Clinical trial results:
Open-label, multicenter, pharmacokinetic, and safety study in children (term newborn infants to 23 months of age) undergoing a contrast-enhanced MRI with an intravenous injection of 0.1 mmol/kg BW gadobutrol 1.0 M (Gadovist 1.0)

Summary

EudraCT number	2010-023003-96
Trial protocol	DE
Global end of trial date	28 November 2013

Results information

Result version number	v1
This version publication date	12 July 2016
First version publication date	19 June 2015

Trial information

Trial identification

Sponsor protocol code	BAY86-4875/91741

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01544166
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000994-PIP01-10
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	28 November 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 November 2013
Global end of trial reached?	Yes
Global end of trial date	28 November 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the pharmacokinetics (PK) of gadobutrol at the standard dose of 0.1 millimole per kilogram (mmol/kg) body weight (BW) in pediatric subjects from birth to less than 2 years of age (term newborn infants to toddlers 23 months of age inclusive).

Protection of trial subjects:

The number of pediatric subjects participating in this study and procedures performed such as blood sampling were minimized as far as feasible. A population-based PK approach was employed allowing sparse sampling for PK analysis.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 May 2012
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: 32
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	United States: 8
Worldwide total number of subjects	44
EEA total number of subjects	32

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	5
Infants and toddlers (28 days-23 months)	39
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:

Pediatric subjects who were less than (<) 2 years of age, scheduled to undergo contrast-enhanced magnetic resonance imaging (MRI) for routine diagnostic purposes were included in the study and were recruited from 9 centres in Canada, Germany and United States of America.

Pre-assignment

Screening details:

Total of 47 subjects were screened worldwide in the study and 44 were enrolled (i.e. assigned to study drug). It included 3 screening failures (3 patients were not treated and did not complete the study).

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	Overall Study

Arm description:

Single intravenous bolus injection of gadobutrol 0.1 mmol/kg BW in term newborns to infants <2 years of age.

Arm type	Experimental
Investigational medicinal product name	Gadobutrol
Investigational medicinal product code	BAY86-4875
Other name	Gadovist, Gadavist
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Single intravenous bolus injection of gadobutrol 0.1 mmol/kg BW.

Number of subjects in period 1	Overall Study
Started	44
Treated	44
Completed	44

Baseline characteristics

Reporting groups	
Reporting group title	Overall study
Reporting group description:	
Single intravenous bolus injection of gadobutrol 0.1 mmol/kg BW in term newborns to infants <2 years of age.	

Reporting group values	Overall study	Total	
Number of subjects	44	44	
Age categorical			
Units: Subjects			
Newborns (0-27 days)	5	5	
Infants and toddlers (28 days-23 months)	39	39	
Age continuous			
Units: months			
arithmetic mean	8.8		
standard deviation	± 7.1	-	
Gender categorical			
Units: Subjects			
Female	18	18	
Male	26	26	

End points

End points reporting groups

Reporting group title	Overall Study
Reporting group description:	
Single intravenous bolus injection of gadobutrol 0.1 mmol/kg BW in term newborns to infants <2 years of age.	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
FAS included all subjects who had combined unenhanced and enhanced image sets available regardless of any other protocol deviation.	
Subject analysis set title	Per-Protocol Set (PPS)
Subject analysis set type	Per protocol
Subject analysis set description:	
PPS included those subjects who received the appropriate dose of gadobutrol based on the dose specification of 0.1 mmol/kg BW plus/minus 10% and had quantifiable gadolinium plasma concentrations in at least 1 valid PK sample.	
Subject analysis set title	Safety Analysis Set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
SAF included all subjects who received any amount of gadobutrol.	
Subject analysis set title	Unenhanced MRI Assessment
Subject analysis set type	Full analysis
Subject analysis set description:	
Assessment was provided for the unenhanced image set alone in all FAS subjects.	
Subject analysis set title	Combined MRI Assessment
Subject analysis set type	Full analysis
Subject analysis set description:	
Assessment was provided for the combined unenhanced and enhanced image set in all FAS subjects.	

Primary: Area Under the Plasma Concentration Versus Time Curve (AUC) From Time 0 to Infinity of Gadobutrol: Individual

End point title	Area Under the Plasma Concentration Versus Time Curve (AUC) From Time 0 to Infinity of Gadobutrol: Individual[1]
End point description:	
AUC is a measure of systemic drug exposure, which is obtained by collecting a series of blood samples and measuring the concentrations of drug in each sample. AUC from time 0 (start of injection) to infinity was reported.	
End point type	Primary
End point timeframe:	
Blood samples were collected at 3 timepoints between 15 minutes and 8 hours post administration of gadobutrol	

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: Statistical analysis was not performed since as planned all continuous and ordinal categorical variables were analyzed by descriptive statistics only.

End point values	Overall Study			
Subject group type	Reporting group			
Number of subjects analysed	43[2]			
Units: micromole*hour per liter (micromole*h/L)				
median (full range (min-max))	776 (544 to 1470)			

Notes:

[2] - PK parameters were analysed using PPS, number of subjects analysed = 43.

Statistical analyses

No statistical analyses for this end point

Primary: Body Weight-Normalized Total Body Clearance (CL) of Gadobutrol From Plasma: Individual

End point title	Body Weight-Normalized Total Body Clearance (CL) of Gadobutrol From Plasma: Individual[3]

End point description:

Clearance is the volume of the fluid presented to the eliminating organ that is effectively completely cleared of drug per unit time and depends on the rate of elimination. CL of gadobutrol normalized for body weight, was reported.

End point type	Primary

End point timeframe:

Blood samples were collected at 3 timepoints between 15 minutes and 8 hours post administration of gadobutrol

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: Statistical analysis was not performed since as planned all continuous and ordinal categorical variables were analyzed by descriptive statistics only.

End point values	Overall Study			
Subject group type	Reporting group			
Number of subjects analysed	43[4]			
Units: Liter per hour per kilogram [L/(h*kg)]				
median (full range (min-max))	0.128 (0.0666 to 0.184)			

Notes:

[4] - PK parameters were analysed using PPS, number of subjects analysed = 43.

Statistical analyses

No statistical analyses for this end point

Primary: Body Weight-Normalized Apparent Volume of Distribution at Steady State (Vss) of Gadobutrol in Plasma: Individual

End point title	Body Weight-Normalized Apparent Volume of Distribution at Steady State (Vss) of Gadobutrol in Plasma: Individual[5]

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:

Blood samples were collected at 3 timepoints between 15 minutes and 8 hours post administration of gadobutrol

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: Statistical analysis was not performed since as planned all continuous and ordinal categorical variables were analyzed by descriptive statistics only.

End point values	Overall Study			
Subject group type	Reporting group			
Number of subjects analysed	43[6]			
Units: Liter per kilogram (L/kg)				
median (full range (min-max))	0.277 (0.236 to 0.409)			

Notes:

[6] - PK parameters were analysed using PPS, number of subjects analysed = 43.

Statistical analyses

No statistical analyses for this end point

Primary: Terminal Elimination Half-Life (t1/2) of Gadobutrol From Plasma: Individual

End point title	Terminal Elimination Half-Life (t1/2) of Gadobutrol From Plasma: Individual[7]

End point description:

Half-life refers to the elimination of the drug, that is, the time it takes for the blood plasma concentration to reach half the concentration. Terminal elimination half-life of gadobutrol from plasma is expressed in hours and is derived from the terminal slope of the concentration versus time curve.

End point type	Primary

End point timeframe:

Blood samples were collected at 3 timepoints between 15 minutes and 8 hours post administration of gadobutrol

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: Statistical analysis was not performed since as planned all continuous and ordinal categorical variables were analyzed by descriptive statistics only.

End point values	Overall Study			
Subject group type	Reporting group			
Number of subjects analysed	43[8]			
Units: hours				
median (full range (min-max))	1.62 (1.16 to 3.37)			

Notes:

[8] - PK parameters were analysed using PPS, number of subjects analysed = 43.

Statistical analyses

No statistical analyses for this end point

Primary: Mean Residence Time (MRT) of Gadobutrol in Plasma: Individual

End point title	Mean Residence Time (MRT) of Gadobutrol in Plasma: Individual[9]

End point description:

MRT is the average time that the molecules introduced into the body stay in the body. MRT of Gadobutrol is expressed in hours.

End point type	Primary

End point timeframe:

Blood samples were collected at 3 timepoints between 15 minutes and 8 hours post administration of gadobutrol

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: Statistical analysis was not performed since as planned all continuous and ordinal categorical variables were analyzed by descriptive statistics only.

End point values	Overall Study			
Subject group type	Reporting group			
Number of subjects analysed	43[10]			
Units: hours				
median (full range (min-max))	2.18 (1.57 to 4.68)			

Notes:

[10] - PK parameters were analysed using PPS, number of subjects analysed = 43.

Statistical analyses

No statistical analyses for this end point

Primary: Simulation of Plasma Concentration of Gadobutrol at 20 Minutes Post-Injection (C20)

End point title	Simulation of Plasma Concentration of Gadobutrol at 20 Minutes Post-Injection (C20)[11]

End point description:

Simulation is the use of the model to predict data other than observed data, in this case early Gadobutrol plasma concentration after intravenous injection. Plasma concentration serves as a surrogate for efficacy (signal and contrast enhancement) in MRI. C20 was simulated for virtual pediatric subjects with homogenous distribution over age. Simulated median (5th and 95th percentile in parenthesis) gadolinium plasma concentrations for a dose of 0.1 mmol/kg body weight were presented.

End point type	Primary

End point timeframe:

20 minutes 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: Statistical analysis was not performed since as planned all continuous and ordinal categorical variables were analyzed by descriptive statistics only.

End point values	Overall Study			
Subject group type	Reporting group			
Number of subjects analysed	43[12]			
Units: micromole(s)/liter (micromole/L)				
median (full range (min-max))	339 (230 to 456)			

Notes:

[12] - PPS. Here number of subjects analysed= 43. C20 was simulated for 2400 virtual paediatric subjects.

Statistical analyses

No statistical analyses for this end point

Primary: Simulation of Plasma Concentration of Gadobutrol at 30 Minutes Post-Injection (C30)

End point title	Simulation of Plasma Concentration of Gadobutrol at 30 Minutes Post-Injection (C30)[13]

End point description:

Simulation is the use of the model to predict data other than observed data, in this case early Gadobutrol plasma concentration after intravenous injection. Plasma concentration serves as a surrogate for efficacy (signal and contrast enhancement) in MRI. C30 was simulated for virtual pediatric subjects with homogenous distribution over age. Simulated median (5th and 95th percentile in parenthesis) gadolinium plasma concentrations for a dose of 0.1 mmol/kg body weight were presented.

End point type	Primary

End point timeframe:

30 minutes post-injection

Notes:

[13] - 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: Statistical analysis was not performed since as planned all continuous and ordinal categorical variables were analyzed by descriptive statistics only.

End point values	Overall Study			
Subject group type	Reporting group			
Number of subjects analysed	43[14]			
Units: micromole(s)/liter (micromole/L)				
median (full range (min-max))	292 (194 to 394)			

Notes:

[14] - PPS. Here number of subjects analysed= 43. C30 was simulated for 2400 virtual paediatric subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Anatomical Area Evaluated

End point title	Number of Subjects With Anatomical Area Evaluated

End point description:

Subjects were referred for MRI of any body region. The primary anatomical area to be evaluated by MRI was assessed. Anatomical Area was recorded prior to gadobutrol injection for the unenhanced MRI procedure and after gadobutrol injection for the gadobutrol-enhanced MRI procedure. Evaluation was done on pre-injection and combined (pre- and post-injection) images.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection (within about 15 minutes)

End point values	Unenhanced MRI Assessment	Combined MRI Assessment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44[15]	44[16]		
Units: Subjects				
Abdomen: Liver	1	1		
Brain: Brain	20	20		
Brain: Orbit and brain	1	1		
Chest/thorax: Lung	2	2		
Head/neck: Head	3	3		
Head/neck: Neck	1	1		
Head/neck: Skull base/mandible	1	1		
Lymphatic system: Right arm	1	1		
Pelvic area: Trochanter major, femur neck	1	1		
Pelvic area: Testis	1	1		
Retroperitoneal: Kidney	6	6		
Retroperitoneal: Adrenal gland	1	1		
Spine: Spinal cord	4	4		
Spine: Lumbar spine	1	1		

Notes:

[15] - FAS

[16] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Technical Adequacy for Diagnosis

End point title	Number of Subjects With Technical Adequacy for Diagnosis

End point description:

The technical adequacy of the unenhanced image set and the combined unenhanced and enhanced image set was assessed based on the following 4-point scale: 1=Region visualized with artifacts compromising quality and interpretability of images, 2=Only partial evaluation of images possible, region not covered adequately anatomically, 3=Region visualized with artifacts, partially compromising image quality but evaluation and diagnosis still possible, 4=Region clearly visualized, excellent quality. Evaluation was done on pre-injection and combined (pre- and post-injection) images. Number of subjects with any of the score for unenhanced and combined (pre- and post-contrast) MRI sets were reported.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection (within about 15 minutes)

End point values	Unenhanced MRI Assessment	Combined MRI Assessment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44[17]	44[18]		
Units: Subjects				
Score = 1	0	0		
Score = 2	0	0		
Score = 3	4	3		
Score = 4	40	41		

Notes:

[17] - FAS

[18] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Technical Adequacy for Diagnosis by Body Region

End point title	Number of Subjects With Technical Adequacy for Diagnosis by Body Region

End point description:

The technical adequacy of the the unenhanced image set and the combined unenhanced and enhanced image set was assessed based 4-point scale and body region. Four-point scale: 1=Region visualized with artifacts compromising quality and interpretability of images, 2=Only partial evaluation of images possible, region not covered adequately anatomically, 3=Region visualized with artifacts, partially compromising image quality but evaluation and diagnosis still possible, 4=Region clearly visualized, excellent quality. Evaluation was done on pre-injection and combined (pre- and post-injection) images. Results per body regions were reported. All subjects only have images with score 3 and 4.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection (within about 15 minutes)

End point values	Unenhanced MRI Assessment	Combined MRI Assessment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44[19]	44[20]		
Units: Subjects				
Abdomen: Score 4	1	1		
Brain: Score 3	1	1		
Brain: Score 4	20	20		
Chest/thorax: Score 4	2	2		
Head/neck: Score 3	1	1		
Head/neck: Score 4	4	4		
Lymphatic system: Score 4	1	1		
Pelvic area: Score 4	2	2		
Retroperitoneal area: Score 4	7	7		
Spine: Score 3	2	1		
Spine: Score 4	3	4		

Notes:
[19] - FAS
[20] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects by Overall Contrast Quality

End point title	Number of Subjects by Overall Contrast Quality

End point description:

A qualitative assessment of the overall contrast using the following pre-defined 5-point scale: 1= None (for example, in case of a non-enhancing vessel), 2= Poor, 3= Moderate, 4= Good, 5= Excellent, was done. This parameter was assessed in the postcontrast MRI only, which is evaluated together with the unenhanced, this is why it is called combined. Data for combined MRI set was reported.

End point type	Secondary

End point timeframe:

Images were taken post-injection (within about 15 minutes)

End point values	Combined MRI Assessment			
Subject group type	Subject analysis set			
Number of subjects analysed	44[21]			
Units: Subjects				
None	1			
Poor	0			
Moderate	0			
Good	5			
Excellent	38			

Notes:
[21] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects by Overall Contrast Quality by Body Region

End point title	Number of Subjects by Overall Contrast Quality by Body Region

End point description:

A qualitative assessment of the overall contrast using the following pre-defined 5-point scale: 1= None (for example, in case of a non-enhancing vessel), 2= Poor, 3= Moderate, 4= Good, 5= Excellent, was done on the postcontrast MRI only, which is evaluated together with the unenhanced, this is why it is called combined. Results per body regions were reported. Only subjects with scores "none, good, and excellent" were reported.

End point type	Secondary

End point timeframe:

Images were taken post-injection (within about 15 minutes)

End point values	Combined MRI Assessment			
Subject group type	Subject analysis set			
Number of subjects analysed	44[22]			
Units: Subjects				
Abdomen: Excellent	1			
Brain: Good	2			
Brain: Excellent	19			
Chest/Thorax: Good	1			
Chest/Thorax: Excellent	1			
Head/Neck: Excellent	5			
Lymphatic system: Excellent	1			
Pelvic area: Excellent	2			
Retroperitoneal: None	1			
Retroperitoneal: Good	1			
Retroperitoneal: Excellent	5			
Spine: Good	1			
Spine: Excellent	4			

Notes:

[22] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Presence of Pathology

End point title	Number of Subjects with Presence of Pathology

End point description:

Presence of pathology was assessed for unenhanced and combined MRI sets and recorded as "yes/no". The number of subjects with presence of pathology for each MRI set was reported. The number of lesions identified for each MRI set was recorded as shown in the endpoint "Number of Subjects With Number of Lesions Detected".

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection (within about 15 minutes)

End point values	Unenhanced MRI Assessment	Combined MRI Assessment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44[23]	44[24]		
Units: Subjects				
Yes	33	33		
No	11	11		

Notes:
[23] - FAS
[24] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Presence of Pathology by Body Region

End point title	Number of Subjects with Presence of Pathology by Body Region

End point description:

Presence of pathology was assessed for unenhanced and combined MRI sets and recorded as "yes/no". The number of subjects with presence of pathology for each MRI set per body region was reported. The number of lesions identified for each MRI set was recorded. Results per body region were reported. Evaluation was done on pre-injection and combined (pre- and post-injection) images.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection (within about 15 minutes)

End point values	Unenhanced MRI Assessment	Combined MRI Assessment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44[25]	44[26]		
Units: Subjects				
Abdomen: No	0	0		
Abdomen: Yes	1	1		
Brain: No	10	10		
Brain: Yes	11	11		
Chest/Thorax: No	0	0		
Chest/Thorax: Yes	2	2		
Head/Neck: No	0	0		
Head/Neck: Yes	5	5		
Lymphatic system: No	0	0		
Lymphatic system: Yes	1	1		
Pelvic area: No	0	0		
Pelvic area: Yes	2	2		
Retroperitoneal: No	0	0		
Retroperitoneal: Yes	7	7		
Spine: No	1	1		
Spine: Yes	4	4		

Notes:
[25] - FAS
[26] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Number of Lesions Detected

End point title	Number of Subjects With Number of Lesions Detected

End point description:

Presence of pathology included presence of lesions and was recorded as "yes/no". If "yes" the number of subjects with specified lists of lesions and body region was reported. Evaluation was done on pre-injection and combined (pre- and post-injection) images.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection (within about 15 minutes)

End point values	Unenhanced MRI Assessment	Combined MRI Assessment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44[27]	44[28]		
Units: Subjects				
Number of lesions=missing	2	1		
Number of lesions=1	29	29		
Number of lesions=2	2	2		
Number of lesions=10	0	1		

Notes:

[27] - 44 subjects in the FAS were analyzed. The number of subjects with presence of pathology was 33.
[28] - 44 subjects in the FAS were analyzed. The number of subjects with presence of pathology was 33.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Number of Lesions Detected by Body Region

End point title	Number of Subjects With Number of Lesions Detected by Body Region

End point description:

Presence of pathology included presence of lesions and was recorded as "yes/no". If "yes" the number of subjects with specified lists of lesions and body region was reported. Evaluation was done on pre-injection and combined (pre- and post-injection) images. Data of subjects with missing number of lesions or at least one lesion in unenhanced and combined MRI sets were reported.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection (within about 15 minutes)

End point values	Unenhanced MRI Assessment	Combined MRI Assessment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44[29]	44[30]		
Units: Subjects				
Abdomen: Missing lesion	1	1		
Abdomen: 1 lesion	0	0		
Abdomen: 2 lesion	0	0		
Abdomen: 10 lesion	0	0		
Brain: Missing lesion	0	0		
Brain: 1 lesion	10	10		
Brain: 2 lesion	1	1		
Brain: 10 lesion	0	0		
Chest/Thorax: Missing lesion	0	0		
Chest/Thorax: 1 lesion	2	2		
Chest/Thorax: 2 lesion	0	0		
Chest/Thorax: 10 lesion	0	0		
Head/Neck: Missing lesion	1	0		
Head/Neck: 1 lesion	4	4		
Head/Neck: 2 lesion	0	0		
Head/Neck: 10 lesion	0	1		
Lymphatic system: Missing lesion	0	0		
Lymphatic system: 1 lesion	1	1		
Lymphatic system: 2 lesion	0	0		
Lymphatic system: 10 lesion	0	0		
Pelvic area: Missing lesion	0	0		
Pelvic area: 1 lesion	2	2		
Pelvic area: 2 lesion	0	0		
Pelvic area: 10 lesion	0	0		
Retroperitoneal: Missing lesion	0	0		
Retroperitoneal: 1 lesion	6	6		
Retroperitoneal: 2 lesion	1	1		
Retroperitoneal: 10 lesion	0	0		
Spine: Missing lesion	0	0		
Spine: 1 lesion	4	4		
Spine: 2 lesion	0	0		
Spine: 10 lesion	0	0		

Notes:

[29] - 44 subjects in the FAS were analyzed. The number of subjects with presence of pathology was 33.

[30] - 44 subjects in the FAS were analyzed. The number of subjects with presence of pathology was 33.

Statistical analyses

No statistical analyses for this end point

Secondary: Contrast Enhancement in Lesion or Vessel

End point title	Contrast Enhancement in Lesion or Vessel

End point description:

The contrast-enhancement for each lesion or vessel was recorded on a 4-point scale: 1 = None, lesion or vessel is not enhanced; 2 = Moderate, lesion or vessel is weakly enhanced; 3 = Good, lesion or vessel is clearly enhanced; 4 = Excellent, lesion or vessel is clearly and brightly enhanced. Evaluation

was done on pre-injection and combined (pre- and post-injection) images.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection (within about 15 minutes)

End point values	Unenhanced MRI Assessment	Combined MRI Assessment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44[31]	44[32]		
Units: Subjects				
None	44	3		
Moderate	0	0		
Good	0	6		
Excellent	0	35		

Notes:

[31] - FAS

[32] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Contrast Enhancement in Lesion or Vessel by Body Region

End point title	Contrast Enhancement in Lesion or Vessel by Body Region

End point description:

The contrast-enhancement for each lesion or vessel was recorded on a 4-point scale: 1 = None, lesion or vessel is not enhanced; 2 = Moderate, lesion or vessel is weakly enhanced; 3 = Good, lesion or vessel is clearly enhanced; 4 = Excellent, lesion or vessel is clearly and brightly enhanced. Results per body regions were reported. Evaluation was done on pre-injection and combined (pre- and post-injection) images. Evaluation was done on pre-injection and combined (pre- and post-injection) images. Only subjects with scores "none, good, and excellent" for unenhanced and combined MRI sets were reported.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection (within about 15 minutes)

End point values	Unenhanced MRI Assessment	Combined MRI Assessment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44[33]	44[34]		
Units: Subjects				
Abdomen: None	1	1		
Blood vessel: None	2	0		
Blood vessel: Excellent	0	2		
Brain: None	19	0		
Brain: Good	0	1		

Brain: Excellent	0	18		
Chest/Thorax: None	2	1		
Chest/Thorax: Good	0	1		
Head/Neck: None	5	0		
Head/Neck: Good	0	1		
Head/Neck: Excellent	0	4		
Lymphatic system: None	1	0		
Lymphatic system: Excellent	0	1		
Pelvic area: None	2	0		
Pelvic area: Good	0	2		
Retroperitoneal: None	7	1		
Retroperitoneal: Excellent	0	6		
Spine: None	5	0		
Spine: Good	0	1		
Spine: Excellent	0	4		

Notes:

[33] - FAS

[34] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Border Delineation of Lesion of Vessel

End point title	Number of Subjects With Border Delineation of Lesion of Vessel

End point description:

The border delineation for each lesion or vessel was recorded on a 4-point scale: 1 = None, no or unclear delineation of the boundary between the lesion or vessel and the surrounding tissue; 2 = Moderate, some aspects of border delineation covered; 3 = Good, almost clear delineation, but not complete on relevant slices; 4 = Excellent, clear and complete delineation.Evaluation was done on pre-injection and combined (pre- and post-injection) images.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection (within about 15 minutes)

End point values	Unenhanced MRI Assessment	Combined MRI Assessment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44[35]	44[36]		
Units: Subjects				
None	5	1		
Moderate	6	0		
Good	9	1		
Excellent	24	42		

Notes:

[35] - FAS

[36] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Border Delineation of Lesion of Vessel by Body Region

End point title	Number of Subjects With Border Delineation of Lesion of Vessel by Body Region

End point description:

The border delineation for each lesion or vessel was recorded on a 4-point scale: 1 = None, no or unclear delineation of the boundary between the lesion or vessel and the surrounding tissue; 2 = Moderate, some aspects of border delineation covered; 3 = Good, almost clear delineation, but not complete on relevant slices; 4 = Excellent, clear and complete delineation.The results per body regions were reported. Evaluation was done on pre-injection and combined (pre- and post-injection) images.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection (within about 15 minutes)

End point values	Unenhanced MRI Assessment	Combined MRI Assessment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44[37]	44[38]		
Units: Subjects				
Abdomen: Excellent	1	1		
Blood vessel: Excellent	2	2		
Brain: Moderate	3	0		
Brain: Good	6	0		
Brain: Excellent	10	19		
Chest/Thorax: Good	1	0		
Chest/Thorax: Excellent	1	2		
Head/Neck: Good	2	1		
Head/Neck: Excellent	3	4		
Lymphatic system: Excellent	1	1		
Pelvic area: Moderate	1	0		
Pelvic area: Excellent	1	2		
Retroperitoneal: None	3	1		
Retroperitoneal: Excellent	4	6		
Spine: None	2	0		
Spine: Moderate	2	0		
Spine: Excellent	1	5		

Notes:

[37] - FAS

[38] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects by Lesion Characterization or Homogeneity of Vessel Enhancement

End point title	Number of Subjects by Lesion Characterization or Homogeneity of Vessel Enhancement

End point description:

The degree of information on internal morphology and structure was recorded on a 3-point scale: 1 = Poor, the structure and internal morphology of the lesion or vessel is poorly visible; 2 = Moderate, the structure and internal morphology of the lesion or vessel is visible but sufficient information cannot be obtained; 3 = Good, the structure and internal morphology of the lesion or vessel is sufficiently visible for diagnostic purposes.Evaluation was done on pre-injection and combined (pre- and post-injection) images.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection (within about 15 minutes)

End point values	Unenhanced MRI Assessment	Combined MRI Assessment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44[39]	44[40]		
Units: Subjects				
Poor	6	1		
Moderate	11	0		
Good	27	43		

Notes:

[39] - FAS

[40] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects by Lesion Characterization or Homogeneity of Vessel Enhancement by Body Region

End point title	Number of Subjects by Lesion Characterization or Homogeneity of Vessel Enhancement by Body Region

End point description:

The degree of information on internal morphology and structure was recorded on a 3-point scale: 1 = Poor, the structure and internal morphology of the lesion or vessel is poorly visible; 2 = Moderate, the structure and internal morphology of the lesion or vessel is visible but sufficient information cannot be obtained; 3 = Good, the structure and internal morphology of the lesion or vessel is sufficiently visible for diagnostic purposes. Results per body regions were reported. Evaluation was done on pre-injection and combined (pre- and post-injection) images.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection (within about 15 minutes)

End point values	Unenhanced MRI Assessment	Combined MRI Assessment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44[41]	44[42]		
Units: Subjects				
Abdomen: Good	1	1		
Blood vessel: Good	2	2		

Brain: Poor	1	0		
Brain: Moderate	5	0		
Brain: Good	13	19		
Chest/Thorax: Moderate	1	0		
Chest/Thorax: Good	1	2		
Head/Neck: Poor	1	0		
Head/Neck: Good	4	5		
Lymphatic system: Good	1	1		
Pelvic area: Moderate	2	0		
Pelvic area: Good	0	2		
Retroperitoneal: Poor	3	1		
Retroperitoneal: Good	4	6		
Spine: Poor	1	0		
Spine: Moderate	3	0		
Spine: Good	1	5		

Notes:

[41] - FAS

[42] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Diagnoses

End point title	Number of Subjects With Diagnoses

End point description:

The following diagnoses were reported for both the unenhanced MRI and the combined MRI image sets: Other diagnoses, No lesions/normal, Congenital disease/syndrome, Malignant lesion, Inflammation, Structural malformation, Benign lesion, and Vascular malformation. Evaluation was done on pre-injection and combined (pre- and post-injection) images.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection (within about 15 minutes)

End point values	Unenhanced MRI Assessment	Combined MRI Assessment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44[43]	44[44]		
Units: Subjects				
Benign lesion	1	2		
Malignant lesion	4	4		
Vascular malformation	1	1		
Structural malformation	2	2		
Inflammation	2	3		
Congenital disease / syndrome	6	8		
No lesion/Normal	10	11		
Other	18	13		

Notes:
[43] - FAS
[44] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Diagnoses by Body Region

End point title	Number of Subjects With Diagnoses by Body Region

End point description:

The following diagnoses were reported for both the unenhanced MRI and the combined MRI image sets: Other diagnoses, No lesions/normal, Congenital disease/syndrome, Malignant lesion, Inflammation, Structural malformation, Benign lesion, and Vascular malformation. Results per body regions were reported. Evaluation was done on pre-injection and combined (pre- and post-injection) images.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection (within about 15 minutes)

End point values	Unenhanced MRI Assessment	Combined MRI Assessment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44[45]	44[46]		
Units: Subjects				
Abdomen: Other	1	1		
Brain: Malignant lesion	1	1		
Brain: Inflammation	1	1		
Brain: Congenital disease/syndrome	3	3		
Brain: No lesion/Normal	9	10		
Brain: Other	7	6		
Chest/Thorax: Structural malformation	1	1		
Chest/Thorax: Other	1	1		
Head/Neck: Benign lesion	1	1		
Head/Neck: Malignant lesion	1	1		
Head/Neck: Inflammation	1	1		
Head/Neck: Other	2	2		
Lymphatic system: Vascular malformation	1	1		
Pelvic area: Benign lesion	0	1		
Pelvic area: Inflammation	0	1		
Pelvic area: Other	2	0		
Retroperitoneal: Malignant lesion	1	1		
Retroperitoneal: Congenital disease/syndrome	3	5		
Retroperitoneal: Other	3	1		
Spine: Malignant lesion	1	1		
Spine: Structural malformation	1	1		

Spine: No lesion/Normal	1	1		
Spine: Other	2	2		

Notes:

[45] - FAS

[46] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Additional Diagnostic Gain

End point title	Number of Subjects with Additional Diagnostic Gain

End point description:

Additional diagnostic gain by the contrast-enhanced image set was assessed on a 3-point scale: scale 1 = Initial diagnosis unchanged, scale 2 = Initial diagnosis changed - improved, i.e. more specific, and scale 3 = Initial diagnosis changed -new diagnosis. Evaluation was done on combined (pre- and post-injection) images.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection (within about 15 minutes)

End point values	Combined MRI Assessment			
Subject group type	Subject analysis set			
Number of subjects analysed	44[47]			
Units: Subjects				
Scale 1	19			
Scale 2	24			
Scale 3	1			

Notes:

[47] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Additional Diagnostic Gain by Body Region

End point title	Number of Subjects with Additional Diagnostic Gain by Body Region

End point description:

Additional diagnostic gain by the contrast-enhanced image set was assessed on a 3-point scale: scale 1 = Initial diagnosis unchanged, scale 2 = Initial diagnosis changed - improved, i.e. more specific, and scale 3 = Initial diagnosis changed -new diagnosis. Results per body regions were reported. Evaluation was done on pre-injection and combined (pre- and post-injection) images.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection (within about 15 minutes)

End point values	Combined MRI Assessment			
Subject group type	Subject analysis set			
Number of subjects analysed	44[48]			
Units: Subjects				
Abdomen: Scale 2	1			
Brain: Scale 1	11			
Brain: Scale 2	9			
Brain: Scale 3	1			
Chest/Thorax: Scale 2	2			
Head/Neck: Scale 1	3			
Head/Neck: Scale 2	2			
Lymphatic system: Scale 2	1			
Pelvic area: Scale 2	2			
Retroperitoneal: Scale 1	3			
Retroperitoneal: Scale 2	4			
Spine: Scale 1	2			
Spine: Scale 2	3			

Notes:

[48] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Confidence in Diagnosis

End point title	Number of Subjects with Confidence in Diagnosis

End point description:

Diagnostic confidence based on the unenhanced MRI image sets and thereafter on the combined MRI image sets were assessed on a 3-point scale, as 1 = Not confident, 2 = Confident, 3 = Very confident. Evaluation was done on pre-injection and combined (pre- and post-injection) images.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection (within about 15 minutes)

End point values	Unenhanced MRI Assessment	Combined MRI Assessment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44[49]	44[50]		
Units: Subjects				
Not confident	6	1		
Confident	14	3		
Very confident	24	40		

Notes:
[49] - FAS
[50] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Confidence in Diagnosis by Body Region

End point title	Number of Subjects with Confidence in Diagnosis by Body Region

End point description:

Diagnostic confidence based on the unenhanced MRI image sets and thereafter on the combined MRI image sets were assessed on a 3-point scale, as 3 = Very confident, 2 = Confident, and 1 = Not confident. Results per body regions were reported. Evaluation was done on pre-injection and combined (pre- and post-injection) images.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection (within about 15 minutes)

End point values	Unenhanced MRI Assessment	Combined MRI Assessment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44[51]	44[52]		
Units: Subjects				
Abdomen: Confident	1	1		
Brain: Not confident	1	0		
Brain: Confident	8	0		
Brain: Very confident	12	21		
Chest/Thorax: Confident	1	0		
Chest/Thorax: Very confident	1	2		
Head/Neck: Confident	2	0		
Head/Neck: Very confident	3	5		
Lymphatic system: Very confident	1	1		
Pelvic area: Not confident	2	0		
Pelvic area: Confident	0	2		
Retroperitoneal: Not confident	3	1		
Retroperitoneal: Very confident	4	6		
Spine: Confident	2	0		
Spine: Very confident	3	5		

Notes:
[51] - FAS
[52] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Final Diagnosis

End point title	Number of Subjects With Final Diagnosis

End point description:

The final diagnosis of the subjects was based on all clinical information available and was provided separately within 4 weeks after MRI. Evaluation was done on pre-injection and combined (pre- and post-injection) images.

End point type	Secondary

End point timeframe:

Up to 4 weeks post-injection

End point values	Overall Study			
Subject group type	Reporting group			
Number of subjects analysed	44[53]			
Units: Subjects				
Other diagnoses	24			
Congenital disease/syndrome	6			
No lesions/normal	6			
Malignant lesions	4			
Benign lesions	2			
Infectious disease	1			
Structural malformation	1			

Notes:

[53] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Final Diagnosis by Body Region

End point title	Number of Subjects With Final Diagnosis by Body Region

End point description:

The final diagnosis of the subjects was based on all clinical information available and was provided separately within 4 weeks after MRI. Results per body regions were reported. Evaluation was done on pre-injection and combined (pre- and post-injection) images. Only subjects with final diagnosis were reported.

End point type	Secondary

End point timeframe:

Up to 4 weeks post-injection

End point values	Overall Study			
Subject group type	Reporting group			
Number of subjects analysed	44[54]			
Units: Subjects				
Abdomen: Other	1			
Brain: Other	10			
Chest/ thorax: No lesion/Normal	6			

Chest/ thorax: Congenital disease / syndrome	3			
Chest/ thorax: Other	2			
Chest/ thorax: Infectious disease	1			
Chest/ thorax: Malignant lesion	1			
Head/ neck: Other	3			
Head/ neck: Benign lesion	1			
Head/ neck: Malignant lesion	1			
Lymphatic system: Other	1			
Pelvic area: Benign lesion	1			
Pelvic area: Other	1			
Retroperitoneal: Congenital disease / syndrome	3			
Retroperitoneal: Other	3			
Retroperitoneal: Malignant lesion	1			
Spine: Other	3			
Spine: Malignant lesion	1			
Spine: Structural malformation	1			

Notes:

[54] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Change in Diagnosis From Unenhanced to Combined MRI by Body Region

End point title	Number of Subjects With Change in Diagnosis From Unenhanced to Combined MRI by Body Region

End point description:

The analysis value for change in diagnosis was recorded as "yes/no". Results per body regions were reported. Evaluation was done on pre-injection and combined (pre- and post-injection) images.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection (within about 15 minutes)

End point values	Overall Study			
Subject group type	Reporting group			
Number of subjects analysed	44[55]			
Units: Subjects				
Abdomen: No	1			
Abdomen: Yes	0			
Brain: No	20			
Brain: Yes	1			
Chest/Thorax: No	2			
Chest/Thorax: Yes	0			
Head/Neck: No	5			
Head/Neck: Yes	0			
Lymphatic system: No	1			

Lymphatic system: Yes	0			
Pelvic area: No	0			
Pelvic area: Yes	2			
Retroperitoneal: No	5			
Retroperitoneal: Yes	2			
Spine: No	5			
Spine: Yes	0			

Notes:

[55] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Change in Diagnosis From Unenhanced to Combined MRI

End point title	Number of Subjects With Change in Diagnosis From Unenhanced to Combined MRI

End point description:

The analysis value for change in diagnosis was recorded as "yes/no". Evaluation was done on pre-injection and combined (pre- and post-injection) images.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection (within about 15 minutes)

End point values	Overall Study			
Subject group type	Reporting group			
Number of subjects analysed	44[56]			
Units: Subjects				
No	39			
Yes	5			

Notes:

[56] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Change in Diagnosis From Unenhanced MRI to Final Diagnosis

End point title	Number of Subjects With Change in Diagnosis From Unenhanced MRI to Final Diagnosis

End point description:

The analysis value for change in diagnosis was recorded as "yes/no". Evaluation was done on pre-injection and combined (pre- and post-injection) images.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection (within about 15 minutes)

End point values	Overall Study			
Subject group type	Reporting group			
Number of subjects analysed	44[57]			
Units: Subjects				
No	33			
Yes	11			

Notes:

[57] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Change in Diagnosis From Unenhanced MRI to Final Diagnosis by Body Region

End point title	Number of Subjects With Change in Diagnosis From Unenhanced MRI to Final Diagnosis by Body Region

End point description:

The analysis value for change in diagnosis was recorded as "yes/no". Results per body regions were reported.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection (within about 15 minutes)

End point values	Overall Study			
Subject group type	Reporting group			
Number of subjects analysed	44[58]			
Units: Subjects				
Abdomen: No	1			
Abdomen: Yes	0			
Brain: No	17			
Brain: Yes	4			
Chest/Thorax: No	1			
Chest/Thorax: Yes	1			
Head/Neck: No	4			
Head/Neck: Yes	1			
Lymphatic system: No	0			
Lymphatic system: Yes	1			
Pelvic area: No	1			
Pelvic area: Yes	1			
Retroperitoneal: No	5			
Retroperitoneal: Yes	2			
Spine: No	4			
Spine: Yes	1			

Notes:
[58] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Change in Diagnosis From Combined MRI to Final Diagnosis

End point title	Number of Subjects With Change in Diagnosis From Combined MRI to Final Diagnosis

End point description:

The analysis value for change in diagnosis was recorded as "yes/no". Evaluation was done on pre-injection and combined (pre- and post-injection) images.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection (within about 15 minutes)

End point values	Overall Study			
Subject group type	Reporting group			
Number of subjects analysed	44[59]			
Units: Subjects				
No	32			
Yes	12			

Notes:
[59] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Change in Diagnosis From Combined MRI to Final Diagnosis by Body Region

End point title	Number of Subjects With Change in Diagnosis From Combined MRI to Final Diagnosis by Body Region

End point description:

The analysis value for change in diagnosis was recorded as "yes/no". Results per body regions were reported. Evaluation was done on pre-injection and combined (pre- and post-injection) images.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection (within about 15 minutes)

End point values	Overall Study			
Subject group type	Reporting group			
Number of subjects analysed	44[60]			
Units: Subjects				
Abdomen: No	1			
Abdomen: Yes	0			
Brain: No	16			
Brain: Yes	5			
Chest/Thorax: No	1			
Chest/Thorax: Yes	1			
Head/Neck: No	4			
Head/Neck: Yes	1			
Lymphatic system: No	0			
Lymphatic system: Yes	1			
Pelvic area: No	1			
Pelvic area: Yes	1			
Retroperitoneal: No	5			
Retroperitoneal: Yes	2			
Spine: No	4			
Spine: Yes	1			

Notes:

[60] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Change in Management From Unenhanced to Combined MRI

End point title	Number of Subjects With Change in Management From Unenhanced to Combined MRI

End point description:

The subject management was indicated based on the unenhanced images alone. The analysis value for change in subject management was recorded as "yes/no". Evaluation was done on pre-injection and combined (pre- and post-injection) images.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection (within about 15 minutes)

End point values	Overall Study			
Subject group type	Reporting group			
Number of subjects analysed	44[61]			
Units: Subjects				
No	36			
Yes	8			

Notes:

[61] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Change in Management From Unenhanced to Combined MRI by Body Region

End point title	Number of Subjects With Change in Management From Unenhanced to Combined MRI by Body Region

End point description:

The subject management was indicated based on the unenhanced images alone. The analysis value for change in subject management was recorded as "yes/no". Results per body regions were reported. Evaluation was done on pre-injection and combined (pre- and post-injection) images.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection (within about 15 minutes)

End point values	Overall Study			
Subject group type	Reporting group			
Number of subjects analysed	44[62]			
Units: Subjects				
Abdomen: No	1			
Abdomen: Yes	0			
Brain: No	19			
Brain: Yes	2			
Chest/Thorax: No	2			
Chest/Thorax: Yes	0			
Head/Neck: No	5			
Head/Neck: Yes	0			
Lymphatic system: No	1			
Lymphatic system: Yes	0			
Pelvic area: No	0			
Pelvic area: Yes	2			
Retroperitoneal: No	3			
Retroperitoneal: Yes	4			
Spine: No	5			
Spine: Yes	0			

Notes:

[62] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Estimated Glomerular Filtration Rate (eGFR) Prior to Gadobutrol Injection

End point title	Estimated Glomerular Filtration Rate (eGFR) Prior to Gadobutrol Injection

End point description:

The estimated glomerular filtration rate (eGFR) is used to assess the renal function in the pediatric population. eGFR was calculated based on the Schwartz formula with blood sampling for serum

creatinine (Scr) not exceeding 14 days prior to gadobutrol injection. If Scr was measured with routine methods that had not been recalibrated to be traceable to isotope dilution mass spectrometry (IDMS), the eGFR was obtained from the original Schwartz formula: eGFR = k * height / Scr; where k is a proportionality constant (k = 0.45 in term newborn infants < 1 year of age, and k = 0.55 in children up to 13 years of age). If Scr was measured by an enzymatic creatinine method that had been calibrated to be traceable to IDMS, the updated Schwartz formula was used to obtain the eGFR: eGFR = 0.413 * height / Scr. eGFR was reported in the following age groups: < 1 month, 1 to < 2 months, 2 to < 6 months, 6 to < 12 months, and 12 to < 24 months.

End point type	Secondary

End point timeframe:

Before gadobutrol injection

End point values	Overall Study			
Subject group type	Reporting group			
Number of subjects analysed	44[63]			
Units: milliliter/minute/1.73 square meters				
arithmetic mean (standard deviation)				
< 1 month (n=5)	61.8 (± 19.2)			
1 to < 2 months (n=4)	91.7 (± 24.8)			
2 to < 6 months (n=9)	136.3 (± 67.1)			
6 to < 12 months (n=11)	115.2 (± 45.9)			
12 to < 24 months (n=15)	150.4 (± 33.9)			

Notes:

[63] - Here "n" included subjects who were evaluable at specified age group.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Significant Abnormal Laboratory Values

End point title	Number of Subjects With Clinically Significant Abnormal Laboratory Values

End point description:

Change in post-injection test values, such as resulting in a change in subject management or which were not the result of laboratory error and were considered clinically significant by the investigator was reported.

End point type	Secondary

End point timeframe:

Baseline (not exceeding 24 hours before Gadobutrol injection) up to 24 hours post injection

End point values	Overall Study			
Subject group type	Reporting group			
Number of subjects analysed	44[64]			
Units: Subjects	0			

Notes:
[64] - SAF

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Drug Related Serious and Non-Serious Adverse Events

End point title	Number of Subjects With Drug Related Serious and Non-Serious Adverse Events

End point description:

An Adverse Event (AE) was any untoward medical occurrence attributed to study drug in a subject who received study drug. A Serious Adverse Event (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly.
Drug-related adverse events are AEs as determined by the Investigator. The relatedness between adverse events and the administration of treatment was determined by the Investigator based on his/her clinical decision based on all available information. The assessment of the causal relationship to study drug was based on the question whether there was a "reasonable causal relationship" to the study treatment in question.

End point type	Other pre-specified

End point timeframe:

From baseline to approximately 7 days after injection

End point values	Overall Study			
Subject group type	Reporting group			
Number of subjects analysed	44[65]			
Units: Subjects				
Any study drug-related AE	1			
Any study drug-related SAE	0			

Notes:
[65] - SAF included all subjects who received any amount of gadobutrol.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the date of informed consent signed up to approximately 7 days after injection.

Adverse event reporting additional description:

(S)AEs detailed below are both drug-unrelated and related. One non-serious adverse drug reaction (ADR) of Vomiting was reported in one subject (2.3%). Please refer to "other pre-specified endpoint " in end points section.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Overall Study

Reporting group description: -

Serious adverse events	Overall Study		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 44 (6.82%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infected cyst			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subdural empyema			
subjects affected / exposed	1 / 44 (2.27%)		
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	Overall Study		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 44 (38.64%)		
Investigations			
Body temperature increased			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Oxygen saturation decreased			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	2		
General disorders and administration site conditions			
Catheter site erythema			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	5 / 44 (11.36%)		
occurrences (all)	5		
Gastrointestinal disorders			
Abnormal faeces			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 44 (11.36%)		
occurrences (all)	5		
Dyspnoea			

subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Pneumothorax			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	2		
Respiratory distress			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Rhonchi			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Renal and urinary disorders			
Urine odour abnormal			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	4		
Rash pustular			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		

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.

Results for Typical PK parameters were provided by the median value of the population together with the min-max range (individual PK). Typical PK parameter as described in study protocol was reflected by the Median PK parameter in the study report.

Notes: