EU Clinical Trials Register

Clinical trial results:
Open-label, multi-center, two-stage, age stratified, pharmacokinetic, safety, and efficacy study in children 2 months to < 2 years of age undergoing Magnevist Injection enhanced MRI

Summary

EudraCT number	2009-013081-17
Trial protocol	DE
Global end of trial date	09 September 2010

Results information

Result version number	v2 (current)
This version publication date	03 September 2016
First version publication date	25 July 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	BAY86-6661/91784

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00937391
WHO universal trial number (UTN)	-
Other trial identifiers	Study number: 312046

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 December 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 September 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. To determine the optimal efficacious dose [0.05 millimoles per kilogram body weight (mmol/kg BW) or 0.1 mmol/kg BW) of Magnevist injection in Stage 1.
2. To evaluate pharmacokinetics (PK) of Magnevist injection at the optimal efficacious dose from Stage 1 in this population in Stage 2.

Protection of trial subjects:

To take into account that this clinical trial enrolled children, the following specific ethical considerations and provisions were followed:
1. Minimized as far as feasible the number of pediatric study subjects and examinations to allow for meaningful assessment of PK parameters (the primary objective of this trial)
2. Employed population based PK approach allowing sparse sampling for PK analysis [according to International Conference on Harmonization Efficacy module 11 (ICH E11)]
3. Employed for PK measurements, a sensitive analytical assay requiring only small blood samples and a laboratory experienced with handling small volume samples for safety (in accord with ICH E11)
4. Drew volumes of blood as low as feasible for safety and PK investigations [that is, total sample volumes for safety and PK assessments about 4 to 5 milliliter (mL)]
5. Used indwelling catheters rather than multiple venous punctures whenever feasible and considered topical anesthesia where catheter was placed
6. Minimized, in general, any discomfort, inconvenience, pain, fright, and time of separation from parents or familiar surroundings
7. Provided a child friendly and familiar environment
8. Ensured that only Investigators and staff with pediatric experience participated in this study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 January 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 48
Country: Number of subjects enrolled	United States: 6
Worldwide total number of subjects	54
EEA total number of subjects	48

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)	54
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The date of the first subject, first visit was 21 January 2010. The date of the last subject, last visit was 09 September 2010. The date of the Blinded Read for Stage 1 was 27 April 2010. The date of the Blinded Read for Stage 2 was 08 September 2010.

Pre-assignment

Screening details:

A subject was enrolled in either Stage 1 or Stage 2 and not both. Overall for both stages, 61 subjects were screened, 7 were screen failures, and 54 were enrolled and treated of which 53 subjects completed the study (20 unique subjects in Stage 1 and 33 unique subjects in Stage 2).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Gadopentetate dimeglumine (Magnevist, BAY86-6661) - Stage 1

Arm description:

Subjects received an intravenous (IV) injection of 0.05 mmol/kg BW (0.1 mL/kg BW) gadopentetate dimeglumine. Upon completion of the magnetic resonance (MR) imaging, the subjects received another injection of 0.05 mmol/kg for a total cumulative dose of 0.1 mmol/kg BW (0.2 mL/kg BW).

Arm type	Experimental
Investigational medicinal product name	Gadopentetate dimeglumine
Investigational medicinal product code	BAY86-6661
Other name	Magnevist
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received an IV injection of 0.05 mmol/kg BW (0.1 mL/kg BW) gadopentetate dimeglumine. Upon completion of the MR imaging, the subjects received another injection of 0.05 mmol/kg for a total cumulative dose of 0.1 mmol/kg BW (0.2 mL/kg BW).

Arm title	Gadopentetate dimeglumine (Magnevist, BAY86-6661) – Stage 2

Arm description:

Subjects received the optimal efficacious dose established in Stage 1 as a single IV injection of gadopentetate dimeglumine [0.1 mmol/kg BW (0.2 mL/kg BW)].

Arm type	Experimental
Investigational medicinal product name	Gadopentetate dimeglumine
Investigational medicinal product code	BAY86-6661
Other name	Magnevist
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received the optimal efficacious dose established in Stage 1 as a single IV injection of gadopentetate dimeglumine [0.1 mmol/kg BW (0.2 mL/kg BW)].

Number of subjects in period 1	Gadopentetate dimeglumine (Magnevist, BAY86-6661) - Stage 1	Gadopentetate dimeglumine (Magnevist, BAY86-6661) – Stage 2
Started	20	34
Completed	20	33
Not completed	0	1
Consent withdrawn by subject	-	1

Baseline characteristics

Reporting groups

Reporting group title	Gadopentetate dimeglumine (Magnevist, BAY86-6661) - Stage 1

Reporting group description:

Subjects received an intravenous (IV) injection of 0.05 mmol/kg BW (0.1 mL/kg BW) gadopentetate dimeglumine. Upon completion of the magnetic resonance (MR) imaging, the subjects received another injection of 0.05 mmol/kg for a total cumulative dose of 0.1 mmol/kg BW (0.2 mL/kg BW).

Reporting group title	Gadopentetate dimeglumine (Magnevist, BAY86-6661) – Stage 2

Reporting group description:

Subjects received the optimal efficacious dose established in Stage 1 as a single IV injection of gadopentetate dimeglumine [0.1 mmol/kg BW (0.2 mL/kg BW)].

Reporting group values	Gadopentetate dimeglumine (Magnevist, BAY86-6661) - Stage 1	Gadopentetate dimeglumine (Magnevist, BAY86-6661) – Stage 2	Total
Number of subjects	20	34	54
Age categorical			
Units: Subjects			
2 to 6 months	6	11	17
6 to 12 months	6	11	17
12 months to 2 years	8	12	20
Gender categorical			
Units: Subjects			
Female	13	13	26
Male	7	21	28
Race, Customized			
Units: Subjects			
White	19	33	52
Asian	1	0	1
Multiple	0	1	1
Body Weight			
Units: kilogram(s)			
arithmetic mean	8.4	8	
standard deviation	± 2.6	± 2	-

End points

End points reporting groups

Reporting group title	Gadopentetate dimeglumine (Magnevist, BAY86-6661) - Stage 1

Reporting group description:

Subjects received an intravenous (IV) injection of 0.05 mmol/kg BW (0.1 mL/kg BW) gadopentetate dimeglumine. Upon completion of the magnetic resonance (MR) imaging, the subjects received another injection of 0.05 mmol/kg for a total cumulative dose of 0.1 mmol/kg BW (0.2 mL/kg BW).

Reporting group title	Gadopentetate dimeglumine (Magnevist, BAY86-6661) – Stage 2

Reporting group description:

Subjects received the optimal efficacious dose established in Stage 1 as a single IV injection of gadopentetate dimeglumine [0.1 mmol/kg BW (0.2 mL/kg BW)].

Subject analysis set title	Gadopentetate Dimeglumine - Stage 1 and 2
Subject analysis set type	Per protocol

Subject analysis set description:

Stage 1: All subjects who received the appropriate dose of gadopentetate dimeglumine injection based on kg BW.
Stage 2: Subjects who received plus or minus (+/-) 10% of the appropriate dose of gadopentetate dimeglumine injection based on kg BW and had values for both PK samples.
Overall, this reporting group consisted of 44 subjects.

Subject analysis set title	Stage 1 (Unenhanced Image)
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects (N=20) for whom unenhanced image was taken before administering any injection in Stage 1.

Subject analysis set title	Primary Analysis Set (PAS)
Subject analysis set type	Per protocol

Subject analysis set description:

In order to ensure that there would be 5 valid subjects per age group, more than 5 subjects were enrolled in Stage 1. The determination of the optimal dose was based on 5 valid subjects per age group. Therefore, the PAS (N=15) was defined as an additional analysis set, consisting of the first 5 PPS subjects of each age group (sorted by date of enrollment). The PAS was used for the determination of the optimal efficacious dose in Stage 1 only.

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

Subject analysis set description:

FAS (N=54) for safety and for efficacy included all subjects who received any amount of the investigational product.

Subject analysis set title	Stage 1 (Combination Image 0.1 mmol/kg)
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects (N=20) received an IV injection of 0.05 mmol/kg BW (0.1 mL/kg BW) gadopentetate dimeglumine.

Subject analysis set title	Stage 2 (Unenhanced Image)
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects (N=34) for whom unenhanced image was taken before administering any injection in Stage 2.

Subject analysis set title	Stage 2 (Combination Image)
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects (N=34) received the optimal efficacious dose established in Stage 1 as a single IV injection of gadopentetate dimeglumine [0.1 mmol/kg BW (0.2 mL/kg BW)].

Subject analysis set title	Per Protocol Set (PPS)
Subject analysis set type	Per protocol

Subject analysis set description:

PPS defined for Stage 1 as all 18 subjects who received the appropriate dose of gadopentetate dimeglumine Injection based on kg BW and in Stage 2 as 26 subjects who received +/- 10% of the appropriate dose based on kg BW and had values for both PK samples.

Subject analysis set title	Stage 1 (Combination Image 0.05 mmol/kg)
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects (N=20) received an IV injection of 0.05 mmol/kg BW (0.1 mL/kg BW) gadopentetate dimeglumine.

Subject analysis set title	Pharmacokinetic Analysis Set (PKS)
Subject analysis set type	Per protocol

Subject analysis set description:

PKS (N=44) was based on the PPS defined for Stage 1 as all subjects (N=18) who received the appropriate dose of gadopentetate dimeglumine injection based on kg BW and in Stage 2 as those subjects (N=26) who received +/- 10% of the appropriate dose based on kg BW and had values for both PK samples.

Primary: Number of Subjects With Diagnostic Adequacy - Open-label Clinical Investigator (CI) (Per Protocol Set)

End point title	Number of Subjects With Diagnostic Adequacy - Open-label Clinical Investigator (CI) (Per Protocol Set)[1]

End point description:

A clinical judgment by the open-label CIs as to whether ("yes") or not ("no") the CI could make a diagnosis from the image.

End point type	Primary

End point timeframe:

Within 5 minutes after 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	Stage 1 (Combination Image 0.1 mmol/kg)	Stage 1 (Combination Image 0.05 mmol/kg)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3[2]	3[3]		
Units: subjects				
No	0	1		
Yes	3	2		

Notes:

[2] - Only first 3 subjects of Stage 1 received 2 IV injections of 0.05 mmol/kg BW.

[3] - Only first 3 subjects of Stage 1 received 2 IV injections of 0.05 mmol/kg BW.

Statistical analyses

No statistical analyses for this end point

Primary: Dose Determined by Blinded Readers (BR) to be Superior for Diagnosis

End point title	Dose Determined by Blinded Readers (BR) to be Superior for Diagnosis[4]

End point description:

Dose superiority was a calculation based upon the BRs' assessment of 4 visualization parameters.

End point type	Primary

End point timeframe:

Within 5 minutes after 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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Primary Analysis Set (PAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: subjects				
BR 1, 0.05 mmol/kg	0			
BR 2, 0.05 mmol/kg	1			
BR 3, 0.05 mmol/kg	6			
BR 1, 0.1 mmol/kg	15			
BR 2, 0.1 mmol/kg	14			
BR 3, 0.1 mmol/kg	9			

Statistical analyses

No statistical analyses for this end point

Primary: Paired-dose Comparison of Number of Subjects With Dose Superiority Determined for 4 Lesion Visualization Variables - Blinded Readers (BRs)

End point title	Paired-dose Comparison of Number of Subjects With Dose Superiority Determined for 4 Lesion Visualization Variables - Blinded Readers (BRs)[5]

End point description:

For each subject, the BR indicated which dose had better contrast enhancement, better border delineation, clearer internal morphology, and provided more diagnostic information. The dose chosen for 3 or 4 of these variables was the selected dose for that BR and subject. If each dose was superior on 2 variables, the dose which provided more diagnostic information was selected for that subject. The dose selected for the majority of subjects was the dose selected by that BR; if chosen by 2 or 3 BRs, it was the selected dose.

End point type	Primary

End point timeframe:

Within 5 minutes after 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	Stage 1 (Combination Image 0.1 mmol/kg)	Stage 1 (Combination Image 0.05 mmol/kg)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15[6]	15[7]		
Units: subjects				
BR 1 - Diagnostic information	15	0		
BR 2 - Diagnostic information	14	1		
BR 3 - Diagnostic information	9	6		

BR 1 - Contrast enhancement	15	0		
BR 2 - Contrast enhancement	14	1		
BR 3 - Contrast enhancement	8	7		
BR 1 - Border delineation	15	0		
BR 2 - Border delineation	14	1		
BR 3 - Border delineation	9	6		
BR 1 - Internal morphology	15	0		
BR 2 - Internal morphology	14	1		
BR 3 - Internal morphology	9	6		

Notes:

[6] - PAS.

[7] - PAS.

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetic Analysis - Total Clearance (CL)

End point title	Pharmacokinetic Analysis - Total Clearance (CL)[8]

End point description:

Total clearance is the fraction of the volume of distribution (Vd) which is completely purified per unit of time and depends also on the plasma half-life of the drug.

End point type	Primary

End point timeframe:

20 to 45 min and 4 to 8 hours post injection

Notes:

[8] - 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	Gadopentetate Dimeglumine - Stage 1 and 2			
Subject group type	Subject analysis set			
Number of subjects analysed	44[9]			
Units: liters/hour				
median (full range (min-max))	1.012 (0.272 to 1.588)			

Notes:

[9] - PKS.

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetic Analysis - Total Clearance (CL)/Body Weight (BW)

End point title	Pharmacokinetic Analysis - Total Clearance (CL)/Body Weight (BW)[10]

End point description:

CL/BW = total clearance normalized by BW.

End point type	Primary

End point timeframe:

20 to 45 min and 4 to 8 hours 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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Gadopentetate Dimeglumine - Stage 1 and 2			
Subject group type	Subject analysis set			
Number of subjects analysed	44[11]			
Units: liters/hour/kg				
median (full range (min-max))	0.129 (0.059 to 0.166)			

Notes:

[11] - PKS.

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetic Analysis - Volume of Distribution at Steady State (Vss)

End point title	Pharmacokinetic Analysis - Volume of Distribution at Steady State (Vss)[12]

End point description:

Vss is an estimate of drug distribution independent of the elimination process and is proportional to the amount of drug in the body versus the drug plasma concentration at steady-state.

End point type	Primary

End point timeframe:

20 to 45 min and 4 to 8 hours 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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Gadopentetate Dimeglumine - Stage 1 and 2			
Subject group type	Subject analysis set			
Number of subjects analysed	44[13]			
Units: liters				
median (full range (min-max))	1.784 (0.68 to 3.11)			

Notes:

[13] - PKS.

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetic Analysis - Volume of Distribution at Steady State (Vss) /Body Weight (BW)

End point title	Pharmacokinetic Analysis - Volume of Distribution at Steady State (Vss) /Body Weight (BW)[14]

End point description:

PK Analysis - Volume of Distribution at Steady State (Vss) /Body Weight (BW).

End point type	Primary

End point timeframe:

20 to 45 min and 4 to 8 hours post injection

Notes:

[14] - 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	Gadopentetate Dimeglumine - Stage 1 and 2			
Subject group type	Subject analysis set			
Number of subjects analysed	44[15]			
Units: liters/kg				
median (full range (min-max))	0.232 (0.192 to 0.27)			

Notes:

[15] - PKS.

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetic Analysis - Area Under the Drug Concentration-time Curve (AUC)

End point title	Pharmacokinetic Analysis - Area Under the Drug Concentration-time Curve (AUC)[16]

End point description:

AUC = Area under the drug concentration-time curve from administration to infinity.

End point type	Primary

End point timeframe:

Samples taken 20 to 45 min and 4 to 8 hours post injection. AUC calculated from time of injection to infinity.

Notes:

[16] - 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	Gadopentetate Dimeglumine - Stage 1 and 2			
Subject group type	Subject analysis set			
Number of subjects analysed	44[17]			
Units: micromoles*hour/liter				
median (full range (min-max))	777.5 (600.8 to 1686.3)			

Notes:

[17] - PKS.

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetic Analysis - Terminal Elimination Half life (t1/2)

End point title	Pharmacokinetic Analysis - Terminal Elimination Half life

End point description:

t1/2 = termination elimination half-life calculated from the area under the drug concentration-time curve from administration to infinity.

End point type	Primary

End point timeframe:

Samples taken at 20 to 45 min and at 4 to 8 hours post injection; t1/2 calculated from area under the drug concentration-time curve from administration to infinity

Notes:

[18] - 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	Gadopentetate Dimeglumine - Stage 1 and 2			
Subject group type	Subject analysis set			
Number of subjects analysed	44[19]			
Units: hour				
median (full range (min-max))	1.483 (1.142 to 8.427)			

Notes:

[19] - PKS.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Number of Lesions Detected - Stage 1

End point title	Number of Subjects With Number of Lesions Detected - Stage 1

End point description:

The BRs and the open-label Clinical Investigators determined the number of subjects with 0, 1, 2, and 3 or more lesions.

End point type	Secondary

End point timeframe:

Within 5 minutes after injection

End point values	Stage 1 (Unenhanced Image)	Stage 1 (Combination Image 0.1 mmol/kg)	Stage 1 (Combination Image 0.05 mmol/kg)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20[20]	20[21]	20[22]	
Units: subjects				
BR 1 - 0 lesions	5	5	5	
BR 2 - 0 lesions	7	7	6	
BR 3 - 0 lesions	8	6	5	

CI - 0 lesions	11	11	11	
BR 1 - 1 lesion	7	7	7	
BR 2 - 1 lesion	8	7	8	
BR 3 - 1 lesion	8	9	10	
CI - 1 lesion	6	6	6	
BR 1 - 2 lesions	5	5	5	
BR 2 - 2 lesions	1	2	2	
BR 3 - 2 lesions	0	1	1	
CI - 2 lesions	1	1	1	
BR 1 - 3 or more lesions	3	3	3	
BR 2 - 3 or more lesions	4	4	4	
BR 3 - 3 or more lesions	4	4	4	
CI - 3 or more lesions	2	2	2	

Notes:

[20] - FAS.

[21] - FAS.

[22] - FAS.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Number of Lesions Detected - Stage 2

End point title	Number of Subjects With Number of Lesions Detected - Stage 2
End point description:	
The BRs and the open-label CIs determined the number of subjects with 0, 1, 2, and 3 or more lesions.	
End point type	Secondary
End point timeframe:	
Within 5 minutes after injection	

End point values	Stage 2 (Unenhanced Image)	Stage 2 (Combination Image)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	34[23]	34[24]		
Units: subjects				
BR 1 - 0 lesions	13	13		
BR 2 - 0 lesions	12	11		
BR 3 - 0 lesions	14	10		
CI - 0 lesions	17	15		
BR 1 - 1 lesions	18	17		
BR 2 - 1 lesions	15	16		
BR 3 - 1 lesions	11	13		
CI - 1 lesions	15	15		
BR 1 - 2 lesions	1	2		
BR 2 - 2 lesions	5	4		
BR 3 - 2 lesions	3	4		
CI - 2 lesions	0	1		
BR 1 - 3 or more lesions	2	2		
BR 2 - 3 or more lesions	2	3		

BR 3 - 3 or more lesions	6	7		
CI - 3 or more lesions	2	3		

Notes:

[23] - FAS.

[24] - FAS.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Quality of Lesion Visualization - Stage 1

End point title	Number of Subjects With Quality of Lesion Visualization - Stage 1

End point description:

The BRs and the open-label CIs determined the quality of lesion visualization with the unenhanced and the combined image sets based on a 3-point scale (1=excellent - lesion clearly seen and diagnosis possible; 2=fair but adequate - most of lesion seen and diagnosis possible; and 3=poor - lesion barely seen and diagnosis not possible).

End point type	Secondary

End point timeframe:

Within 5 minutes after injection

End point values	Stage 1 (Unenhanced Image)	Stage 1 (Combination Image 0.1 mmol/kg)	Stage 1 (Combination Image 0.05 mmol/kg)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20[25]	20[26]	20[27]	
Units: subjects				
BR 1 - Excellent (1)	4	9	7	
BR 2 - Excellent (1)	3	8	6	
BR 3 - Excellent (1)	2	3	3	
CI - Excellent (1)	12	20	16	
BR 1 - Fair but adequate (2)	16	10	12	
BR 2 - Fair but adequate (2)	17	12	14	
BR 3 - Fair but adequate (2)	16	15	15	
CI - Fair but adequate (2)	4	0	4	
BR 1 - Poor (3)	0	1	1	
BR 2 - Poor (3)	0	0	0	
BR 3 - Poor (3)	2	2	2	
CI - Poor (3)	4	0	0	

Notes:

[25] - FAS.

[26] - FAS.

[27] - FAS.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Quality of Lesion Visualization - Stage 2

End point title	Number of Subjects With Quality of Lesion Visualization - Stage 2

End point description:

The BRs and the open-label CIs determined the quality of lesion visualization with the unenhanced and the combined image sets based on a 3-point scale (1=excellent - lesion clearly seen and diagnosis possible; 2=fair but adequate - most of lesion seen and diagnosis possible; and 3=poor - lesion barely seen and diagnosis not possible).

End point type	Secondary

End point timeframe:

Within 5 minutes after injection

End point values	Stage 2 (Unenhanced Image)	Stage 2 (Combination Image)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	34[28]	34[29]		
Units: subjects				
BR 1 - Excellent (1)	3	25		
BR 2 - Excellent (1)	7	25		
BR 3 - Excellent (1)	5	18		
CI - Excellent (1)	12	32		
BR 1 - Fair but adequate (2)	25	8		
BR 2 - Fair but adequate (2)	27	9		
BR 3 - Fair but adequate (2)	28	16		
CI - Fair but adequate (2)	14	2		
BR 1 - Poor (3)	6	1		
BR 2 - Poor (3)	0	0		
BR 3 - Poor (3)	1	0		
CI - Poor (3)	8	0		

Notes:

[28] - FAS.

[29] - FAS.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Quality of Border Delineation - Stage 1

End point title	Number of Subjects With Quality of Border Delineation - Stage 1

End point description:

The BRs and the open-label CIs determined the quality of border delineation based on a 3-point scale (1=excellent - border completely delineated; 2=fair but adequate - some of the border is delineated; and 3=poor - entire or almost the entire border is not delineated) by image set.

End point type	Secondary

End point timeframe:

Within 5 minutes after injection

End point values	Stage 1 (Unenhanced Image)	Stage 1 (Combination Image 0.1 mmol/kg)	Stage 1 (Combination Image 0.05 mmol/kg)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20[30]	20[31]	20[32]	
Units: subjects				
BR 1 - Excellent (1)	4	10	6	
BR 2 - Excellent (1)	3	8	6	
BR 3 - Excellent (1)	3	4	3	
CI - Excellent (1)	12	19	16	
BR 1 - Fair but adequate (2)	15	9	13	
BR 2 - Fair but adequate (2)	16	12	14	
BR 3 - Fair but adequate (2)	13	15	14	
CI - Fair but adequate (2)	5	1	4	
BR 1 - Poor (3)	1	1	1	
BR 2 - Poor (3)	1	0	0	
BR 3 - Poor (3)	4	3	3	
CI - Poor (3)	3	0	0	

Notes:

[30] - FAS.

[31] - FAS.

[32] - FAS.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Quality of Border Delineation - Stage 2

End point title	Number of Subjects With Quality of Border Delineation - Stage 2

End point description:

The BRs and the open-label CIs determined the quality of border delineation based on a 3-point scale (1=excellent - border completely delineated; 2=fair but adequate - some of the border is delineated; and 3=poor - entire or almost the entire border is not delineated) by image set.

End point type	Secondary

End point timeframe:

Within 5 minutes after injection

End point values	Stage 2 (Unenhanced Image)	Stage 2 (Combination Image)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	34[33]	34[34]		
Units: subjects				
BR 1 - Excellent (1)	4	21		
BR 2 - Excellent (1)	6	17		
BR 3 - Excellent (1)	8	24		
CI - Excellent (1)	12	32		
BR 1 - Fair but adequate (2)	24	12		
BR 2 - Fair but adequate (2)	28	17		

BR 3 - Fair but adequate (2)	25	10			
CI - Fair but adequate (2)	14	2			
BR 1 - Poor (3)	6	1			
BR 2 - Poor (3)	0	0			
BR 3 - Poor (3)	1	0			
CI - Poor (3)	8	0			

Notes:

[33] - FAS.

[34] - FAS.

Statistical analyses

No statistical analyses for this end point

Secondary: Most Frequent Diagnostic Findings With Unenhanced Images - Stage 1

End point title	Most Frequent Diagnostic Findings With Unenhanced Images - Stage 1[35]

End point description:

The BRs and the open-label CIs determined the most frequent diagnostic findings with the unenhanced images.

End point type	Secondary

End point timeframe:

Within 5 minutes after injection

Notes:

[35] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Since this endpoint was analysed only in Stage 2, statistics were not reported for other arm in the baseline period, that is, "Gadopentetate dimeglumine (Magnevist, BAY86-6661) - Stage 1".

End point values	Gadopentetate dimeglumine (Magnevist, BAY86-6661) - Stage 1			
Subject group type	Reporting group			
Number of subjects analysed	20[36]			
Units: subjects				
BR 1 - No lesion	4			
BR 2 - No lesion	7			
BR 3 - No lesion	8			
CI - No lesion	6			
BR 1 - Brain lesion	8			
BR 2 - Brain lesion	6			
BR 3 - Brain lesion	4			
CI - Brain lesion	7			

Notes:

[36] - FAS.

