Blinded reader 1 (n=444/8225)	97.6			
Blinded reader 2 (n=457/8844)	97.2			
Blinded reader 3 (n=457/9079)	98			
Clinical investigators (n=457/8926)	99.2			

Notes:

[13] - FAS

Attachments (see zip file)	14607_Statistical Analysis_Primary

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Difference in Vessel Diameter (millimeter [mm]) at Normal Point and Narrowest point in Gadobutrol-Enhanced and Unenhanced Images Compared to CTA by Blinded Readers and the Clinical Investigators

End point title	Mean Difference in Vessel Diameter (millimeter [mm]) at Normal Point and Narrowest point in Gadobutrol-Enhanced and Unenhanced Images Compared to CTA by Blinded Readers and the Clinical Investigators

End point description:

The segment 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. Mean of vessel diameters was calculated by segment separately for CTA and MRA readers. Number of subjects/segments analyzed in below ordered categories (Normal-BRs; Narrowest-BRs; Normal-CIs; Narrowest-CIs) in CTA minus Unenhanced MRA group was 425/2063, 425/2063, 352/816, 352/804 respectively; and was 436/2683, 436/2683, 410/1184, 410/1175 for same categories in CTA minus enhanced MRA group respectively.

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	457[14]	457[15]		
Units: millimeter(s) (mm)				
arithmetic mean (standard deviation)				
Vessel diameter at normal point: BR	0 (± 0.79)	0.21 (± 0.8)		
Vessel diameter at narrowest point: BR	0.01 (± 0.8)	0.29 (± 0.87)		
Vessel diameter at normal point: CI	0.33 (± 1.01)	0.48 (± 0.98)		
Vessel diameter at narrowest point: CI	0.11 (± 0.79)	0.02 (± 0.81)		

Notes:

[14] - Evaluable subjects in FAS.

[15] - 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.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection

End point values	Gadobutrol-Enhanced MRA	Unenhanced MRA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	457[16]	457[17]		
Units: percentage of segments				
number (not applicable)				
Blinded reader 1	46.6	97.1		
Blinded reader 2	14	54.9		
Blinded reader 3	16.2	41.2		

Notes:

[16] - FAS

[17] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Types of Artifacts on a Segment Basis by Blinded Reader 1

End point title	Types of Artifacts on a Segment Basis 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	Unenhanced MRA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	457[18]	457[19]		
Units: percentage of segments				
number (not applicable)				
Motion artifact	18.6	41.9		
Venous opacification	9.8	0.8		
Saturation artifact	21.6	38.2		
Susceptibility artifacts	0.1	0.2		
Ringing artifact	0.5	29.3		
Bolus timing error	4.3	4		
Other	9.3	48		

Notes:

[18] - FAS

[19] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Types of Artifacts on a Segment Basis by Blinded Reader 2

End point title	Types of Artifacts on a Segment Basis by Blinded Reader 2

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	Unenhanced MRA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	457[20]	457[21]		
Units: percentage of segments				
number (not applicable)				
Motion artifact	5.6	39.8		
Venous opacification	5.7	0.3		
Saturation artifact	2	24.5		
Susceptibility artifacts	0.8	3.7		
Ringing artifact	0.2	0		
Bolus timing error	1.1	0		
Other	0.5	0.3		

Notes:

[20] - FAS

[21] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Types of Artifacts on a Segment Basis by Blinded Reader 3

End point title	Types of Artifacts on a Segment Basis by Blinded Reader 3

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	Unenhanced MRA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	457[22]	457[23]		
Units: percentage of segments				
number (not applicable)				
Motion artifact	0.6	13.2		
Venous opacification	1.7	0.1		
Saturation artifact	13.8	39.4		
Susceptibility artifacts	0.2	0.5		
Ringing artifact	0.6	6.4		
Bolus timing error	1.6	0.4		
Other	0.4	0.1		

Notes:

[22] - FAS

[23] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: The Percentage of Location of Stenosis (>=70%) in the Proximal Segments Assessed by Gadobutrol-Enhanced MRA and Unenhanced MRA

End point title	The Percentage of Location of Stenosis (>=70%) in the Proximal Segments Assessed by Gadobutrol-Enhanced MRA and Unenhanced MRA

End point description:

Location within a segment was based on the point of greatest stenosis and was recorded for stenosis >=70% (including occlusions) as:
- At the bifurcation or proximal origin of a segment (occlusion proximal to the origin of the segment)
- Within 5 mm of the bifurcation or proximal origin of a segment
- Beyond 5 mm from the bifurcation or proximal origin of a segment.

In the below table, "n" signifies location of stenosis which were evaluable for the specified parameter for each arm, respectively.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection

End point values	Gadobutrol-Enhanced MRA	Unenhanced MRA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	457[24]	457[25]		
Units: pecentage of location				
number (not applicable)				
At the bifurcation: BR 1 (n=353,89)	50.4	59.6		
At the bifurcation: BR 2 (n=429,429)	52.2	58.7		
At the bifurcation: BR 3 (n=525,559)	44	54.2		
Within 5 mm of the bifurcation: BR 1 (n=353,89)	16.7	12.4		
Within 5 mm of the bifurcation: BR 2 (n=429,429)	14.7	10.7		
Within 5 mm of the bifurcation: BR 3 (n=525,559)	34.7	27		
Beyond 5 mm of the bifurcation: BR 1 (n=353,89)	32.9	28.1		
Beyond 5 mm of the bifurcation: BR 2 (n=429,429)	33.1	30.5		
Beyond 5 mm of the bifurcation: BR 3 (n=525,559)	21.3	18.8		

Notes:

[24] - FAS

[25] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Length of Stenosis (>=70%) in the Proximal Segments Assessed by Gadobutrol-Enhanced MRA and Unenhanced MRA

End point title	Length of Stenosis (>=70%) in the Proximal Segments Assessed by Gadobutrol-Enhanced MRA and Unenhanced MRA

End point description:

The length of stenosis was based on the most proximal (first point) in a segment where a stenosis

exceeded 10% and the most distal point (last point) in the segment where a stenosis exceeded 10%. If a stenosis spanned more than one segment then the measurement was only included to the beginning or end (boundary) of the segment being evaluated. If there was no stenosis of >=70% in a segment then the length was designated as 0. In the below table, "n" signifies location of stenosis which were evaluable for the specified parameter for each arm, respectively.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection

End point values	Gadobutrol-Enhanced MRA	Unenhanced MRA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	457[26]	457[27]		
Units: millimeter(s)				
arithmetic mean (standard deviation)				
Reader 1 (n=290,66)	11.26 (± 11.77)	13.36 (± 11.47)		
Reader 2 (n=315,281)	6.25 (± 6.99)	7.18 (± 6.07)		
Reader 3 (n=277,268)	4.89 (± 4.69)	5.36 (± 3.76)		

Notes:

[26] - FAS

[27] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: The Percentage of Presence of Secondary Radiologic Indicators for Diagnosis of Clinically Relevant Disease

End point title	The Percentage of Presence of Secondary Radiologic Indicators for Diagnosis of Clinically Relevant Disease

End point description:

Each segment was assessed for secondary signs of stenosis for diagnosis of clinically significant disease. The following indicators were considered for the MRA studies:
- post-stenotic dilation or ulceration (segmental),
- post-stenotic signal dropout, narrowing and intensity reduction, and
- thrombus.

Each of the three parameters were assessed as present or absent in the region distal to the stenosis. If they were found in any segment distal to the stenosis then they were assessed as present. This end point was analyzed on a segment basis, in the below table, "n" signifies segments that were evaluable for the 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	Unenhanced MRA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	457[28]	457[29]		
Units: percentage of radiologic indicator				
number (not applicable)				
Reader 1 (n=9203, 9336)	3.9	0.7		
Reader 2 (n=9177, 9444)	2.8	2		
Reader 3 (n=9009, 9285)	2.4	2.7		

Notes:

[28] - FAS

[29] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Type of Secondary Radiologic Indicators for Diagnosis of Clinically Relevant Disease

End point title	Type of Secondary Radiologic Indicators for Diagnosis of Clinically Relevant Disease

End point description:

Each segment was assessed for secondary signs of stenosis for diagnosis of clinically significant disease. The following indicators were considered for the MRA studies:
- post-stenotic dilation or ulceration (segmental),
- post-stenotic signal dropout, narrowing and intensity reduction, and
- thrombus.

Each of the three parameters were assessed as present or absent in the region distal to the stenosis. If they were found in any segment distal to the stenosis then they were assessed as present. If there were tandem (serial) stenosis in a vessel then the secondary signs were assigned to the stenosis of >=70% that was proximal and closest in proximity to the secondary sign. This end point was analyzed on a segment basis, in the below table, "n" signifies segments that were evaluable for the 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	Unenhanced MRA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	457[30]	457[31]		
Units: percentage of segments				
number (not applicable)				
Post-stenotic dilation: BR 1 (n=390,63)	49.7	20.6		
Post-stenotic dilation: BR 2 (n=271,188)	74.2	56.4		
Post-stenotic dilation: BR 3 (n=236,246)	7.2	1.6		
Post-stenotic signal dropout: BR 1 (n=390,63)	49.5	77.8		
Post-stenotic signal dropout: BR 2 (n=271,188)	25.5	43.6		
Post-stenotic signal dropout: BR 3 (n=236,246)	92.8	98.4		
Thrombus: BR 1 (n=390,63)	0.8	1.6		

Thrombus: BR 2 (n=271,188)	0.4	0		
Thrombus: BR 3 (n=236,246)	0	0		

Notes:

[30] - FAS

[31] - 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. This outcome measure was analyzed on a segment basis, in the below table, "n" signifies segments that were evaluable for the 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	Unenhanced MRA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	457[32]	456[33]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Reader 1 (n=9408, 9231)	3.2 (± 1)	1.3 (± 0.6)		
Reader 2 (n=9535, 9301)	2.9 (± 0.6)	2.2 (± 0.9)		
Reader 3 (n=9539, 9302)	2.8 (± 0.5)	2.4 (± 0.8)		

Notes:

[32] - FAS

[33] - 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 Unenhanced and Gadobutrol-Enhanced 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 Unenhanced and Gadobutrol-Enhanced 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 would have recommended an additional imaging study for each subject and was recorded.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection

End point values	Gadobutrol-Enhanced MRA	Unenhanced MRA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	457[34]	457[35]		
Units: percentage of subjects				
number (not applicable)				
Reader 1	71.1	100		
Reader 2	44.2	98.2		
Reader 3	22.1	83.2		
Clinical investigators	11.2	43.1		

Notes:

[34] - FAS

[35] - 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 Unenhanced and Gadobutrol-Enhanced MRA Images – Blinded Reader 1

End point title	Types of Additional Imaging Studies Recommended by the Blinded Readers After Evaluation of the Unenhanced and Gadobutrol-Enhanced 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	Unenhanced MRA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	325[36]	457[37]		
Units: subjects				
Non-contrast MRA	0	0		
Contrast-enhanced MRA	64	448		
CTA	124	4		
Ultrasound	0	0		
DSCA	137	5		
Nuclear medicine study	0	0		

Notes:

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

[37] - 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 Unenhanced and Gadobutrol-Enhanced MRA Images – Blinded Reader 2

End point title	Types of Additional Imaging Studies Recommended by the Blinded Readers After Evaluation of the Unenhanced and Gadobutrol-Enhanced 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	Unenhanced MRA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	202[38]	449[39]		
Units: subjects				
Non-contrast MRA	50	2		
Contrast-enhanced MRA	30	415		
CTA	113	30		
Ultrasound	0	0		
DSCA	9	2		
Nuclear medicine study	0	0		

Notes:

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

[39] - 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 Unenhanced and Gadobutrol-Enhanced MRA Images – Blinded Reader 3

End point title	Types of Additional Imaging Studies Recommended by the Blinded Readers After Evaluation of the Unenhanced and Gadobutrol-Enhanced 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	Unenhanced MRA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	101[40]	380[41]		
Units: subjects				
Non-contrast MRA	0	0		
Contrast-enhanced MRA	12	64		
CTA	88	316		
Ultrasound	0	0		
DSCA	1	0		
Nuclear medicine study	0	0		

Notes:

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

[41] - 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	Unenhanced MRA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51[42]	197[43]		
Units: subjects				
Non-contrast MRA	1	0		
Contrast-enhanced MRA	0	142		
CTA	44	51		
Ultrasound	1	0		
DSCA	5	4		

Nuclear medicine study	0	0		

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

From the time the consent was signed until 24 (+/-6) hours follow-up after the study MRA but was continued until completion of the CTA in those subjects who had the CTA performed after the MRA (as part of the study)

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

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.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: The pre-specified frequency threshold for non-serious adverse events was set at >=1%. There were quite a few non-serious adverse events but none reached above the pre-specified threshold.

Serious adverse events	Gadobutrol (Gadavist, BAY 86-4875)		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 479 (0.21%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Nervous system disorders			
Cerebrovascular accident			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

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	0 / 479 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 April 2013	The blinded readers interpreted the initial batches of CTA images for the SoR and found the rate of disease prevalence (even with the restriction of 70% or greater stenosis) to be lower than that seen at the sites, and most importantly, the site-reads were used to predict the blinded reader disease prevalence. Therefore the targeted prevalence of disease for the sitereads had to be increased proportionately in order for the blinded reader disease prevalence to approach 40%, as planned. This was accomplished by further restricting the enrollment to only those subjects with a clinically significant stenosis, 70 to 99%, in order to drive the site disease prevalence for the study closer to 60%. (Note: Site disease prevalence for the study could only be increased to 60% in order to maintain consistency between the individual blinded read batch's disease prevalence, as required by the FDA).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported