



Clinical trial results:

Multicenter open-label study to evaluate efficacy of gadobutrol-enhanced cardiac magnetic resonance imaging (CMRI) for detection of significant coronary artery disease (CAD) in subjects with known or suspected CAD by a blinded image analysis

Summary

EudraCT number	2012-002563-10
Trial protocol	DE GB FR
Global end of trial date	31 August 2017

Results information

Result version number	v1
This version publication date	24 March 2018
First version publication date	24 March 2018

Trial information

Trial identification

Sponsor protocol code	BAY86-4875 / 15961
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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	10 April 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	31 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives (assessed by 3 study-independent blinded readers and all 3 endpoints simultaneously confirmed by the same 2 out of the 3 readers) were to:

- 1) Demonstrate that subject-based sensitivity of gadobutrol-enhanced cardiac magnetic resonance imaging (CMRI) at vasodilator stress/rest (lower bound of 95% confidence interval [CI]) exceeds the predefined minimum performance threshold of 60%
- 2) Demonstrate that subject-based specificity of gadobutrol-enhanced CMRI at vasodilator stress/rest (lower bound of 95% CI) exceeds the predefined minimum performance threshold of 55%
- 3) Demonstrate subject-based superior sensitivity of gadobutrol-enhanced CMRI over unenhanced wall motion CMRI.

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. 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	19 July 2013
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	Germany: 210
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 108
Country: Number of subjects enrolled	Switzerland: 44
Country: Number of subjects enrolled	United States: 31
Country: Number of subjects enrolled	United Kingdom: 28
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	New Zealand: 1
Worldwide total number of subjects	426
EEA total number of subjects	242

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)	292
From 65 to 84 years	134
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 23 study centers in 7 countries (Germany, South Korea, United Kingdom, France, United States, New Zealand and Switzerland), between 19 July 2013 (first subject first visit) and 10 April 2015 (last subject last visit).

Pre-assignment

Screening details:

Overall, 456 subjects were enrolled, of them 19 did not finish their baseline visit (6 screening failure, 13 dropped out), 1 additional subject discontinued the study due to an AE. A total of 436 subjects entered the diagnostic imaging phase, of them 426 were treated with gadobutrol and entered the follow-up phase.

Period 1

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

Arms

Arm title	Gadobutrol 0.1 mmol/kg body weight
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Arm description:

Subjects received gadobutrol at the total approved standard dose of 0.1 millimole per kilogram body weight (mmol/kg BW) in 2 separate bolus injections: 0.05 mmol/kg BW at peak pharmacologic stress and 0.05 mmol/kg BW at rest via a power injector.

Arm type	Experimental
Investigational medicinal product name	Gadobutrol
Investigational medicinal product code	BAY86-4875
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Subjects received gadobutrol at the total approved standard dose of 0.1 mmol/kg BW in 2 separate bolus injections: 0.05 mmol/kg BW at peak pharmacologic stress and 0.05 mmol/kg BW at rest via a power injector.

Number of subjects in period 1	Gadobutrol 0.1 mmol/kg body weight
Started	426
Completed	415
Not completed	11
Other	10
Adverse event	1

Baseline characteristics

Reporting groups

Reporting group title	Gadobutrol 0.1 mmol/kg body weight
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Reporting group description:

Subjects received gadobutrol at the total approved standard dose of 0.1 millimole per kilogram body weight (mmol/kg BW) in 2 separate bolus injections: 0.05 mmol/kg BW at peak pharmacologic stress and 0.05 mmol/kg BW at rest via a power injector.

Reporting group values	Gadobutrol 0.1 mmol/kg body weight	Total	
Number of subjects	426	426	
Age categorical			
Units: Subjects			

Age Continuous			
Units: Years			
arithmetic mean	58.4		
standard deviation	± 11.9	-	
Sex: Female, Male			
Units: Subjects			
Female	129	129	
Male	297	297	
Childbearing Potential			
Units: Subjects			
Of childbearing potential (only females)	20	20	
No childbearing potential (only females)	109	109	
No childbearing potential (only males)	297	297	
Ethnicity (NIH/OMB)			
Units: Subjects			
Not Hispanic or Latino	414	414	
Hispanic or Latino	5	5	
Not reported	7	7	
Race (NIH/OMB)			
Units: Subjects			
White	310	310	
Asian	111	111	
Black	2	2	
Not reported	3	3	
Country			
Units: Subjects			
Germany	210	210	
South Korea	108	108	
Switzerland	44	44	
United States of America	31	31	
United Kingdom	28	28	
France	4	4	

New Zealand	1	1	
Age Categorical Units: Subjects			
< 45 years	60	60	
>=45 to <= 64 years	232	232	
>= 65 years	134	134	
Body Weight Units: Kilogram (kg)			
arithmetic mean	79.75		
standard deviation	± 16.29	-	
Height Units: Centimeter			
arithmetic mean	170.99		
standard deviation	± 9.17	-	
Body Mass Index Units: Kilogram per square meter (kg/m ²)			
arithmetic mean	27.160		
standard deviation	± 4.561	-	
Estimated glomerular filtration rate			
eGFR (based on serum/blood creatinine from local laboratory) was measured/evaluated within 2 weeks before the first gadobutrol injection (at the latest on the day of gadobutrol-enhanced CMRI before the first gadobutrol injection).			
Units: mL/min/1.73m ²			
arithmetic mean	84.2		
standard deviation	± 18.37	-	

End points

End points reporting groups

Reporting group title	Gadobutrol 0.1 mmol/kg body weight
Reporting group description: Subjects received gadobutrol at the total approved standard dose of 0.1 millimole per kilogram body weight (mmol/kg BW) in 2 separate bolus injections: 0.05 mmol/kg BW at peak pharmacologic stress and 0.05 mmol/kg BW at rest via a power injector.	
Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description: FAS (n=376) included all participants who underwent pharmacologic stress and for whom electronic case report form (eCRF) entries, adequate image sets for unenhanced and gadobutrol-enhanced cardiac magnetic resonance imaging (CMRI), and the complete image set for the standard of reference (SoR) diagnosis were available.	

Primary: Presence of a Myocardial Perfusion Defect Indicating Significant CAD per Subject on Gadobutrol-enhanced CMRI (Based on RPS) – Primary Analysis of Sensitivity Based on Blinded Readers' Assessment

End point title	Presence of a Myocardial Perfusion Defect Indicating Significant CAD per Subject on Gadobutrol-enhanced CMRI (Based on RPS) – Primary Analysis of Sensitivity Based on Blinded Readers' Assessment ^[1]
End point description: Blinded readers evaluated 6 myocardial regions based on regional perfusion score (RPS), 0=normal; 1=abnormal, reversible perfusion defect (stress); 2=abnormal, mixed perfusion defect (reversible and fixed/permanent components); 3=abnormal, fixed/permanent perfusion defect/scar (stress and rest)]. A myocardial region was rated to have a perfusion defect in case of a RPS of ≥ 1 and was rated to have normal perfusion in case of a RPS of 0. Significant CAD was defined as quantitative coronary angiography (QCA) stenosis of $\geq 50\%$ for primary analysis, and was determined based on the presence of a myocardial perfusion defect on gadobutrol-enhanced cardiac magnetic resonance imaging (CMRI) verified by standard of reference (SoR). Sensitivity= true positive/ (true positive + false negative).	
End point type	Primary
End point timeframe: 0 to 30/40 minute (min) 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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Gadobutrol 0.1 mmol/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	141 ^[2]			
Units: Sensitivity %				
number (confidence interval 95%)				
Reader 1	76.6 (68.7 to 83.3)			
Reader 2	65.2 (56.8 to 73.1)			
Reader 3	64.5 (56.0 to 72.4)			

Notes:

[2] - FAS with evaluable subjects for this endpoint.

Statistical analyses

No statistical analyses for this end point

Primary: Presence of a Myocardial Perfusion Defect Indicating Significant CAD per Subject on Gadobutrol-enhanced CMRI (Based on RPS) – Additional Secondary analysis of Sensitivity Based on the Blinded Readers' Assessment

End point title	Presence of a Myocardial Perfusion Defect Indicating Significant CAD per Subject on Gadobutrol-enhanced CMRI (Based on RPS) – Additional Secondary analysis of Sensitivity Based on the Blinded Readers' Assessment ^[3]
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End point description:

Blinded readers evaluated 6 myocardial regions based on regional perfusion score (RPS), 0=normal; 1=abnormal, reversible perfusion defect (stress); 2=abnormal, mixed perfusion defect (reversible and fixed/permanent components); 3=abnormal, fixed/permanent perfusion defect/scar (stress and rest)]. A myocardial region was rated to have a perfusion defect in case of a RPS of ≥ 1 and was rated to have normal perfusion in case of a RPS of 0. Significant CAD was defined as quantitative coronary angiography (QCA) stenosis of $\geq 70\%$ for secondary analysis, and was determined based on the presence of a myocardial perfusion defect on gadobutrol-enhanced cardiac magnetic resonance imaging (CMRI) verified by standard of reference (SoR). Sensitivity= true positive/ (true positive + false negative). This additional secondary analysis of sensitivity was prospective analysis.

End point type	Primary
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End point timeframe:

0 to 30/40 min post-injection

Notes:

[3] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Gadobutrol 0.1 mmol/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	108 ^[4]			
Units: Sensitivity %				
number (confidence interval 95%)				
Reader 1	89.8 (82.5 to 94.8)			
Reader 2	79.6 (70.8 to 86.8)			
Reader 3	78.7 (69.8 to 86.0)			

Notes:

[4] - FAS with evaluable subjects for this endpoint.

Statistical analyses

No statistical analyses for this end point

Primary: Absence of a Myocardial Perfusion Defect Excluding Significant CAD per Subject on Gadobutrol-enhanced CMRI (Based on RPS) – Primary Analysis of Specificity Based on the Blinded Readers' Assessment

End point title	Absence of a Myocardial Perfusion Defect Excluding Significant CAD per Subject on Gadobutrol-enhanced CMRI (Based on RPS) – Primary Analysis of Specificity Based on the Blinded Readers' Assessment ^[5]
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End point description:

Blinded readers evaluated 6 myocardial regions based on regional perfusion score (RPS), 0=normal;

1=abnormal, reversible perfusion defect (stress); 2=abnormal, mixed perfusion defect (reversible and fixed/permanent components); 3=abnormal, fixed/permanent perfusion defect/scar (stress and rest)]. A myocardial region a perfusion defect in case of a RPS of ≥ 1 and was rated to have normal perfusion in case of a RPS of 0. Significant CAD was defined as quantitative coronary angiography (QCA) stenosis of $\geq 50\%$ for primary analysis, and was determined based on the presence of a myocardial perfusion defect on gadobutrol-enhanced cardiac magnetic resonance imaging (CMRI) verified by standard of reference (SoR). Specificity= true negative/ (true negative + false positive).

End point type	Primary
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End point timeframe:

0 to 30/40 min post-injection

Notes:

[5] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Gadobutrol 0.1 mmol/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	235 ^[6]			
Units: Specificity %				
number (confidence interval 95%)				
Reader 1	85.1 (79.9 to 89.4)			
Reader 2	92.3 (88.2 to 95.4)			
Reader 3	91.9 (87.7 to 95.1)			

Notes:

[6] - FAS with evaluable subjects for this endpoint.

Statistical analyses

No statistical analyses for this end point

Primary: Absence of a Myocardial Perfusion Defect Excluding Significant CAD per Subject on Gadobutrol-enhanced CMRI (Based on RPS) – Additional Secondary Analysis of Specificity Based on the Blinded Readers' Assessment

End point title	Absence of a Myocardial Perfusion Defect Excluding Significant CAD per Subject on Gadobutrol-enhanced CMRI (Based on RPS) – Additional Secondary Analysis of Specificity Based on the Blinded Readers' Assessment ^[7]
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End point description:

Blinded readers evaluated 6 myocardial regions based on regional perfusion score (RPS), 0=normal; 1=abnormal, reversible perfusion defect (stress); 2=abnormal, mixed perfusion defect (reversible and fixed/permanent components); 3=abnormal, fixed/permanent perfusion defect/scar (stress and rest)]. A myocardial region was rated to have a perfusion defect in case of a RPS of ≥ 1 and was rated to have normal perfusion in case of a RPS of 0. Significant CAD was defined as quantitative coronary angiography (QCA) stenosis of $\geq 70\%$ for primary analysis, and was determined based on the presence of a myocardial perfusion defect on gadobutrol-enhanced cardiac magnetic resonance imaging (CMRI) verified by standard of reference (SoR). Specificity= true negative/ (true negative + false positive). This additional secondary analysis of specificity was prospective analysis.

End point type	Primary
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End point timeframe:

0 to 30/40 min 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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Gadobutrol 0.1 mmol/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	268 ^[8]			
Units: Specificity %				
number (confidence interval 95%)				
Reader 1	82.8 (77.8 to 87.2)			
Reader 2	91.0 (87.0 to 94.2)			
Reader 3	90.7 (86.5 to 93.9)			

Notes:

[8] - FAS with evaluable subjects for this endpoint.

Statistical analyses

No statistical analyses for this end point

Primary: Presence of a Myocardial Perfusion Defect Indicating Significant CAD per Subject on Gadobutrol-enhanced CMRI Versus Unenhanced Wall Motion CMRI Images – Primary Analysis of Sensitivity Comparison Based on the Blinded Readers' Assessment

End point title	Presence of a Myocardial Perfusion Defect Indicating Significant CAD per Subject on Gadobutrol-enhanced CMRI Versus Unenhanced Wall Motion CMRI Images – Primary Analysis of Sensitivity Comparison Based on the Blinded Readers' Assessment ^[9]
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End point description:

Presence of a myocardial perfusion defect on gadobutrol-enhanced CMRI versus the presence of wall motion abnormalities on unenhanced CMRI images (based on regional perfusion/regional wall motion score of the 6 myocardial regions) was calculated by investigator's assessment. Significant CAD was defined as quantitative coronary angiography (QCA) stenosis of $\geq 50\%$ for primary analysis, and was determined based on the presence of a myocardial perfusion defect on gadobutrol-enhanced cardiac magnetic resonance imaging (CMRI) verified by standard of reference (SoR). Sensitivity= true positive/ (true positive + false negative).

End point type	Primary
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End point timeframe:

0 to 30/40 min post-injection

Notes:

[9] - 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 not allow to report only one treatment group in statistical analyses section. 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 0.1 mmol/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	141 ^[10]			
Units: Sensitivity %				
number (not applicable)				
Gadobutrol-enhanced CMRI-Reader 1	76.6			
Gadobutrol-enhanced CMRI-Reader 2	65.2			
Gadobutrol-enhanced CMRI-Reader 3	64.5			
Unenhanced CMRI-Reader 1	77.3			
Unenhanced CMRI-Reader 2	36.2			
Unenhanced CMRI-Reader 3	40.4			

Notes:

[10] - FAS with evaluable subjects for this endpoint.

Attachments (see zip file)	15961_Primary Outcome 5.pdf
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Statistical analyses

No statistical analyses for this end point

Primary: Presence of a Myocardial Perfusion Defect Indicating Significant CAD per Subject on Gadobutrol-enhanced CMRI Versus Unenhanced Wall Motion CMRI Images – Additional Secondary Analysis of Sensitivity Comparison Based on the Blinded Readers' Assessment

End point title	Presence of a Myocardial Perfusion Defect Indicating Significant CAD per Subject on Gadobutrol-enhanced CMRI Versus Unenhanced Wall Motion CMRI Images – Additional Secondary Analysis of Sensitivity Comparison Based on the Blinded Readers' Assessment ^[11]
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End point description:

Presence of a myocardial perfusion defect on gadobutrol-enhanced CMRI versus the presence of wall motion abnormalities on unenhanced CMRI images (based on regional perfusion/regional wall motion score of the 6 myocardial regions) was calculated by investigator's assessment. Significant CAD was defined as quantitative coronary angiography (QCA) stenosis of $\geq 70\%$ for primary analysis, and was determined based on the presence of a myocardial perfusion defect on gadobutrol-enhanced cardiac magnetic resonance imaging (CMRI) verified by standard of reference (SoR). Sensitivity= true positive/ (true positive + false negative). This additional secondary analysis of sensitivity was prospective analysis.

End point type	Primary
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End point timeframe:

0 to 30/40 min post-injection

Notes:

[11] - 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 not allow to report only one treatment group in statistical analyses section. 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 0.1 mmol/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	108 ^[12]			
Units: Sensitivity %				
number (not applicable)				
Gadobutrol-enhanced CMRI-Reader 1	89.8			
Gadobutrol-enhanced CMRI-Reader 2	79.6			
Gadobutrol-enhanced CMRI-Reader 3	78.7			
Unenhanced CMRI-Reader 1	82.4			
Unenhanced CMRI-Reader 2	45.4			
Unenhanced CMRI-Reader 3	48.1			

Notes:

[12] - FAS with evaluable subjects for this endpoint.

Attachments (see zip file)	15961_Primary Outcome 6.pdf
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Statistical analyses

No statistical analyses for this end point

Secondary: Presence of a Myocardial Perfusion Defect Indicating Significant CAD per Subject on Gadobutrol-enhanced CMRI – Secondary Analysis of Sensitivity Based on Investigator's Assessment

End point title	Presence of a Myocardial Perfusion Defect Indicating Significant CAD per Subject on Gadobutrol-enhanced CMRI – Secondary Analysis of Sensitivity Based on Investigator's Assessment
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End point description:

Presence of a myocardial perfusion defect on gadobutrol-enhanced CMRI versus the presence of wall motion abnormalities on unenhanced CMRI images (based on regional perfusion/regional wall motion score of the 6 myocardial regions) was calculated by investigator's assessment. Significant CAD was determined based on the presence of a myocardial perfusion defect on gadobutrol-enhanced CMRI or the presence of wall motion abnormalities on unenhanced CMRI images verified by SoR (significant CAD defined as QCA stenosis of $\geq 50\%$). Sensitivity= true positive/ (true positive + false negative).

End point type	Secondary
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End point timeframe:

0 to 30/40 min post-injection

End point values	Gadobutrol 0.1 mmol/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	140 ^[13]			
Units: Sensitivity %				
number (confidence interval 95%)	74.3 (66.2 to 81.3)			

Notes:

[13] - FAS with evaluable subjects for this endpoint.

Statistical analyses

Secondary: Presence of a Myocardial Perfusion Defect Indicating Significant CAD per Subject on Gadobutrol-enhanced CMRI – Additional Secondary Analysis of Sensitivity Comparison Based on Investigator's Assessment

End point title	Presence of a Myocardial Perfusion Defect Indicating Significant CAD per Subject on Gadobutrol-enhanced CMRI – Additional Secondary Analysis of Sensitivity Comparison Based on Investigator's Assessment
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End point description:

Presence of a myocardial perfusion defect on gadobutrol-enhanced CMRI versus the presence of wall motion abnormalities on unenhanced CMRI images (based on regional perfusion/regional wall motion score of the 6 myocardial regions) was calculated by investigator's assessment. Significant CAD was determined based on the presence of a myocardial perfusion defect on gadobutrol-enhanced CMRI or the presence of wall motion abnormalities on unenhanced CMRI images verified by SoR (significant CAD defined as QCA stenosis of $\geq 70\%$). Sensitivity= true positive/ (true positive + false negative). This additional secondary analysis of sensitivity was prospective analysis.

End point type	Secondary
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End point timeframe:

0 to 30/40 min post-injection

End point values	Gadobutrol 0.1 mmol/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	108 ^[14]			
Units: Sensitivity %				
number (confidence interval 95%)	89.8 (82.5 to 94.8)			

Notes:

[14] - FAS with evaluable subjects for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Absence of a Myocardial Perfusion Defect Excluding Significant CAD per Subject on Gadobutrol-enhanced CMRI – Secondary Analysis of Specificity Based on Investigator's Assessment

End point title	Absence of a Myocardial Perfusion Defect Excluding Significant CAD per Subject on Gadobutrol-enhanced CMRI – Secondary Analysis of Specificity Based on Investigator's Assessment
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End point description:

Investigator's assessment evaluated 6 myocardial regions based on regional perfusion score (RPS), 0=normal; 1=abnormal, reversible perfusion defect (stress); 2=abnormal, mixed perfusion defect (reversible and fixed/permanent components); 3=abnormal, fixed/permanent perfusion defect/scar (stress and rest). A myocardial region was rated to have a perfusion defect in case of a RPS of ≥ 1 and was rated to have normal perfusion in case of a RPS of 0. The investigator's assessment of subject-based specificity of gadobutrol-enhanced CMRI was analyzed with significant CAD defined as maximum stenosis severity of $\geq 50\%$ by QCA, which were secondary analysis. Specificity= true negative/ (true negative + false positive).

End point type	Secondary
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End point timeframe:

0 to 30/40 min post-injection

End point values	Gadobutrol 0.1 mmol/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	234 ^[15]			
Units: Specificity %				
number (confidence interval 95%)	85.9 (80.8 to 90.1)			

Notes:

[15] - FAS with evaluable subjects for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Absence of a Myocardial Perfusion Defect Excluding Significant CAD per Subject on Gadobutrol-enhanced CMRI – Additional Secondary Analysis of Specificity Based on Investigator's Assessment

End point title	Absence of a Myocardial Perfusion Defect Excluding Significant CAD per Subject on Gadobutrol-enhanced CMRI – Additional Secondary Analysis of Specificity Based on Investigator's Assessment
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End point description:

Investigator's assessment evaluated 6 myocardial regions based on regional perfusion score (RPS), 0=normal; 1=abnormal, reversible perfusion defect (stress); 2=abnormal, mixed perfusion defect (reversible and fixed/permanent components); 3=abnormal, fixed/permanent perfusion defect/scar (stress and rest). A myocardial region was rated to have a perfusion defect in case of a RPS of ≥ 1 and was rated to have normal perfusion in case of a RPS of 0. The investigator's assessment of subject-based specificity of gadobutrol-enhanced CMRI was analyzed with significant CAD defined as maximum stenosis severity of $\geq 70\%$ by QCA, which were secondary analysis. Specificity= true negative/ (true negative + false positive). This additional secondary analysis of specificity was prospective analysis.

End point type	Secondary
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End point timeframe:

0 to 30/40 min post-injection

End point values	Gadobutrol 0.1 mmol/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	266 ^[16]			
Units: Specificity %				
number (confidence interval 95%)	85.0 (80.1 to 89.0)			

Notes:

[16] - FAS with evaluable subjects for this endpoint.

Statistical analyses

Secondary: Presence of a Myocardial Perfusion Defect Indicating Significant CAD per Subject on Gadobutrol-enhanced CMRI Versus Unenhanced Wall Motion CMRI Images – Secondary Analysis of Sensitivity Comparison Based on Investigator's Assessment

End point title	Presence of a Myocardial Perfusion Defect Indicating Significant CAD per Subject on Gadobutrol-enhanced CMRI Versus Unenhanced Wall Motion CMRI Images – Secondary Analysis of Sensitivity Comparison Based on Investigator's Assessment
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End point description:

Investigator's assessment evaluated 6 myocardial regions based on regional perfusion score (RPS), 0=normal; 1=abnormal, reversible perfusion defect (stress); 2=abnormal, mixed perfusion defect (reversible and fixed/permanent components); 3=abnormal, fixed/permanent perfusion defect/scar (stress and rest). A myocardial region was rated to have a perfusion defect in case of a RPS of ≥ 1 and was rated to have normal perfusion in case of a RPS of 0. The investigator's assessment of subject-based sensitivity and specificity of gadobutrol-enhanced CMRI was analyzed with significant CAD defined as maximum stenosis severity of $\geq 50\%$ by QCA, which were secondary analysis. Sensitivity= true positive/ (true positive + false negative).

End point type	Secondary
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End point timeframe:

0 to 30/40 min post-injection

End point values	Gadobutrol 0.1 mmol/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	141 ^[17]			
Units: Sensitivity %				
number (not applicable)				
Gadobutrol-enhanced CMRI	74.3			
Unenhanced CMRI	46.4			

Notes:

[17] - FAS with evaluable subjects for this endpoint.

Attachments (see zip file)	15961_Secondary Outcome 11.pdf
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Statistical analyses

No statistical analyses for this end point

Secondary: Presence of a Myocardial Perfusion Defect Indicating Significant CAD per Subject on Gadobutrol-enhanced CMRI Versus Unenhanced Wall Motion CMRI Images – Additional Secondary Analysis of Sensitivity Comparison Based on Investigator's Assessment

End point title	Presence of a Myocardial Perfusion Defect Indicating Significant CAD per Subject on Gadobutrol-enhanced CMRI Versus Unenhanced Wall Motion CMRI Images – Additional Secondary Analysis of Sensitivity Comparison Based on Investigator's Assessment
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End point description:

Investigator's assessment evaluated 6 myocardial regions based on regional perfusion score (RPS), 0=normal; 1=abnormal, reversible perfusion defect (stress); 2=abnormal, mixed perfusion defect (reversible and fixed/permanent components); 3=abnormal, fixed/permanent perfusion defect/scar

(stress and rest). A myocardial region was rated to have a perfusion defect in case of a RPS of ≥ 1 and was rated to have normal perfusion in case of a RPS of 0. The investigator's assessment of subject-based sensitivity and specificity of gadobutrol-enhanced CMRI was analyzed with significant CAD defined as maximum stenosis severity of $\geq 70\%$ by QCA, which were secondary analysis. Sensitivity= true positive/ (true positive + false negative). This additional secondary analysis of sensitivity was prospective analysis.

End point type	Secondary
End point timeframe:	
0 to 30/40 min post-injection	

End point values	Gadobutrol 0.1 mmol/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	108 ^[18]			
Units: Sensitivity %				
number (not applicable)				
Gadobutrol enhanced : True Positive (Sensitivity)	89.8			
Unenhanced : True Positive (Sensitivity)	57.4			

Notes:

[18] - FAS with evaluable subjects for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Localization of a Myocardial Perfusion Defect to a Coronary Territory on Gadobutrol-Enhanced CMRI – Secondary Analysis of Sensitivity Based on Blinded Readers' and Investigator's Assessments

End point title	Localization of a Myocardial Perfusion Defect to a Coronary Territory on Gadobutrol-Enhanced CMRI – Secondary Analysis of Sensitivity Based on Blinded Readers' and Investigator's Assessments
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End point description:

Sensitivity was calculated coronary territory based, a coronary territory (left anterior descending artery [LAD] / non-LAD / right coronary artery [RCA] / left circumflex artery [LCX]) was rated positive for significant CAD (significant CAD defined as QCA stenosis of $\geq 50\%$), if ≥ 1 myocardial region within the same coronary territory showed a myocardial perfusion defect with a RPS of ≥ 1 . A coronary territory (LAD / non-LAD) was rated negative for significant CAD, if no myocardial region within the respective coronary territory showed a myocardial perfusion defect (RPS 0). Sensitivity was displayed for all 3 blinded readers and the investigator.

End point type	Secondary
End point timeframe:	
0 to 30/40 min post-injection	

End point values	Gadobutrol 0.1 mmol/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	103 ^[19]			
Units: Sensitivity %				
number (not applicable)				
Localization to LAD territory: Reader 1	43.8			
Localization to LAD territory: Reader 2	31.3			
Localization to LAD territory: Reader 3	34.4			
Localization to LAD territory: Investigator	45.3			
Localization to non-LAD territory: Reader 1	84.5			
Localization to non-LAD territory: Reader 2	68.9			
Localization to non-LAD territory: Reader 3	71.8			
Localization to non-LAD territory: Investigator	76.7			
Localization to RCA territory: Reader 1	85.5			
Localization to RCA territory: Reader 2	69.7			
Localization to RCA territory: Reader 3	69.7			
Localization to RCA territory: Investigator	71.1			
Localization to LCX territory: Reader 1	69.4			
Localization to LCX territory: Reader 2	48.6			
Localization to LCX territory: Reader 3	47.2			
Localization to LCX territory: Investigator	55.6			

Notes:

[19] - FAS with evaluable subjects for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Localization of a Myocardial Perfusion Defect to a Coronary Territory on Gadobutrol-enhanced CMRI – Additional Secondary Analysis of Sensitivity Based on Blinded Readers' and Investigator's Assessments

End point title	Localization of a Myocardial Perfusion Defect to a Coronary Territory on Gadobutrol-enhanced CMRI – Additional Secondary Analysis of Sensitivity Based on Blinded Readers' and Investigator's Assessments
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End point description:

Sensitivity was calculated coronary territory based, a coronary territory (LAD / non-LAD / RCA / LCX) was rated positive for significant CAD (significant CAD defined as QCA stenosis of $\geq 70\%$), if ≥ 1 myocardial region within the same coronary territory showed a myocardial perfusion defect with a RPS of ≥ 1 . A coronary territory (LAD / non-LAD) was rated negative for significant CAD, if no myocardial region within the respective coronary territory showed a myocardial perfusion defect (RPS 0). Sensitivity was displayed for all 3 blinded readers and the investigator. This additional secondary analysis of sensitivity was prospective analysis.

End point type	Secondary
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End point timeframe:

0 to 30/40 min post-injection

End point values	Gadobutrol 0.1 mmol/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	87 ^[20]			
Units: Sensitivity %				
number (not applicable)				
Localization to LAD territory: Reader 1	70.6			
Localization to LAD territory: Reader 2	52.9			
Localization to LAD territory: Reader 3	56.9			
Localization to LAD territory: Investigator	68.6			
Localization to non-LAD territory: Reader 1	90.8			
Localization to non-LAD territory: Reader 2	78.2			
Localization to non-LAD territory: Reader 3	80.5			
Localization to non-LAD territory: Investigator	88.5			
Localization to RCA territory: Reader 1	90.3			
Localization to RCA territory: Reader 2	80.6			
Localization to RCA territory: Reader 3	82.3			
Localization to RCA territory: Investigator	83.9			
Localization to LCX territory: Reader 1	77.1			
Localization to LCX territory: Reader 2	50.0			
Localization to LCX territory: Reader 3	50.0			
Localization to LCX territory: Investigator	70.8			

Notes:

[20] - FAS with evaluable subjects for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Localization of a Myocardial Perfusion Defect to a Coronary Territory on Gadobutrol-enhanced CMRI – Secondary Analysis of Specificity Based on Blinded Readers' and Investigator's Assessments

End point title	Localization of a Myocardial Perfusion Defect to a Coronary Territory on Gadobutrol-enhanced CMRI – Secondary Analysis of Specificity Based on Blinded Readers' and Investigator's Assessments
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End point description:

Specificity was calculated coronary territory based, a coronary territory (LAD / non-LAD / RCA / LCX) was rated positive for significant CAD (significant CAD defined as QCA stenosis of $\geq 50\%$), if ≥ 1 myocardial region within the same coronary territory showed a myocardial perfusion defect with a RPS of ≥ 1 . A coronary territory (LAD / non-LAD) was rated negative for significant CAD, if no myocardial region within the respective coronary territory showed a myocardial perfusion defect (RPS 0). Specificity was displayed for all 3 blinded readers and the investigator.

End point type	Secondary
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End point timeframe:
0 to 30/40 min post-injection

End point values	Gadobutrol 0.1 mmol/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	138 ^[21]			
Units: Specificity %				
number (not applicable)				
Localization to LAD territory: Reader 1	92.8			
Localization to LAD territory: Reader 2	97.1			
Localization to LAD territory: Reader 3	93.5			
Localization to LAD territory: Investigator	91.2			
Localization to non-LAD territory: Reader 1	91.9			
Localization to non-LAD territory: Reader 2	97.7			
Localization to non-LAD territory: Reader 3	96.5			
Localization to non-LAD territory: Investigator	95.3			
Localization to RCA territory: Reader 1	82.3			
Localization to RCA territory: Reader 2	91.1			
Localization to RCA territory: Reader 3	87.9			
Localization to RCA territory: Investigator	87.7			
Localization to LCX territory: Reader 1	88.9			
Localization to LCX territory: Reader 2	94.4			
Localization to LCX territory: Reader 3	95.4			
Localization to LCX territory: Investigator	93.5			

Notes:

[21] - FAS with evaluable subjects for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Localization of a Myocardial Perfusion Defect to a Coronary Territory on Gadobutrol-enhanced CMRI – Additional Secondary Analysis of Specificity Based on Blinded Readers' and Investigator's Assessments

End point title	Localization of a Myocardial Perfusion Defect to a Coronary Territory on Gadobutrol-enhanced CMRI – Additional Secondary Analysis of Specificity Based on Blinded Readers' and Investigator's Assessments
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End point description:

Specificity was calculated coronary territory based, a coronary territory (LAD / non-LAD / RCA / LCX) was rated positive for significant CAD (significant CAD defined as QCA stenosis of $\geq 70\%$), if ≥ 1 myocardial region within the same coronary territory showed a myocardial perfusion defect with a RPS of ≥ 1 . A coronary territory (LAD / non-LAD) was rated negative for significant CAD, if no myocardial region within the respective coronary territory showed a myocardial perfusion defect (RPS 0). Specificity was displayed for all 3 blinded readers and the investigator. This additional secondary analysis of

specificity was prospective analysis.

End point type	Secondary
End point timeframe:	
0 to 30/40 min post-injection	

End point values	Gadobutrol 0.1 mmol/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	190 ^[22]			
Units: Specificity %				
number (not applicable)				
Localization to LAD territory: Reader 1	90.0			
Localization to LAD territory: Reader 2	95.3			
Localization to LAD territory: Reader 3	91.1			
Localization to LAD territory: Investigator	86.7			
Localization to non-LAD territory: Reader 1	85.7			
Localization to non-LAD territory: Reader 2	92.9			
Localization to non-LAD territory: Reader 3	91.8			
Localization to non-LAD territory: Investigator	91.8			
Localization to RCA territory: Reader 1	74.8			
Localization to RCA territory: Reader 2	87.1			
Localization to RCA territory: Reader 3	85.0			
Localization to RCA territory: Investigator	85.5			
Localization to LCX territory: Reader 1	78.7			
Localization to LCX territory: Reader 2	85.8			
Localization to LCX territory: Reader 3	87.2			
Localization to LCX territory: Investigator	87.9			

Notes:

[22] - FAS with evaluable subjects for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Detection of Myocardial Perfusion Defect(s) on Gadobutrol-enhanced CMRI in Subject with Significant LMS Stenosis – Based on Blinded Readers' and Investigator's Assessments

End point title	Detection of Myocardial Perfusion Defect(s) on Gadobutrol-enhanced CMRI in Subject with Significant LMS Stenosis – Based on Blinded Readers' and Investigator's Assessments
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End point description:

Sensitivity was calculated for detection of myocardial perfusion defects on gadobutrol-enhanced CMRI in subjects with significant left main stem (LMS) stenosis and the myocardial perfusion defect pattern was described. If ≥ 1 myocardial region showed a myocardial perfusion defect with a RPS of ≥ 1 , subjects will be rated positive for significant CAD (significant CAD defined as QCA stenosis of $\geq 50\%$).

Sensitivity= true positive/ (true positive + false negative). In the below table first, second, third... indicates the subjects.

End point type	Secondary
End point timeframe:	
0 to 30/40 min post-injection	

End point values	Gadobutrol 0.1 mmol/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	9 ^[23]			
Units: Subjects				
Isolated, Reader 1	1			
Single-vessel, Reader 1	2			
2-vessel, Reader 1	1			
3-vessel, Reader 1	3			
Isolated, Reader 2	0			
Single-vessel, Reader 2	2			
2-vessel, Reader 2	1			
3-vessel, Reader 2	3			
Isolated, Reader 3	0			
Single-vessel, Reader 3	2			
2-vessel, Reader 3	1			
3-vessel, Reader 3	3			
Isolated, Investigator	0			
Single-vessel, Investigator	2			
2-vessel, Investigator	2			
3-vessel, Investigator	3			

Notes:

[23] - FAS with evaluable subjects for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Presence/Absence of a MPD Indicating/Excluding Significant CAD in Subjects With Multi Versus Single Vessel Disease Evaluated on Gadobutrol-enhanced CMRI-Secondary Analysis of Sensitivity Based on Blinded Readers' and Investigator's Assessments

End point title	Presence/Absence of a MPD Indicating/Excluding Significant CAD in Subjects With Multi Versus Single Vessel Disease Evaluated on Gadobutrol-enhanced CMRI-Secondary Analysis of Sensitivity Based on Blinded Readers' and Investigator's Assessments
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End point description:

Sensitivity was calculated for detection of myocardial perfusion defects (MPD) on gadobutrol-enhanced CMRI in subjects with single and multi-vessel diseases. If ≥ 1 myocardial region showed a myocardial perfusion defect with a RPS of ≥ 1 , subjects will be rated positive for significant CAD (significant CAD defined as QCA stenosis of $\geq 50\%$). Sensitivity= true positive/ (true positive + false negative).

End point type	Secondary
End point timeframe:	
0 to 30/40 min post-injection	

End point values	Gadobutrol 0.1 mmol/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	75 ^[24]			
Units: Sensitivity %				
number (confidence interval 95%)				
Single-vessel disease - Reader 1	56.1 (42.4 to 69.3)			
Single-vessel disease - Reader 2	50.9 (37.3 to 64.4)			
Single-vessel disease - Reader 3	49.1 (35.6 to 62.7)			
Single-vessel disease - Investigator	57.1 (43.2 to 70.3)			
Multi-vessel disease - Reader 1	92.0 (83.4 to 97.0)			
Multi-vessel disease - Reader 2	76.0 (64.7 to 85.1)			
Multi-vessel disease - Reader 3	76.0 (64.7 to 85.1)			
Multi-vessel disease - Investigator	86.7 (76.8 to 93.4)			

Notes:

[24] - FAS with evaluable subjects for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Presence/Absence of a MPD Indicating/Excluding Significant CAD in Subjects With Multi Vs Single Vessel Disease Evaluated on Gadobutrol-enhanced CMRI-Additional Secondary Analysis of Sensitivity Based on Blinded Readers' and Investigator's Assessments

End point title	Presence/Absence of a MPD Indicating/Excluding Significant CAD in Subjects With Multi Vs Single Vessel Disease Evaluated on Gadobutrol-enhanced CMRI-Additional Secondary Analysis of Sensitivity Based on Blinded Readers' and Investigator's Assessments
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End point description:

Sensitivity was calculated for detection of MPD on gadobutrol-enhanced CMRI in subjects with single and multi-vessel diseases. If ≥ 1 myocardial region showed a myocardial perfusion defect with a RPS of ≥ 1 , subjects will be rated positive for significant CAD (significant CAD defined as QCA stenosis of $\geq 70\%$). Sensitivity= true positive/ (true positive + false negative). This additional secondary analysis of sensitivity was prospective analysis.

End point type	Secondary
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End point timeframe:

0 to 30/40 min post-injection

End point values	Gadobutrol 0.1 mmol/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	68 ^[25]			
Units: Sensitivity %				
number (not applicable)				
Single-vessel disease - Reader 1	85.3			
Single-vessel disease - Reader 2	76.5			
Single-vessel disease - Reader 3	76.5			
Single-vessel disease - Investigator	86.8			
Multi-vessel disease - Reader 1	97.5			
Multi-vessel disease - Reader 2	85.0			
Multi-vessel disease - Reader 3	82.5			
Multi-vessel disease - Investigator	95.0			

Notes:

[25] - FAS with evaluable subjects for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects by Their Lowest Confidence in Diagnosis Obtained on Gadobutrol-enhanced CMRI and Unenhanced Wall Motion CMRI – Based on Blinded Readers' and Investigator's Assessments

End point title	Percentage of Subjects by Their Lowest Confidence in Diagnosis Obtained on Gadobutrol-enhanced CMRI and Unenhanced Wall Motion CMRI – Based on Blinded Readers' and Investigator's Assessments
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End point description:

Score for confidence in diagnosis (not confident, somewhat confident, and confident) was described descriptively for each of the 6 myocardial regions. The frequency over the worst confidence in diagnosis obtained within a subject was displayed. All these analyses were done separately for gadobutrol-enhanced CMRI and unenhanced wall motion CMRI.

End point type	Secondary
End point timeframe:	0 to 30/40 min post-injection

End point values	Gadobutrol 0.1 mmol/kg body weight			
Subject group type	Reporting group			
Number of subjects analysed	376 ^[26]			
Units: Percentage of subjects				
number (not applicable)				
Unenhanced- Reader 1- Confident	74.7			
Unenhanced- Reader 1- Somewhat confident	15.7			
Unenhanced- Reader 1- Not confident	9.6			
Unenhanced- Reader 1- Missing	0			
Unenhanced- Reader 2- Confident	86.4			

Unenhanced- Reader 2- Somewhat confident	12.8			
Unenhanced- Reader 2- Not confident	0.8			
Unenhanced- Reader 2- Missing	0			
Unenhanced- Reader 3- Confident	63.0			
Unenhanced- Reader 3- Somewhat confident	36.4			
Unenhanced- Reader 3- Not confident	0.5			
Unenhanced- Reader 3- Missing	0			
Unenhanced- Investigator - Confident	91.2			
Unenhanced- Investigator - Somewhat confident	8.2			
Unenhanced- Investigator - Not confident	0.3			
Unenhanced- Investigator- Missing	0.3			
Gadobutrolenhanced - Reader 1- Confident	88.3			
Gadobutrolenhanced - Reader 1- Somewhat confident	8.2			
Gadobutrolenhanced - Reader 1- Not confident	3.5			
Gadobutrolenhanced - Reader 1- Missing	0			
Gadobutrolenhanced - Reader 2- Confident	75.5			
Gadobutrolenhanced - Reader 2- Somewhat confident	23.4			
Gadobutrolenhanced - Reader 2- Not confident	1.1			
Gadobutrolenhanced - Reader 2- Missing	0			
Gadobutrolenhanced - Reader 3- Confident	74.7			
Gadobutrolenhanced - Reader 3- Somewhat confident	23.7			
Gadobutrolenhanced - Reader 3- Not confident	1.6			
Gadobutrolenhanced - Reader 3- Missing	0			
Gadobutrolenhanced - Investigator - Confident	79.0			
Gadobutrolenhanced-Investigator- Somewhat confident	19.1			
Gadobutrolenhanced - Investigator - Not confident	1.3			
Gadobutrolenhanced - Investigator- Missing	0.5			

Notes:

[26] - FAS with evaluable subjects for this endpoint.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time of gadobutrol injection until 24 ± 6 hours follow-up

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	Gadobutrol 0.1 mmol/kg body weight
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Reporting group description:

Subjects received gadobutrol at the total approved standard dose of 0.1 mmol/kg BW in 2 separate bolus injections: 0.05 mmol/kg BW at peak pharmacologic stress and 0.05 mmol/kg BW at rest via a power injector.

Serious adverse events	Gadobutrol 0.1 mmol/kg body weight		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 426 (0.23%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 426 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Gadobutrol 0.1 mmol/kg body weight		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 426 (11.03%)		
Investigations			
Blood pressure decreased			
subjects affected / exposed	2 / 426 (0.47%)		
occurrences (all)	2		
Oxygen saturation decreased			

subjects affected / exposed	1 / 426 (0.23%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 426 (0.23%)		
occurrences (all)	1		
Hypertensive crisis			
subjects affected / exposed	2 / 426 (0.47%)		
occurrences (all)	2		
Microangiopathy			
subjects affected / exposed	1 / 426 (0.23%)		
occurrences (all)	1		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	5 / 426 (1.17%)		
occurrences (all)	6		
Bradycardia			
subjects affected / exposed	1 / 426 (0.23%)		
occurrences (all)	1		
Extrasystoles			
subjects affected / exposed	1 / 426 (0.23%)		
occurrences (all)	1		
Palpitations			
subjects affected / exposed	1 / 426 (0.23%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 426 (0.70%)		
occurrences (all)	3		
Head discomfort			
subjects affected / exposed	2 / 426 (0.47%)		
occurrences (all)	2		
Headache			
subjects affected / exposed	8 / 426 (1.88%)		
occurrences (all)	8		
Paraesthesia			

subjects affected / exposed	2 / 426 (0.47%)		
occurrences (all)	2		
Presyncope			
subjects affected / exposed	1 / 426 (0.23%)		
occurrences (all)	1		
Sciatica			
subjects affected / exposed	1 / 426 (0.23%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	1 / 426 (0.23%)		
occurrences (all)	1		
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	10 / 426 (2.35%)		
occurrences (all)	11		
Chest pain			
subjects affected / exposed	2 / 426 (0.47%)		
occurrences (all)	2		
Feeling hot			
subjects affected / exposed	5 / 426 (1.17%)		
occurrences (all)	5		
Pain			
subjects affected / exposed	1 / 426 (0.23%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 426 (0.23%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	1 / 426 (0.23%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	1 / 426 (0.23%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	1 / 426 (0.23%) 1		
Dyspnoea subjects affected / exposed occurrences (all)	4 / 426 (0.94%) 4		
Dysphonia subjects affected / exposed occurrences (all)	2 / 426 (0.47%) 2		
Hyperventilation subjects affected / exposed occurrences (all)	1 / 426 (0.23%) 1		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	1 / 426 (0.23%) 1		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	1 / 426 (0.23%) 1		
Panic reaction subjects affected / exposed occurrences (all)	1 / 426 (0.23%) 1		
Sleep disorder subjects affected / exposed occurrences (all)	1 / 426 (0.23%) 1		
Musculoskeletal and connective tissue disorders Musculoskeletal pain subjects affected / exposed occurrences (all)	2 / 426 (0.47%) 2		
Pain in extremity subjects affected / exposed occurrences (all)	2 / 426 (0.47%) 2		
Muscle tightness subjects affected / exposed occurrences (all)	2 / 426 (0.47%) 2		

Musculoskeletal discomfort subjects affected / exposed	1 / 426 (0.23%)		
occurrences (all)	1		
Limb discomfort subjects affected / exposed	1 / 426 (0.23%)		
occurrences (all)	1		

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