Statistical analyses

No statistical analyses for this end point

Secondary: Most Frequent Diagnostic Findings With Unenhanced Images - Stage 2

End point title	Most Frequent Diagnostic Findings With Unenhanced Images - Stage 2
End point description:	
The BRs and the open-label CIs determined the most frequent diagnostic findings with the unenhanced images.	
End point type	Secondary
End point timeframe:	
Within 5 minutes after injection	

End point values	Stage 2 (Combination Image)			
Subject group type	Subject analysis set			
Number of subjects analysed	34			
Units: subjects				
BR 1 - No lesion	13			
BR 2 - No lesion	12			
BR 3 - No lesion	14			
CI - No lesion	11			
BR 1 - Brain lesion	9			
BR 2 - Brain lesion	10			
BR 3 - Brain lesion	10			
CI - Brain lesion	10			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Number of Subjects With Change in Diagnosis From Unenhanced to Combined Images - Stage 1

End point title	Overall Number of Subjects With Change in Diagnosis From Unenhanced to Combined Images - Stage 1
End point description:	
The BRs and the open-label CIs determined the number of subjects with a change in diagnosis from unenhanced to combined images.	
End point type	Secondary
End point timeframe:	
Within 5 minutes after injection	

End point values	Stage 1 (Combination Image 0.1 mmol/kg)	Stage 1 (Combination Image 0.05 mmol/kg)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20[37]	20[38]		
Units: subjects				

BR 1	6	6			
BR 2	0	1			
BR 3	6	6			
CI	4	4			

Notes:

[37] - FAS.

[38] - FAS.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Number of Subjects With Change in Diagnosis From Unenhanced to Combined Images - Stage 2

End point title	Overall Number of Subjects With Change in Diagnosis From Unenhanced to Combined Images - Stage 2[39]

End point description:

The BRs and the open-label CIs determined the number of subjects with a change in diagnosis from unenhanced to combined images.

End point type	Secondary

End point timeframe:

Within 5 minutes after injection

Notes:

[39] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Since this endpoint was analysed only in Stage 2, statistics were not reported for other arm in the baseline period, that is, "Gadopentetate dimeglumine (Magnevist, BAY86-6661) - Stage 1".

End point values	Gadopentetate dimeglumine (Magnevist, BAY86-6661) – Stage 2				
Subject group type	Reporting group				
Number of subjects analysed	34[40]				
Units: subjects					
BR 1	10				
BR 2	6				
BR 3	10				
CI	8				

Notes:

[40] - FAS.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Specific Change in the Diagnosis From Unenhanced to Combined Images - Stage 1

End point title	Number of Subjects With Specific Change in the Diagnosis From Unenhanced to Combined Images - Stage 1

End point description:

Those subjects for whom the diagnosis changed for at least 1 BR from unenhanced to combined images are presented for Stage 1. For completeness, the corresponding data for these subjects are presented

for the open-label CIs.

End point type	Secondary

End point timeframe:

Within 5 minutes after injection

End point values	Stage 1 (Combination Image 0.1 mmol/kg)	Stage 1 (Combination Image 0.05 mmol/kg)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20[41]	20[42]		
Units: subjects				
BR 1 - from "metastasis" to "liver lesion"	0	1		
BR 2 - from "no lesion" to "vascular malformation"	0	1		
BR 3 - from "no lesion" to "vascular malformation"	0	2		
BR 3 - from "no lesion" to "brain lesion"	2	1		
BR 1 - from "vasc. malform." to "vasc. malfrom."	2	2		
BR 1 - from "brain lesion" to "brain lesion"	2	2		
BR 3 - from "brain lesion" to "brain lesion"	2	2		
BR 1 - from "other" to "other"	1	1		
BR 3 - from "other" to "vascular malformation"	1	1		
BR 1 - from "metastasis" to "metastasis"	1	0		
BR 3 - from "liver lesion" to "metastasis"	1	0		

Notes:

[41] - FAS.

[42] - FAS.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Specific Change in the Diagnosis From Unenhanced to Combined Images - Stage 2

End point title	Number of Subjects With Specific Change in the Diagnosis From Unenhanced to Combined Images - Stage 2[43]

End point description:

Those subjects for whom the diagnosis changed for at least 1 BR from unenhanced to combined images are presented for Stage 2. For completeness, the corresponding data for these subjects are presented for the open-label CIs.

End point type	Secondary

End point timeframe:

Within 5 minutes after injection

Notes:

[43] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Since this endpoint was analysed only in Stage 2, statistics were not reported for other arm in the baseline period, that is, "Gadopentetate dimeglumine (Magnevist, BAY86-6661) - Stage 1".

End point values	Gadopentetate dimeglumine (Magnevist, BAY86-6661) – Stage 2			
Subject group type	Reporting group			
Number of subjects analysed	34[44]			
Units: subjects				
BR 1 - from "no lesion" to "brain lesion"	1			
BR 2 - from "no lesion" to "other"	1			
BR 3 - from "no lesion" to "other"	2			
BR 3 - from "no lesion" to "infectious disorder"	2			
BR 1 - from "vasc. malform." to "vasc. malform."	1			
BR 1 - from "inf. disorder" to "inf. disorder"	1			
BR 1 - from "brain lesion" to "no lesion"	1			
BR 1 - from "brain lesion" to "inf. disorder"	1			
BR 1 - from "brain lesion" to "brain lesion"	4			
BR 2 - from "brain lesion" to "brain lesion"	1			
BR 3 - from "brain lesion" to "brain lesion"	2			
BR 2 - from "renal lesion" to "renal lesion"	1			
BR 3 - from "renal lesion" to "renal lesion"	1			
BR 3 - from "not assessable" to "other"	1			
BR 1 - from "other" to "vascular malformation"	1			
BR 2 - from "other" to "vascular malformation"	2			
BR 2 - from "other" to "other"	1			
BR 3 - from "other" to "other"	2			

Notes:

[44] - FAS.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Diagnostic Confidence - Stage 1

End point title	Number of Subjects With Diagnostic Confidence - Stage 1
End point description:	

The overall diagnostic confidence of the BRs and the open-label CIs was indicated on a 3-point scale: 1=not confident; 2=confident; and 3=very confident.

End point type	Secondary

End point timeframe:

Within 5 minutes after injection

End point values	Stage 1 (Unenhanced Image)	Stage 1 (Combination Image 0.1 mmol/kg)	Stage 1 (Combination Image 0.05 mmol/kg)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20[45]	20[46]	20[47]	
Units: subjects				
BR 1 - not confident	1	0	0	
BR 2 - not confident	3	0	0	
BR 3 - not confident	2	1	0	
CI - not confident	8	0	1	
BR 1 - confident	17	17	17	
BR 2 - confident	14	6	7	
BR 3 - confident	13	10	13	
CI - confident	3	1	5	
BR 1 - very confident	2	3	3	
BR 2 - very confident	3	14	13	
BR 3 - very confident	5	9	7	
CI - very confident	9	19	14	

Notes:

[45] - FAS.

[46] - FAS.

[47] - FAS.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Diagnostic Confidence - Stage 2

End point title	Number of Subjects With Diagnostic Confidence - Stage 2
End point description:	

The overall diagnostic confidence of the BRs and the open-label CIs was indicated on a 3-point scale: 1=not confident; 2=confident; and 3=very confident.

End point type	Secondary
End point timeframe:	

Within 5 minutes after injection

End point values	Stage 2 (Unenhanced Image)	Stage 2 (Combination Image)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	34[48]	34[49]		
Units: subjects				
BR 1 - not confident	3	0		
BR 2 - not confident	3	1		

BR 3 - not confident	1	0			
CI - not confident	10	0			
BR 1 - confident	28	18			
BR 2 - confident	23	4			
BR 3 - confident	27	8			
CI - confident	18	4			
BR 1 - very confident	3	16			
BR 2 - very confident	8	29			
BR 3 - very confident	6	26			
CI - very confident	6	30			

Notes:

[48] - FAS.

[49] - FAS.

Statistical analyses

No statistical analyses for this end point

Secondary: Management Based on Unenhanced Images - Stage 1

End point title	Management Based on Unenhanced Images - Stage 1[50]

End point description:

For Stage 1 based on unenhanced images, the recommended management is presented as determined by the open-label CIs.

End point type	Secondary

End point timeframe:

Within 5 minutes before injection

Notes:

[50] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Since this endpoint was analysed only in Stage 1, statistics were not reported for other arm in the baseline period, that is, "Gadopentetate dimeglumine (Magnevist, BAY86-6661) - Stage 2".

End point values	Gadopentetate dimeglumine (Magnevist, BAY86-6661) - Stage 1			
Subject group type	Reporting group			
Number of subjects analysed	18[51]			
Units: subjects				
biopsy	1			
surgery	2			
follow-up	3			
medical treatment	2			
imaging	10			

Notes:

[51] - FAS with only subjects for whom information on management was given.

Statistical analyses

No statistical analyses for this end point

Secondary: Management Based on Unenhanced Images - Stage 2

End point title	Management Based on Unenhanced Images - Stage 2[52]

End point description:

For Stage 2 based on unenhanced images, the recommended management is presented as determined by the open-label CIs.

End point type	Secondary

End point timeframe:

Within 5 minutes before injection

Notes:

[52] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Since this endpoint was analysed only in Stage 2, statistics were not reported for other arm in the baseline period, that is, "Gadopentetate dimeglumine (Magnevist, BAY86-6661) - Stage 1".

End point values	Gadopentetate dimeglumine (Magnevist, BAY86-6661) – Stage 2			
Subject group type	Reporting group			
Number of subjects analysed	32[53]			
Units: subjects				
follow-up	2			
imaging	30			

Notes:

[53] - FAS with only subjects for whom information on management was given.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Number of Subjects With Change in Management From Unenhanced to Combined Images - Stage 1

End point title	Overall Number of Subjects With Change in Management From Unenhanced to Combined Images - Stage 1

End point description:

For Stage 1, the number of subjects for whom the recommended management of the open-label CIs changed from unenhanced to combined images is presented for both doses.

End point type	Secondary

End point timeframe:

Within 5 minutes after injection

End point values	Stage 1 (Combination Image 0.1 mmol/kg)	Stage 1 (Combination Image 0.05 mmol/kg)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20[54]	20[55]		
Units: subjects	12	5		

Notes:

[54] - FAS.

[55] - FAS.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Number of Subjects With Change in Management From Unenhanced to Combined Images - Stage 2

End point title	Overall Number of Subjects With Change in Management From Unenhanced to Combined Images - Stage 2[56]

End point description:

For Stage 2, the number of subjects for whom the recommended management of the open-label CIs changed from unenhanced to combined images is presented for the optimal efficacious dose determined in Stage 1.

End point type	Secondary

End point timeframe:

Within 5 minutes after injection

Notes:

[56] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Since this endpoint was analysed only in Stage 2, statistics were not reported for other arm in the baseline period, that is, "Gadopentetate dimeglumine (Magnevist, BAY86-6661) - Stage 1".

End point values	Gadopentetate dimeglumine (Magnevist, BAY86-6661) – Stage 2			
Subject group type	Reporting group			
Number of subjects analysed	34[57]			
Units: subjects	30			

Notes:

[57] - FAS.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Specific Change in Management From Unenhanced to Combined Images - Stage 1

End point title	Number of Subjects With Specific Change in Management From Unenhanced to Combined Images - Stage 1

End point description:

The actual change in management from unenhanced to combined images recommended by the open-label CIs is presented for both doses in Stage 1.

End point type	Secondary

End point timeframe:

Within 5 minutes after injection

End point values	Stage 1 (Combination Image 0.1 mmol/kg)	Stage 1 (Combination Image 0.05 mmol/kg)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20[58]	20[59]		
Units: subjects				
from "follow-up" to "surgery"	1	1		
from "imaging" to "surgery"	3	2		
from "imaging" to "follow-up"	1	0		
from "imaging" to "imaging"	0	1		
from "imaging" to "other"	6	0		
from "other" to "follow-up"	1	1		

Notes:

[58] - FAS.

[59] - FAS.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Specific Change in Management From Unenhanced to Combined Images - Stage 2

End point title	Number of Subjects With Specific Change in Management From Unenhanced to Combined Images - Stage 2[60]

End point description:

The actual change in management from unenhanced to combined images recommended by the open-label CIs is presented in Stage 2 for the optimal efficacious dose determined in Stage 1.

End point type	Secondary

End point timeframe:

Within 5 minutes after injection

Notes:

[60] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Since this endpoint was analysed only in Stage 2, statistics were not reported for other arm in the baseline period, that is, "Gadopentetate dimeglumine (Magnevist, BAY86-6661) - Stage 1".

End point values	Gadopentetate dimeglumine (Magnevist, BAY86-6661) – Stage 2				
Subject group type	Reporting group				
Number of subjects analysed	34[61]				
Units: subjects					
from "imaging" to "surgery"	3				
from "imaging" to "follow-up"	16				
from "imaging" to "medical treatment"	3				
from "imaging" to "imaging"	3				
from "imaging" to "other"	7				

Notes:

[61] - FAS.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of treatment up to 30 days after last dose (follow-up)

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	Gadopentetate Dimeglumine - Stage 1

Reporting group description:

Subjects received an IV injection of 0.05 mmol/kg BW (0.1 mL/kg BW) gadopentetate dimeglumine. Upon completion of the MR imaging, the subjects received another injection of 0.05 mmol/kg for a total cumulative dose of 0.1 mmol/kg BW (0.2 mL/kg BW).

Reporting group title	Gadopentetate Dimeglumine - Stage 2

Reporting group description:

Subjects received the optimal efficacious dose established in Stage 1 as a single IV injection of gadopentetate dimeglumine [0.1 mmol/kg BW (0.2 mL/kg BW)].

Serious adverse events	Gadopentetate Dimeglumine - Stage 1	Gadopentetate Dimeglumine - Stage 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 20 (20.00%)	8 / 34 (23.53%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma			
subjects affected / exposed	0 / 20 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Krabbe's disease			
subjects affected / exposed	0 / 20 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alagille syndrome			

subjects affected / exposed	0 / 20 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital aortic anomaly			
subjects affected / exposed	0 / 20 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Adenoidectomy			
subjects affected / exposed	0 / 20 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Intracranial venous sinus thrombosis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Motor developmental delay			
subjects affected / exposed	0 / 20 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal cyst			
subjects affected / exposed	0 / 20 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Laryngeal stenosis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			

subjects affected / exposed	1 / 20 (5.00%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Neurogenic bladder			
subjects affected / exposed	1 / 20 (5.00%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Gadopentetate Dimeglumine - Stage 1	Gadopentetate Dimeglumine - Stage 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 20 (30.00%)	2 / 34 (5.88%)	
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 20 (5.00%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 20 (15.00%)	1 / 34 (2.94%)	
occurrences (all)	3	1	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 20 (5.00%)	1 / 34 (2.94%)	
occurrences (all)	1	1	

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 20 (5.00%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 20 (5.00%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Rhinitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 34 (0.00%)	
occurrences (all)	1	0	

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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Decimal places were automatically truncated if last decimal equals zero.

Notes: