Clinical trial results:
LowEr Administered Dose with highEr Relaxivity: Gadovist vs Dotarem (LEADER 75)

Summary

EudraCT number	2018-000690-78
Trial protocol	FR GB IT
Global end of trial date	26 May 2020

Results information

Result version number	v1 (current)
This version publication date	05 June 2021
First version publication date	05 June 2021

Trial information

Trial identification

Sponsor protocol code	BAY86-4875/19773

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03602339
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser Wilhelm Allee, 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	26 May 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 May 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to demonstrate non-inferiority of gadobutrol-enhanced central nervous system (CNS) imaging (0.075 mmol/kg body weight [BW]) compared to gadoterate-enhanced CNS imaging (0.1 mmol/kg BW) based on the blinded read for 3 lesion visualization parameters (degree of lesion contrast enhancement, assessment of lesion border delineation, internal morphology of lesions).

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. Only after the subject voluntarily signed the informed consent form was he/she able to enter the study. If the subject was not capable of providing a signature, an oral statement of consent could have been given in the presence of a witness. Each subject was assured of the right to 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	14 November 2018
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	France: 16
Country: Number of subjects enrolled	Germany: 33
Country: Number of subjects enrolled	Italy: 39
Country: Number of subjects enrolled	Korea, Republic of: 23
Country: Number of subjects enrolled	Switzerland: 15
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	United States: 29
Worldwide total number of subjects	157
EEA total number of subjects	88

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)	94
From 65 to 84 years	62
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Study was conducted at multiple centers in 7 countries between 14 November 2018 (first subject first visit) and 13 March 2020 (last subject last visit).

Pre-assignment

Screening details:

From 166 subjects screened, 9 subjects were sceening failure and a total of 157 subjects were enrolled, 157 received study drug for period 1 however 142 received study drug for period 2.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Gadoterate 0.1 mmol/kg BW-Gadobutrol 0.075 mmol/kg BW

Arm description:

Subjects received gadoterate at the standard dose of 0.1 mmol/kg body weight (BW) by single intravenous (IV) injection in period 1 and gadobutrol at a dose of 0.075 mmol/kg BW by single IV injection in period 2.

Arm type	Experimental
Investigational medicinal product name	Gadoterate
Investigational medicinal product code	
Other name	Dotarem, Clariscan
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects administrered gadoterate at the dose of 0.1 mmol per kg body weight by single IV injection.

Investigational medicinal product name	Gadobutrol
Investigational medicinal product code	BAY86-4875
Other name	Gadovist, Gadavist
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects administered gadobutrol at the dose of 0.075 mmol per kg body weight by single IV (intravenous) injection.

Number of subjects in period 1	Gadoterate 0.1 mmol/kg BW-Gadobutrol 0.075 mmol/kg BW
Started	157
Completed period 1 (Gadoterate)	155
Started period 2 (Gadobutrol)	142
Completed	142
Not completed	15

Consent withdrawn by subject	9
Physician decision	2
Other reason	4

Baseline characteristics

Reporting groups	
Reporting group title	Gadoterate 0.1 mmol/kg BW-Gadobutrol 0.075 mmol/kg BW
Reporting group description:	
Subjects received gadoterate at the standard dose of 0.1 mmol/kg body weight (BW) by single intravenous (IV) injection in period 1 and gadobutrol at a dose of 0.075 mmol/kg BW by single IV injection in period 2.	

Reporting group values	Gadoterate 0.1 mmol/kg BW-Gadobutrol 0.075 mmol/kg BW	Total	
Number of subjects	157	157	
Age Categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	94	94	
From 65-84 years	62	62	
85 years and over	1	1	
Age Continuous Units: years			
arithmetic mean	58.9		
standard deviation	± 13.3	-	
Gender Categorical Units: Subjects			
Female	71	71	
Male	86	86	
Race Units: Subjects			
Multiple	0	0	
White	109	109	
Black or African American	2	2	
Asian	27	27	
American Indian or Alaska Native	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Not Reported	19	19	
Ethnicity Units: Subjects			
Not Hispanic or Latino	106	106	
Hispanic or Latino	32	32	
Not reported	19	19	

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

Subject analysis set description:

All subjects for whom electronic case report form (eCRF) entries and images are available for unenhanced MRI, combined unenhanced and gadobutrol enhanced MRI, and combined unenhanced and gadoterate enhanced MRI.

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

Subject analysis set description:

The SAF included all enrolled subjects who received at least 1 study treatment administration.

Subject analysis set title	Gadoterate 0.1 mmol/kg BW
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received gadoterate at the standard dose of 0.1 mmol/kg body weight (BW) by single intravenous (IV) injection.

Subject analysis set title	Gadobutrol 0.075 mmol/kg BW
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received gadobutrol at a dose of 0.075 mmol/kg BW by single intravenous (IV) injection.

Reporting group values	Full analysis set (FAS)	Safety analysis set (SAF)	Gadoterate 0.1 mmol/kg BW
Number of subjects	141	157	156
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	88	94	93
From 65-84 years	52	62	62
85 years and over	1	1	1
Age Continuous Units: years arithmetic mean standard deviation	±	±	±
Gender Categorical Units: Subjects			
Female Male			
Race Units: Subjects			
Multiple White Black or African American Asian American Indian or Alaska Native Native Hawaiian or Other Pacific Islander			

Not Reported			
Ethnicity Units: Subjects			
Not Hispanic or Latino Hispanic or Latino Not reported			

Reporting group values	Gadobutrol 0.075 mmol/kg BW		
Number of subjects	143		
Age Categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	90		
From 65-84 years	52		
85 years and over	1		
Age Continuous Units: years			
arithmetic mean			
standard deviation	±		
Gender Categorical Units: Subjects			
Female			
Male			
Race Units: Subjects			
Multiple			
White			
Black or African American			
Asian			
American Indian or Alaska Native			
Native Hawaiian or Other Pacific Islander			
Not Reported			
Ethnicity Units: Subjects			
Not Hispanic or Latino			
Hispanic or Latino			
Not reported			

End points

End points reporting groups

Reporting group title	Gadoterate 0.1 mmol/kg BW-Gadobutrol 0.075 mmol/kg BW
Reporting group description:	
Subjects received gadoterate at the standard dose of 0.1 mmol/kg body weight (BW) by single intravenous (IV) injection in period 1 and gadobutrol at a dose of 0.075 mmol/kg BW by single IV injection in period 2.	
Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects for whom electronic case report form (eCRF) entries and images are available for unenhanced MRI, combined unenhanced and gadobutrol enhanced MRI, and combined unenhanced and gadoterate enhanced MRI.	
Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
The SAF included all enrolled subjects who received at least 1 study treatment administration.	
Subject analysis set title	Gadoterate 0.1 mmol/kg BW
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects received gadoterate at the standard dose of 0.1 mmol/kg body weight (BW) by single intravenous (IV) injection.	
Subject analysis set title	Gadobutrol 0.075 mmol/kg BW
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects received gadobutrol at a dose of 0.075 mmol/kg BW by single intravenous (IV) injection.	

Primary: Degree of lesion contrast enhancement

End point title	Degree of lesion contrast enhancement
End point description:	
Degree of lesion contrast enhancement is assessed by 3 blinded Readers (Full Analysis Set). Results are presented as the Average Reader score. Blinded Readers scored up to 5 lesions using image sequences and a 4-point scale (1 - No = Lesion not enhanced; 2 - Moderate = Lesion weakly enhanced; 3 - Good = Lesion clearly enhanced; 4 - Excellent = Lesion clearly and brightly enhanced).	
End point type	Primary
End point timeframe:	
Up to 20 days	

End point values	Gadoterate 0.1 mmol/kg BW	Gadobutrol 0.075 mmol/kg BW		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	141	141		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Unenhanced	0.884 (± 0.252)	0.863 (± 0.201)		
Combined unenhanced/enhanced	3.007 (± 0.813)	2.979 (± 0.837)		

Statistical analyses

Statistical analysis title	Degree of lesion contrast enhancement
Statistical analysis description:	
Difference (gadobutrol minus unenhanced) - (gadoterate minus unenhanced)	
Comparison groups	Gadoterate 0.1 mmol/kg BW v Gadobutrol 0.075 mmol/kg BW
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.0001
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	0.455
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.347
upper limit	0.562

Notes:

[1] - The score to evaluate the non-inferiority is calculated for each subject as (combined unenhanced/gadobutrol-enhanced - unenhanced) - 0.8*(combined unenhanced/gadoterate-enhanced - unenhanced). The non-inferiority for gadobutrol is achieved if the one-sided p-value for "H0: (gadobutrol minus unenhanced) - 0.8*(gadoterate minus unenhanced) ≤ 0" is lower than 0.025.

Primary: Lesion border delineation

End point title	Lesion border delineation
End point description:	
Lesion border delineation is assessed by 3 blinded Readers (Full Analysis Set). Results are presented as the Average Reader score. Blinded Readers scored the delineation of up to 5 lesions using image sequences and a 4-point scale (1 - None = No or unclear delineation; 2 - Moderate = Partial delineation; 3 - Good = Almost clear, but incomplete delineation; 4 - Excellent = Clear and complete delineation).	
End point type	Primary
End point timeframe:	
Up to 20 days	

End point values	Gadoterate 0.1 mmol/kg BW	Gadobutrol 0.075 mmol/kg BW		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	141	141		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Unenhanced	2.279 (± 0.820)	2.278 (± 0.864)		
Combined unenhanced/enhanced	3.096 (± 0.781)	3.099 (± 0.828)		

Statistical analyses

Statistical analysis title	Lesion border delineation

Statistical analysis description:

Difference (gadobutrol minus unenhanced) - (gadoterate minus unenhanced)

Comparison groups	Gadoterate 0.1 mmol/kg BW v Gadobutrol 0.075 mmol/kg BW
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
P-value	= 0.0151
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.017
upper limit	0.342

Notes:

[2] - The score to evaluate the non-inferiority is calculated for each subject as (combined unenhanced/gadobutrol-enhanced - unenhanced) - 0.8*(combined unenhanced/gadoterate-enhanced - unenhanced). The non-inferiority for gadobutrol is achieved if the one-sided p-value for "H0: (gadobutrol minus unenhanced) - 0.8*(gadoterate minus unenhanced) ≤ 0" is lower than 0.025.

Primary: Lesion internal morphology

End point title	Lesion internal morphology

End point description:

Lesion internal morphology is assessed by 3 blinded Readers (Full Analysis Set). Results are presented as the Average Reader score. Blinded Readers scored the structure and internal morphology of up to 5 lesions using image sequences and a 3-point scale (1 - Poor = Poor visibility; 2 - Moderate = Partial visibility; 3 - Good = Sufficient visibility)

End point type	Primary

End point timeframe:

Up to 20 days

End point values	Gadoterate 0.1 mmol/kg BW	Gadobutrol 0.075 mmol/kg BW		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	141	141		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Unenhanced	1.835 (± 0.620)	1.823 (± 0.589)		
Combined unenhanced/enhanced	2.503 (± 0.496)	2.484 (± 0.545)		

Statistical analyses

Statistical analysis title	Lesion internal morphology
Statistical analysis description:	
Difference (gadobutrol minus unenhanced) - (gadoterate minus unenhanced)	
Comparison groups	Gadoterate 0.1 mmol/kg BW v Gadobutrol 0.075 mmol/kg BW
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	= 0.01
Method	Paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.024
upper limit	0.275

Notes:

[3] - The score to evaluate the non-inferiority is calculated for each subject as (combined unenhanced/gadobutrol-enhanced - unenhanced) - 0.8*(combined unenhanced/gadoterate-enhanced - unenhanced). The non-inferiority for gadobutrol is achieved if the one-sided p-value for "H0: (gadobutrol minus unenhanced) - 0.8*(gadoterate minus unenhanced) ≤ 0" is lower than 0.025.

Secondary: Number of lesions identified

End point title	Number of lesions identified
End point description:	
Number of lesions identified (up to 10) detected by 3 blinded Readers. The mean (SD) number lesions in the Average Reader for gadobutrol and gadoterate in the Full Analysis Set was reported below.	
End point type	Secondary
End point timeframe:	
Up to 20 days	

End point values	Gadoterate 0.1 mmol/kg BW	Gadobutrol 0.075 mmol/kg BW		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	141[4]	141[5]		
Units: Number of lesions identified				
arithmetic mean (standard deviation)	2.064 (± 2.254)	2.137 (± 2.327)		

Notes:

[4] - combined unenhanced/enhanced

[5] - combined unenhanced/enhanced

Statistical analyses

Statistical analysis title	Number of lesions identified
Statistical analysis description:	
Difference (Gadobutrol - Gadoterate)	
Comparison groups	Gadoterate 0.1 mmol/kg BW v Gadobutrol 0.075 mmol/kg BW
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
Parameter estimate	Mean difference (final values)
Point estimate	0.073
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.176

Notes:

[6] - Non-inferiority margin is defined as 0.35. If the lower limit of the 95% CI is >-0.35, then non-inferiority is achieved.

Secondary: Detection of malignant disease

End point title	Detection of malignant disease

End point description:

The 3 blinded Readers had to evaluate if the diagnosis resulting from the combined images was malignant disease or not. Each blinded Reader provided a malignant yes/no response. This was compared to the final diagnosis provided by the Investigator. The majority of Readers (2 or 3 Readers agree) was used to calculate sensitivity, specificity, and accuracy - eg. Final Diagnosis - Malignant (Reader 1-yes, Reader 2-no, Reader 3-yes --- Majority Reader yes) - this would be a match for sensitivity.
The percentage of sensitivity, specificity, and accuracy of detection of malignant disease detected by 3 blinded Readers, gadobutrol versus gadoterate (Full Analysis Set) is reported below for Majority Readers.

End point type	Secondary

End point timeframe:

Up to 20 days

End point values	Gadoterate 0.1 mmol/kg BW	Gadobutrol 0.075 mmol/kg BW		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	141	141		
Units: Percentage (%)				
number (not applicable)				
Accuracy	70.2	70.2		
Sensitivity	58.7	58.7		
Specificity	91.8	91.8		

Statistical analyses

Statistical analysis title	Detection of malignant disease
Statistical analysis description:	
Accuracy Difference (Gadobutrol - Gadoterate)	
Comparison groups	Gadoterate 0.1 mmol/kg BW v Gadobutrol 0.075 mmol/kg BW
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
Parameter estimate	Difference (Gadobutrol - Gadoterate)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	3.4

Notes:

[7] - Non-inferiority margin = 10%, if the lower limit of the confidence interval > -10%, then non-inferiority is achieved. The 95% confidence intervals are based on McNemar's test.

Statistical analysis title	Detection of malignant disease
Statistical analysis description:	
Sensitivity Difference (Gadobutrol - Gadoterate)	
Comparison groups	Gadoterate 0.1 mmol/kg BW v Gadobutrol 0.075 mmol/kg BW
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	non-inferiority[8]
Parameter estimate	Difference (Gadobutrol - Gadoterate)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.22
upper limit	5.22

Notes:

[8] - Non-inferiority margin = 10%, if the lower limit of the confidence interval > -10%, then non-inferiority is achieved. The 95% confidence intervals are based on McNemar's test.

Statistical analysis title	Detection of malignant disease
Statistical analysis description:	
Specificity Difference (Gadobutrol - Gadoterate)	
Comparison groups	Gadoterate 0.1 mmol/kg BW v Gadobutrol 0.075 mmol/kg BW
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	non-inferiority[9]
Parameter estimate	Difference (Gadobutrol - Gadoterate)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Notes:

[9] - Non-inferiority margin = 10%, if the lower limit of the confidence interval > -10%, then non-inferiority is achieved. The 95% confidence intervals are based on McNemar's test. No continuity correction for calculation of the confidence interval was included. Zero cells lead to degenerated confidence interval.

Secondary: Confidence in diagnosis

End point title	Confidence in diagnosis

End point description:

Diagnostic confidence detected by 3 blinded Readers, gadobutrol vs gadoterate (Full Analysis Set). Blinded Readers rated their confidence in diagnosis according to a 4-point scale (1 - Not confident; 2 - Somewhat confident; 3 - Confident; 4 - Very confident). Results for the Average Reader are reported below.

End point type	Secondary

End point timeframe:

Up to 20 days

End point values	Gadoterate 0.1 mmol/kg BW	Gadobutrol 0.075 mmol/kg BW		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	141[10]	141[11]		
Units: Scores on a scale				
arithmetic mean (standard deviation)	3.272 (± 0.567)	3.348 (± 0.591)		

Notes:

[10] - combined unenhanced/enhanced

[11] - combined unenhanced/enhanced

Statistical analyses

Statistical analysis title	Diagnostic confidence
Statistical analysis description:	
Difference (Gadobutrol - Gadoterate)	
Comparison groups	Gadoterate 0.1 mmol/kg BW v Gadobutrol 0.075 mmol/kg BW
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	0.076
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.011
upper limit	0.14

Secondary: Image quality

End point title	Image quality

End point description:

Comparison of image quality between gadobutrol and gadoterate detected by 3 blinded Readers (Full Analysis Set). Blinded Readers assessed the image quality of gadobutrol- and gadoterate-enhanced images (randomly assigned as left [L] and right [R] image positions) according to a 5-point scale (1- Image R is worse; 2 - Image R is slightly worse; 3- Image R is similar; 4 - Image R is slightly better; 5 - Image R is better). After unblinding of data, the above codes were translated into the following scale: -2 = Gadobutrol image set is worse ; -1 = Gadobutrol image set is slightly worse ; 0 = Image sets are the same ; 1 = Gadobutrol image set is slightly better; 2 = Gadobutrol image set is better. Results for the Average Reader are reported below. Statistical Analysis: two sided 95%-CI for the Average Reader is [-0.10;0.11], p= 0.9149 (Wilcoxon signed-rank test).

End point type	Secondary

End point timeframe:

Up to 20 days

End point values	Gadoterate 0.1 mmol/kg BW-Gadobutrol 0.075 mmol/kg BW			
Subject group type	Reporting group			
Number of subjects analysed	141			
Units: Scores on a scale				
arithmetic mean (standard deviation)	0.00 (± 0.61)			

Statistical analyses

No statistical analyses for this end point

Secondary: Contrast enhancement utilizing an exploratory overall contrast enhancement estimation algorithm

End point title	Contrast enhancement utilizing an exploratory overall contrast enhancement estimation algorithm

End point description:

Comparison of contrast enhancement utilizing an overall contrast enhancement estimation algorithm (Full Analysis Set). The exploratory algorithm analyzed the overall enhancement by comparing the axial T1w (longitudinal relaxation time-weighted) enhanced images to the T1w unenhanced images.

End point type	Secondary

End point timeframe:

Up to 20 days

End point values	Gadoterate 0.1 mmol/kg BW	Gadobutrol 0.075 mmol/kg BW		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	88	89		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Relative score	0.19894 (± 0.09905)	0.18564 (± 0.09028)		

Full image score	0.05604 (± 0.08581)	0.05573 (± 0.08036)		
Dice score	0.92984 (± 0.04293)	0.92991 (± 0.05216)		

Statistical analyses

Statistical analysis title	Overall contrast enhancement estimation algorithm
Statistical analysis description: Difference (Gadobutrol-Gadoterate) for Relative score	
Comparison groups	Gadoterate 0.1 mmol/kg BW v Gadobutrol 0.075 mmol/kg BW
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-0.01968
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03491
upper limit	-0.00445

Statistical analysis title	Overall contrast enhancement estimation algorithm
Statistical analysis description: Difference (Gadobutrol-Gadoterate) for Full image score	
Comparison groups	Gadoterate 0.1 mmol/kg BW v Gadobutrol 0.075 mmol/kg BW
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	0.00586
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.00589
upper limit	0.01762

Statistical analysis title	Overall contrast enhancement estimation algorithm
Statistical analysis description: Difference (Gadobutrol-Gadoterate) for Dice score	
Comparison groups	Gadoterate 0.1 mmol/kg BW v Gadobutrol 0.075 mmol/kg BW

Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	0.00139
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.00471
upper limit	0.00749

Secondary: Number of subjects with treatment-emergent adverse events

End point title	Number of subjects with treatment-emergent adverse events

End point description:

Number of subjects with treatment-emergent adverse events (TEAEs) (Safety Analysis Set). TEAEs are defined as any AEs that increase in intensity or that are newly developed during the TE period for Study Period 1 or Study Period 2, where TE period for Study Period 1 goes from the first study drug administration in Study Period 1 to 24 hours post-injection, and TE period for Study Period 2 from the first study drug administration in Study Period 2 to 24 hours post-injection.

End point type	Secondary

End point timeframe:

From the first study drug administration up to 24 hours post injection

End point values	Gadoterate 0.1 mmol/kg BW	Gadobutrol 0.075 mmol/kg BW		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	156	143		
Units: Participants				
Any TEAE	4	1		
Any study drug-related TEAE	2	1		
Any TEAE related to the protocol	0	0		
Any TEAE leading to discontinuation	0	0		
Any TESAE	0	0		
TEAE with outcome death	0	0		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Comparison of degree of lesion contrast enhancement detected by blinded Readers for combined image sets - Equivalence Test

End point title	Comparison of degree of lesion contrast enhancement detected by blinded Readers for combined image sets - Equivalence Test

End point description:

Comparison of degree of lesion contrast enhancement detected by blinded Readers for combined image

sets - Equivalence Test (Full Analysis Set). Results are presented as the average Reader score.
Blinded Readers scored up to 5 lesions using image sequences and a 4-point scale (1 - No = Lesion not enhanced; 2 - Moderate = Lesion weakly enhanced; 3 - Good = Lesion clearly enhanced; 4 - Excellent = Lesion clearly and brightly enhanced).

End point type	Post-hoc

End point timeframe:

Up to 20 days

End point values	Gadoterate 0.1 mmol/kg BW	Gadobutrol 0.075 mmol/kg BW		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	141	141		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Combined unenhanced/enhanced	3.007 (± 0.813)	2.979 (± 0.837)		

Statistical analyses

Statistical analysis title	Equivalence Test

Statistical analysis description:

An equivalence test was calculated using the two one-sided t-tests (TOST) procedure with null hypotheses
H01: (gadobutrol - gadoterate) ≤ -0.05 * (gadoterate), and
H02: (gadobutrol - gadoterate) ≥ +0.05 * (gadoterate).

Comparison groups	Gadoterate 0.1 mmol/kg BW v Gadobutrol 0.075 mmol/kg BW
Number of subjects included in analysis	282
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.0049 [12]
Method	Two one-sided t-tests (TOST)

Notes:

[12] - The overall p-value was calculated as max(p1, p2) where p1 and p2 are the results of null hypotheses H01 and H02 respectively.

Post-hoc: Comparison of border delineation detected by blinded Readers for combined image sets - Equivalence Test

End point title	Comparison of border delineation detected by blinded Readers for combined image sets - Equivalence Test

End point description:

Comparison of border delineation detected by blinded Readers for combined image sets - Equivalence Test (Full Analysis Set). Results are presented as the Average Reader score.
Blinded Readers scored the delineation of up to 5 lesions using image sequences and a 4-point scale (1 - None = No or unclear delineation; 2 - Moderate = Partial delineation; 3 - Good = Almost clear, but incomplete delineation; 4 - Excellent = Clear and complete delineation).

End point type	Post-hoc

End point timeframe:

Up to 20 days

End point values	Gadoterate 0.1 mmol/kg BW	Gadobutrol 0.075 mmol/kg BW		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	141	141		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Combined unenhanced/enhanced	3.096 (± 0.781)	3.099 (± 0.828)		

Statistical analyses

Statistical analysis title	Equivalence Test

Statistical analysis description:

An equivalence test was calculated using the two one-sided t-tests (TOST) procedure with null hypotheses
H01: (gadobutrol - gadoterate) ≤ -0.05 * (gadoterate) and
H02: (gadobutrol - gadoterate) ≥ +0.05 * (gadoterate).

Comparison groups	Gadoterate 0.1 mmol/kg BW v Gadobutrol 0.075 mmol/kg BW
Number of subjects included in analysis	282
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.0013 [13]
Method	Two one-sided t-tests (TOST)

Notes:

[13] - The overall p-value was calculated as max(p1, p2) where p1 and p2 are the results of null hypotheses H01 and H02 respectively.

Post-hoc: Comparison of internal morphology detected by blinded Readers for combined image sets - Equivalence Test

End point title	Comparison of internal morphology detected by blinded Readers for combined image sets - Equivalence Test

End point description:

Comparison of internal morphology detected by blinded Readers for combined image sets - Equivalence Test (Full Analysis Set). Results are presented as the average Reader score.
Blinded Readers scored the structure and internal morphology of up to 5 lesions using image sequences and a 3-point scale (1 - Poor = Poor visibility; 2 - Moderate = Partial visibility; 3 - Good = Sufficient visibility).

End point type	Post-hoc

End point timeframe:

Up to 20 days

End point values	Gadoterate 0.1 mmol/kg BW	Gadobutrol 0.075 mmol/kg BW		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	141	141		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Combined unenhanced/enhanced	2.503 (± 0.496)	2.484 (± 0.545)		

Statistical analyses

Statistical analysis title	Equivalence Test

Statistical analysis description:

An equivalence test was calculated using the two one-sided t-tests (TOST) procedure with null hypotheses
H01: (gadobutrol - gadoterate) ≤ -0.05 * (gadoterate) and
H02: (gadobutrol - gadoterate) ≥ +0.05 * (gadoterate).

Comparison groups	Gadoterate 0.1 mmol/kg BW v Gadobutrol 0.075 mmol/kg BW
Number of subjects included in analysis	282
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.0065 [14]
Method	Two one-sided t-tests (TOST)

Notes:

[14] - The overall p-value was calculated as max(p1, p2) where p1 and p2 are the results of null hypotheses H01 and H02 respectively.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first study drug administration up to 24 hours post injection

Adverse event reporting additional description:

1 out of 157 subjects received gadobutrol instead of gadoterate in study period 1. This subject dropped out. 156 subjects received gadoterate and 143 subjects received gadobutrol. 142 subjects received both doses. Of the 142, 1 subject's dose extravasated and could not be adequately imaged and was removed from the efficacy population.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Gadoterate 0.1 mmol/kg BW

Reporting group description:

Participants received gadoterate at the standard dose of 0.1 mmol/kg body weight (BW) by single intravenous (IV) injection.

Reporting group title	Gadobutrol 0.075 mmol/kg BW

Reporting group description:

Participants received gadobutrol at a dose of 0.075 mmol/kg BW by single IV injection.

Serious adverse events	Gadoterate 0.1 mmol/kg BW	Gadobutrol 0.075 mmol/kg BW	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 156 (0.00%)	0 / 143 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Gadoterate 0.1 mmol/kg BW	Gadobutrol 0.075 mmol/kg BW	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 156 (2.56%)	1 / 143 (0.70%)	
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	0 / 156 (0.00%)	1 / 143 (0.70%)	
occurrences (all)	0	1	
Eye disorders			

Visual impairment subjects affected / exposed occurrences (all)	1 / 156 (0.64%) 1	0 / 143 (0.00%) 0	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	1 / 156 (0.64%) 1	0 / 143 (0.00%) 0	
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) Urticaria subjects affected / exposed occurrences (all)	1 / 156 (0.64%) 1 1 / 156 (0.64%) 1	0 / 143 (0.00%) 0 0 / 143 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 March 2019	The following is the overview of changes to the study as per Amendment 1: - Changes in MRI field strength were made to permit either the previously specified 1.5T or the newer 3.0T field strength and to provide greater flexibility based on the study center's available MRI equipment. - Recommended Pulse sequences were added (T1w spin echo/fast spin echo acquisition should be performed in 2D mode). - Quantitative contrast enhancement estimation, "up to 10 lesions" was removed since the estimation algorithm was not applied to a single lesion or up to 10 lesions, as it was a result of software evaluation for a complete image. - Confidence in diagnosis was modified to clarify that frequency tables for confidence responses were not to be constructed for unenhanced MRI alone. - Analysis of safety variables: Reference to McNemar's tests and/or related CIs were removed, reflecting a changed analysis plan.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported