Clinical trial results:
Open-label multi-center study of magnetic resonance imaging (MRI) with 0.1 mmol/kg BW Gadovist (1.0 M) to assess pharmacokinetics, safety and tolerability in children

Summary

EudraCT number	2006-004153-22
Trial protocol	DE SE DK AT
Global end of trial date	16 April 2008

Results information

Result version number	v1
This version publication date	12 July 2016
First version publication date	04 July 2015

Trial information

Trial identification

Sponsor protocol code	BAY86-4875/91552

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00468819
WHO universal trial number (UTN)	-
Other trial identifiers	Study number: 310788

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	16 April 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 April 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate pharmacokinetic (PK) parameters of Gadovist in plasma at the standard dose of 0.1 millimoles per kilogram (mmol/kg) body weight (BW) in children of different age.

Protection of trial subjects:

The planning and conduct of this clinical study was subject to national laws. Only when all of the requirements of the appropriate regulatory authority had been fulfilled was the study to begin. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization (ICH)-Good Clinical Practice Guideline of 17 January 1997 and guidance dedicated to performance of clinical trials in children (ICH-E11) was also taken into account. For minors, consent was given by the parent(s) or legal guardian(s). The consent of a minor was also requested where such a person was able to do so. His / her refusal or the withdrawal of his / her consent was not disregarded. Adolescents 14 years or older were required to document their assent either on a separate form specifically made for children or on the parents‘ consent form. Younger children could document their assent whenever feasible (at the discretion of the investigator/pediatrician).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 May 2007
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	Austria: 6
Country: Number of subjects enrolled	Sweden: 8
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	Germany: 114
Worldwide total number of subjects	138
EEA total number of subjects	128

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	90
Adolescents (12-17 years)	48
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 140 pediatric subjects aged 2 to less than 18 years, scheduled to undergo a routine contrast-enhanced magnetic resonance imaging (MRI) examination were screened and enrolled in 14 recruiting centers in 4 countries: Austria (1 center), Canada (2 centers), Germany (8 centers), and Sweden (3 centers).

Pre-assignment

Screening details:

Of 140 screened subjects, a total of 138 subjects were treated with study drug and completed the administration of the study drug according to protocol.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Gadobutrol - Age 2 to 6 Years

Arm description:

Subjects in the age range of 2 to 6 years, received Gadobutrol 0.1 mmol/kg BW = 0.1 milliliter per kilogram (mL/kg) BW as single intravenous bolus injection.

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

Dosage and administration details:

Subjects received Gadobutrol 0.1 mmol/kg BW = 0.1 mL/kg BW as single intravenous bolus injection.

Arm title	Gadobutrol - Age 7 to 11 Years

Arm description:

Subjects in the age range of 7 to 11 years, received Gadobutrol 0.1 mmol/kg BW = 0.1 mL/kg BW as single intravenous bolus injection.

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

Dosage and administration details:

Subjects received Gadobutrol 0.1 mmol/kg BW = 0.1 mL/kg BW as single intravenous bolus injection.

Arm title	Gadobutrol - Age 12 to 17 Years

Arm description:

Subjects in the age range of 12 to 17 years, received Gadobutrol 0.1 mmol/kg BW = 0.1 mL/kg BW as single intravenous bolus injection.

Arm type	Experimental

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

Dosage and administration details:

Subjects received Gadobutrol 0.1 mmol/kg BW = 0.1 mL/kg BW as single intravenous bolus injection.

Arm title	Gadobutrol - Age 2 to 17 Years

Arm description:

Subjects received Gadobutrol 0.1 mmol/kg BW = 0.1 mL/kg BW as single intravenous bolus injection. This reporting group consists of the overall study population aged 2 to 17 years which is the sum of all the above 3 reporting groups ("Gadobutrol - Age 2 to 6 Years"+"Gadobutrol - Age 7 to 11 Years"+"Gadobutrol - Age 12 to 17 years").

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

Dosage and administration details:

Subjects received Gadobutrol 0.1 mmol/kg BW = 0.1 mL/kg BW as single intravenous bolus injection.

Number of subjects in period 1	Gadobutrol - Age 2 to 6 Years	Gadobutrol - Age 7 to 11 Years	Gadobutrol - Age 12 to 17 Years
Started	46	44	48
Completed	42	44	46
Not completed	4	0	2
Consent withdrawn by subject	4	-	1
Lost to follow-up	-	-	1

Number of subjects in period 1	Gadobutrol - Age 2 to 17 Years
Started	138
Completed	132
Not completed	6
Consent withdrawn by subject	5
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Gadobutrol - Age 2 to 6 Years
Reporting group description:	
Subjects in the age range of 2 to 6 years, received Gadobutrol 0.1 mmol/kg BW = 0.1 milliliter per kilogram (mL/kg) BW as single intravenous bolus injection.	
Reporting group title	Gadobutrol - Age 7 to 11 Years
Reporting group description:	
Subjects in the age range of 7 to 11 years, received Gadobutrol 0.1 mmol/kg BW = 0.1 mL/kg BW as single intravenous bolus injection.	
Reporting group title	Gadobutrol - Age 12 to 17 Years
Reporting group description:	
Subjects in the age range of 12 to 17 years, received Gadobutrol 0.1 mmol/kg BW = 0.1 mL/kg BW as single intravenous bolus injection.	
Reporting group title	Gadobutrol - Age 2 to 17 Years
Reporting group description:	
Subjects received Gadobutrol 0.1 mmol/kg BW = 0.1 mL/kg BW as single intravenous bolus injection. This reporting group consists of the overall study population aged 2 to 17 years which is the sum of all the above 3 reporting groups ("Gadobutrol - Age 2 to 6 Years"+"Gadobutrol - Age 7 to 11 Years"+"Gadobutrol - Age 12 to 17 years").	

Reporting group values	Gadobutrol - Age 2 to 6 Years	Gadobutrol - Age 7 to 11 Years	Gadobutrol - Age 12 to 17 Years
Number of subjects	46	44	48
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	3.7	9	14.7
standard deviation	± 1.46	± 1.38	± 1.8
Gender categorical			
Units: Subjects			
Female	17	13	23
Male	29	31	25
Body Weight			
Units: kilogram			
arithmetic mean	17.49	57.19	33.75
standard deviation	± 5.434	± 14.245	± 8.956

Reporting group values	Gadobutrol - Age 2 to 17 Years	Total	
Number of subjects	138	138	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	9.2		
standard deviation	± 4.83	-	

Gender categorical Units: Subjects			
Female	53	53	
Male	85	85	
Body Weight Units: kilogram			
arithmetic mean	36.48		
standard deviation	± 19.447	-	

End points

End points reporting groups

Reporting group title	Gadobutrol - Age 2 to 6 Years

Reporting group description:

Subjects in the age range of 2 to 6 years, received Gadobutrol 0.1 mmol/kg BW = 0.1 milliliter per kilogram (mL/kg) BW as single intravenous bolus injection.

Reporting group title	Gadobutrol - Age 7 to 11 Years

Reporting group description:

Subjects in the age range of 7 to 11 years, received Gadobutrol 0.1 mmol/kg BW = 0.1 mL/kg BW as single intravenous bolus injection.

Reporting group title	Gadobutrol - Age 12 to 17 Years

Reporting group description:

Subjects in the age range of 12 to 17 years, received Gadobutrol 0.1 mmol/kg BW = 0.1 mL/kg BW as single intravenous bolus injection.

Reporting group title	Gadobutrol - Age 2 to 17 Years

Reporting group description:

Subjects received Gadobutrol 0.1 mmol/kg BW = 0.1 mL/kg BW as single intravenous bolus injection. This reporting group consists of the overall study population aged 2 to 17 years which is the sum of all the above 3 reporting groups ("Gadobutrol - Age 2 to 6 Years"+"Gadobutrol - Age 7 to 11 Years"+"Gadobutrol - Age 12 to 17 years").

Subject analysis set title	Final Pharmacokinetic (PK) analysis set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The pharmacokinetic analysis was performed based on the per protocol set (PPS). The PPS (number of subjects=135) consisted of all subjects who completed the necessary study procedures for determination of pharmacokinetic variables, who received the appropriate dose of Gadovist, and who had no major protocol deviations. Based on the results of gadolinium concentration measurement, additional 5 patients had to be excluded from PPS due to major deviations relevant for PK analysis. Therefore, a final PK analysis set was defined with a total of 130 subjects.

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

Subject analysis set description:

FAS (number of subjects=138) included all subjects who received any amount of the investigational product.

Subject analysis set title	Urinary analysis set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Urinary analysis set (number of subjects=97) included all subjects those valid for urinary analysis.

Primary: Plasma Clearance Estimates of Gadobutrol by Age Group

End point title	Plasma Clearance Estimates of Gadobutrol by Age Group[1]

End point description:

Total body clearance of Gadobutrol in plasma in Liter per hour (L/h) after intravenous injection.

End point type	Primary

End point timeframe:

From injection of Gadobutrol up to 8 hours 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: Statistical analysis was not performed since as planned all continuous and ordinal categorical variables were analyzed by descriptive statistics only.

End point values	Gadobutrol - Age 2 to 6 Years	Gadobutrol - Age 7 to 11 Years	Gadobutrol - Age 12 to 17 Years	Gadobutrol - Age 2 to 17 Years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45[2]	39[3]	46[4]	130[5]
Units: L/h				
median (inter-quartile range (Q1-Q3))	2.07 (1.45 to 3.83)	3.28 (1.81 to 5.93)	4.9 (2.52 to 7.37)	3.24 (1.53 to 6.62)

Notes:

[2] - Final PK analysis set.

[3] - Final PK analysis set.

[4] - Final PK analysis set.

[5] - Final PK analysis set.

Statistical analyses

No statistical analyses for this end point

Primary: Body Weight-corrected Plasma Clearance Estimates of Gadobutrol by Age Group

End point title	Body Weight-corrected Plasma Clearance Estimates of Gadobutrol by Age Group[6]

End point description:

Total body clearance of Gadobutrol in plasma corrected for body weight liter per hour per kilogram (L/h/kg) after intravenous injection.

End point type	Primary

End point timeframe:

From injection up to 8 hours after Gadobutrol injection

Notes:

[6] - 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	Gadobutrol - Age 2 to 6 Years	Gadobutrol - Age 7 to 11 Years	Gadobutrol - Age 12 to 17 Years	Gadobutrol - Age 2 to 17 Years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45[7]	39[8]	46[9]	130[10]
Units: L/h/kg				
median (inter-quartile range (Q1-Q3))	0.13 (0.09 to 0.17)	0.1 (0.05 to 0.17)	0.09 (0.05 to 0.1)	0.1 (0.05 to 0.17)

Notes:

[7] - Final PK analysis set.

[8] - Final PK analysis set.

[9] - Final PK analysis set.

[10] - Final PK analysis set.

Statistical analyses

No statistical analyses for this end point

Primary: Volume Distribution at Steady State (Vss) Estimates of Gadobutrol by Age Group

End point title	Volume Distribution at Steady State (Vss) Estimates of Gadobutrol by Age Group[11]

End point description:

Apparent volume of distribution at steady state expressed in Liters after intravenous injection.

End point type	Primary

End point timeframe:

From injection up to 8 hours after Gadobutrol 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	Gadobutrol - Age 2 to 6 Years	Gadobutrol - Age 7 to 11 Years	Gadobutrol - Age 12 to 17 Years	Gadobutrol - Age 2 to 17 Years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45[12]	39[13]	46[14]	130[15]
Units: liters				
median (inter-quartile range (Q1-Q3))	3.83 (3.24 to 6.33)	5.98 (4.06 to 11.69)	10.02 (5.16 to 14.12)	5.96 (3.27 to 13.21)

Notes:

[12] - Final PK analysis set.

[13] - Final PK analysis set.

[14] - Final PK analysis set.

[15] - Final PK analysis set.

Statistical analyses

No statistical analyses for this end point

Primary: Body Weight-corrected Volume Distribution at Steady State (Vss) Estimates of Gadobutrol by Age Group

End point title	Body Weight-corrected Volume Distribution at Steady State (Vss) Estimates of Gadobutrol by Age Group[16]

End point description:

Apparent volume of distribution at steady state corrected for body weight (L/h/kg) after intravenous injection.

End point type	Primary

End point timeframe:

From injection to 8 hours after Gadobutrol injection

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

End point values	Gadobutrol - Age 2 to 6 Years	Gadobutrol - Age 7 to 11 Years	Gadobutrol - Age 12 to 17 Years	Gadobutrol - Age 2 to 17 Years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45[17]	39[18]	46[19]	130[20]
Units: liter per kilogram				
median (inter-quartile range (Q1-Q3))	0.24 (0.2 to 0.28)	0.19 (0.14 to 0.23)	0.18 (0.09 to 0.23)	0.2 (0.12 to 0.28)

Notes:

[17] - Final PK analysis set

[18] - Final PK analysis set

[19] - Final PK analysis set

[20] - Final PK analysis set

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Drug Concentration-time Curve of Gadobutrol by Age Group

End point title	Area Under the Drug Concentration-time Curve of Gadobutrol by Age Group[21]

End point description:

Area under the concentration versus time curve from zero to infinity after intravenous injection expressed in micromole*hour per liter (µmol*h/L).

End point type	Primary

End point timeframe:

From injection to 8 hours after Gadobutrol injection

Notes:

[21] - 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	Gadobutrol - Age 2 to 6 Years	Gadobutrol - Age 7 to 11 Years	Gadobutrol - Age 12 to 17 Years	Gadobutrol - Age 2 to 17 Years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45[22]	39[23]	46[24]	130[25]
Units: µmol*h/L				
median (inter-quartile range (Q1-Q3))	815 (494 to 1167)	969 (590 to 2163)	1167 (925 to 1808)	999 (590 to 1808)

Notes:

[22] - Final PK analysis set

[23] - Final PK analysis set

[24] - Final PK analysis set

[25] - Final PK analysis set

Statistical analyses

No statistical analyses for this end point

Primary: Terminal Elimination Half Life Estimates of Gadobutrol by Age Group

End point title	Terminal Elimination Half Life Estimates of Gadobutrol by Age Group[26]

End point description:

Terminal elimination half-life of Gadobutrol from plasma expressed in hours and derived from the terminal slope of the concentration versus time curve.

End point type	Primary

End point timeframe:

From injection to 8 hours after Gadobutrol injection

Notes:

[26] - 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	Gadobutrol - Age 2 to 6 Years	Gadobutrol - Age 7 to 11 Years	Gadobutrol - Age 12 to 17 Years	Gadobutrol - Age 2 to 17 Years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45[27]	39[28]	46[29]	130[30]
Units: hours				
median (inter-quartile range (Q1-Q3))	1.75 (1.34 to 2.3)	1.61 (1.17 to 2.62)	1.65 (1.42 to 2.23)	1.69 (1.34 to 2.32)

Notes:

[27] - Final PK analysis set

[28] - Final PK analysis set

[29] - Final PK analysis set

[30] - Final PK analysis set

Statistical analyses

No statistical analyses for this end point

Primary: Mean Residence Time (MRT) Estimates of Gadobutrol by Age Group

End point title	Mean Residence Time (MRT) Estimates of Gadobutrol by Age Group[31]

End point description:

Mean residence time of Gadobutrol in plasma expressed in hours.

End point type	Primary

End point timeframe:

From injection to 8 hours after Gadobutrol injection

Notes:

[31] - 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	Gadobutrol - Age 2 to 6 Years	Gadobutrol - Age 7 to 11 Years	Gadobutrol - Age 12 to 17 Years	Gadobutrol - Age 2 to 17 Years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45[32]	39[33]	46[34]	130[35]
Units: hours				
median (inter-quartile range (Q1-Q3))	1.88 (1.24 to 2.77)	1.83 (1.03 to 3.37)	2.03 (1.57 to 2.99)	1.94 (1.24 to 2.99)

Notes:

[32] - Final PK analysis set

[33] - Final PK analysis set

[34] - Final PK analysis set

[35] - Final PK analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Urinary Excretion of Gadolinium as Percent of Administered Dose

End point title	Urinary Excretion of Gadolinium as Percent of Administered Dose

End point description:

Amount of gadolinium (a metallic rare-earth element, used as a contrast medium for magnetic resonance imaging) excreted into urine during the collection interval 0 - 6 hours post dose expressed as percentage of administered dose.

End point type	Secondary

End point timeframe:

up to 6 hours after Gadobutrol injection

End point values	Gadobutrol - Age 2 to 6 Years	Gadobutrol - Age 7 to 11 Years	Gadobutrol - Age 12 to 17 Years	Gadobutrol - Age 2 to 17 Years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22[36]	34[37]	41[38]	97[39]
Units: percentage of administered dose				
median (inter-quartile range (Q1-Q3))	93.78 (9.19 to 187.73)	92.14 (18.96 to 117.18)	95.96 (3.48 to 139.03)	94.13 (3.48 to 187.73)

Notes:

[36] - Urinary analysis set

[37] - Urinary analysis set

[38] - Urinary analysis set

[39] - Urinary analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Basic Technical Adequacy of Magnetic Resonance (MR) Images for Diagnosis by Age Group

End point title	Number of Subjects With Basic Technical Adequacy of Magnetic Resonance (MR) Images for Diagnosis by Age Group

End point description:

In the subjects the technical adequacy (evaluability) of MR images was assessed on the following 4-point scale (1=not adequate [compromised quality], 2=partially adequate [evaluation possible], 3=adequate despite artifacts, 4=adequate with excellent quality).

End point type	Secondary

End point timeframe:

Up to 1 hour after Gadobutrol injection

End point values	Gadobutrol - Age 2 to 6 Years	Gadobutrol - Age 7 to 11 Years	Gadobutrol - Age 12 to 17 Years	Gadobutrol - Age 2 to 17 Years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	46[40]	44[41]	48[42]	138[43]
Units: subjects				
not adequate (compromised quality)	0	0	1	1
partially adequate (evaluation possible)	0	0	0	0

adequate despite artifacts	12	13	14	39
adequate with excellent quality	34	31	33	98

Notes:

[40] - FAS

[41] - FAS

[42] - FAS

[43] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Overall Contrast Quality of Post Contrast Images by Age Group

End point title	Number of Subjects With Overall Contrast Quality of Post Contrast Images by Age Group

End point description:

In the subjects qualitative overall contrast quality of post contrast images was assessed on the following 6-point scale (none, poor, moderate, good, excellent, not assessable).

End point type	Secondary

End point timeframe:

up to 1 hour after Gadobutrol injection

End point values	Gadobutrol - Age 2 to 6 Years	Gadobutrol - Age 7 to 11 Years	Gadobutrol - Age 12 to 17 Years	Gadobutrol - Age 2 to 17 Years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	46[44]	44[45]	48[46]	138[47]
Units: subjects				
none	0	0	0	0
poor	0	0	0	0
moderate	0	0	3	3
good	9	17	13	39
excellent	37	27	32	96
not assessable	0	0	0	0

Notes:

[44] - FAS

[45] - FAS

[46] - FAS

[47] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-Contrast Lesions by Location and by Age Group

End point title	Pre-Contrast Lesions by Location and by Age Group

End point description:

Number of lesions on pre-contrast images by organ location and age group.

End point type	Secondary

End point timeframe:
Immediately before Gadobutrol injection

End point values	Gadobutrol - Age 2 to 6 Years	Gadobutrol - Age 7 to 11 Years	Gadobutrol - Age 12 to 17 Years	Gadobutrol - Age 2 to 17 Years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	46[48]	44[49]	48[50]	138[51]
Units: lesions				
Kidney	5	0	8	13
Liver	0	0	0	0
Brain	34	32	30	96
Vessel	0	0	0	0
Spine	7	2	1	10

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

Statistical analyses

No statistical analyses for this end point

Secondary: Post-Contrast Lesions by Location and by Age Group

End point title	Post-Contrast Lesions by Location and by Age Group

End point description:
Number of lesions on post-contrast images by organ location and age group.

End point type	Secondary

End point timeframe:
up to 1 hour after Gadobutrol injection

End point values	Gadobutrol - Age 2 to 6 Years	Gadobutrol - Age 7 to 11 Years	Gadobutrol - Age 12 to 17 Years	Gadobutrol - Age 2 to 17 Years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	46[52]	44[53]	48[54]	138[55]
Units: lesions				
Kidney	6	0	5	11
Liver	0	0	0	0
Brain	33	32	34	99
Vessel	0	0	2	2
Spine	7	2	1	10

Notes:
[52] - FAS
[53] - FAS

[54] - FAS
[55] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-Contrast Delineation of Lesion/Vessel Border by Age Group

End point title	Pre-Contrast Delineation of Lesion/Vessel Border by Age Group

End point description:

In the subjects pre-contrast delineation of each lesion/vessel border was assessed on the following 5-point scale (no, moderate, good, excellent, not assessable).

End point type	Secondary

End point timeframe:

Immediately before Gadobutrol injection

End point values	Gadobutrol - Age 2 to 6 Years	Gadobutrol - Age 7 to 11 Years	Gadobutrol - Age 12 to 17 Years	Gadobutrol - Age 2 to 17 Years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	46[56]	44[57]	48[58]	138[59]
Units: lesions				
no	3	0	1	4
moderate	5	0	5	10
good	20	20	15	55
excellent	18	14	18	50
not assessable	0	0	0	0

Notes:
[56] - FAS
[57] - FAS
[58] - FAS
[59] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Post-Contrast Delineation of Lesion/Vessel Border by Age Group

End point title	Post-Contrast Delineation of Lesion/Vessel Border by Age Group

End point description:

In the subjects post-contrast delineation of each lesion/vessel border was assessed on the following 5-point scale (no, moderate, good, excellent, not assessable).

End point type	Secondary

End point timeframe:

up to 1 hour after Gadobutrol injection

End point values	Gadobutrol - Age 2 to 6 Years	Gadobutrol - Age 7 to 11 Years	Gadobutrol - Age 12 to 17 Years	Gadobutrol - Age 2 to 17 Years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	46[60]	44[61]	48[62]	138[63]
Units: lesions				
no	0	0	5	5
moderate	0	4	7	11
good	14	10	10	34
excellent	30	20	19	69
not assessable	2	0	1	2

Notes:

[60] - FAS

[61] - FAS

[62] - FAS

[63] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-Contrast Lesion Characterization by Age Group

End point title	Pre-Contrast Lesion Characterization by Age Group

End point description:

In the subjects the internal morphology and structure of each pre-contrast lesion was assessed on the following 4-point scale (1=poor, 2=moderate, 3=good, 4=not applicable).

End point type	Secondary

End point timeframe:

Immediately before Gadobutrol injection

End point values	Gadobutrol - Age 2 to 6 Years	Gadobutrol - Age 7 to 11 Years	Gadobutrol - Age 12 to 17 Years	Gadobutrol - Age 2 to 17 Years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	46[64]	44[65]	48[66]	138[67]
Units: lesions				
poor	3	1	2	6
moderate	6	6	6	18
good	36	27	30	93
not applicable	1	0	1	2

Notes:

[64] - FAS

[65] - FAS

[66] - FAS

[67] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Post-Contrast Lesion Characterization by Age Group

End point title	Post-Contrast Lesion Characterization by Age Group

End point description:

In the subjects the internal morphology and structure of each post-contrast lesion was assessed on the following 4-point scale (1=poor, 2=moderate, 3=good, 4=not applicable).

End point type	Secondary

End point timeframe:

up to 1 hour after Gadobutrol injection

End point values	Gadobutrol - Age 2 to 6 Years	Gadobutrol - Age 7 to 11 Years	Gadobutrol - Age 12 to 17 Years	Gadobutrol - Age 2 to 17 Years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	46[68]	44[69]	48[70]	138[71]
Units: lesions				
poor	1	0	6	7
moderate	2	3	6	11
good	42	31	25	98
not applicable	1	0	5	6

Notes:

[68] - FAS

[69] - FAS

[70] - FAS

[71] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Degree of Contrast Enhancement in Lesion/Vessel by Age Group (Given Are Total Numbers of Lesions)

End point title	Degree of Contrast Enhancement in Lesion/Vessel by Age Group (Given Are Total Numbers of Lesions)

End point description:

In the subjects the degree of contrast enhancement in each lesion/vessel was assessed on the following 5-point scale (1=no, 2=moderate, 3=good, 4=excellent, 5=not applicable).

End point type	Secondary

End point timeframe:

up to 1 hour after Gadobutrol injection

End point values	Gadobutrol - Age 2 to 6 Years	Gadobutrol - Age 7 to 11 Years	Gadobutrol - Age 12 to 17 Years	Gadobutrol - Age 2 to 17 Years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	46[72]	44[73]	48[74]	138[75]
Units: lesions				
no	19	19	18	56
moderate	1	1	4	6
good	3	4	2	9
excellent	20	10	16	46
not applicable	3	0	2	5

Notes:

[72] - FAS

[73] - FAS

[74] - FAS

[75] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Change in Diagnostic Confidence by Age Group

End point title	Number of Subjects With Change in Diagnostic Confidence by Age Group

End point description:

In the subjects the change in diagnostic confidence (additional diagnostic gain by the post-contrast scan) was assessed on the following 3-point scale (1=unchanged, 2=improved, 3=worsened).

End point type	Secondary

End point timeframe:

up to 1 hour after Gadobutrol injection

End point values	Gadobutrol - Age 2 to 6 Years	Gadobutrol - Age 7 to 11 Years	Gadobutrol - Age 12 to 17 Years	Gadobutrol - Age 2 to 17 Years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	46[76]	44[77]	48[78]	138[79]
Units: subjects				
missing	0	0	1	1
unchanged	3	3	5	11
improved	43	41	42	126
worsened	0	0	0	0

Notes:

[76] - FAS

[77] - FAS

[78] - FAS

[79] - FAS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Immediately after injection up to 7 days post injection

Adverse event reporting additional description:

As assessed by the investigators, 10 of the 74 adverse events recorded were related to administration of Gadobutrol and 3 of these, that is, crystal urine, pneumonia and meningitis (1.4%) were assessed as serious.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups

Reporting group title	Gadobutrol - Age 2 to 6 Years

Reporting group description:

Subjects in the age range of 2 to 6 years, received Gadobutrol 0.1 mmol/kg BW = 0.1 mL/kg BW as single intravenous bolus injection.

Reporting group title	Gadobutrol - Age 7 to 11 Years

Reporting group description:

Subjects in the age range of 7 to 11 years, received Gadobutrol 0.1 mmol/kg BW = 0.1 mL/kg BW as single intravenous bolus injection.

Reporting group title	Gadobutrol - Age 12 to 17 Years

Reporting group description:

Subjects in the age range of 12 to 17 years, received Gadobutrol 0.1 mmol/kg BW = 0.1 mL/kg BW as single intravenous bolus injection.

Reporting group title	Gadobutrol - Age 2 to 17 Years

Reporting group description:

Subjects received Gadobutrol 0.1 mmol/kg BW = 0.1 mL/kg BW as single intravenous bolus injection. This reporting group consists of the overall study population aged 2 to 17 years which is the sum of all the above 3 reporting groups ("Gadobutrol - Age 2 to 6 Years"+"Gadobutrol - Age 7 to 11 Years"+"Gadobutrol - Age 12 to 17 Years").

Serious adverse events	Gadobutrol - Age 2 to 6 Years	Gadobutrol - Age 7 to 11 Years	Gadobutrol - Age 12 to 17 Years
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 46 (2.17%)	1 / 44 (2.27%)	0 / 48 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Crystal urine			
subjects affected / exposed	0 / 46 (0.00%)	1 / 44 (2.27%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Meningitis			

subjects affected / exposed	1 / 46 (2.17%)	0 / 44 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 46 (0.00%)	1 / 44 (2.27%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Gadobutrol - Age 2 to 17 Years		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 138 (1.45%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Crystal urine			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Meningitis			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Gadobutrol - Age 2 to 6 Years	Gadobutrol - Age 7 to 11 Years	Gadobutrol - Age 12 to 17 Years
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 46 (36.96%)	16 / 44 (36.36%)	16 / 48 (33.33%)
General disorders and administration site conditions			

Chest pain			
subjects affected / exposed	0 / 46 (0.00%)	1 / 44 (2.27%)	0 / 48 (0.00%)
occurrences (all)	0	1	0
Feeling hot			
subjects affected / exposed	0 / 46 (0.00%)	0 / 44 (0.00%)	2 / 48 (4.17%)
occurrences (all)	0	0	2
Pyrexia			
subjects affected / exposed	2 / 46 (4.35%)	2 / 44 (4.55%)	1 / 48 (2.08%)
occurrences (all)	2	2	1
Respiratory, thoracic and mediastinal disorders			
Bronchial obstruction			
subjects affected / exposed	1 / 46 (2.17%)	0 / 44 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
Pharyngolaryngeal pain			
subjects affected / exposed	0 / 46 (0.00%)	0 / 44 (0.00%)	1 / 48 (2.08%)
occurrences (all)	0	0	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 46 (0.00%)	0 / 44 (0.00%)	1 / 48 (2.08%)
occurrences (all)	0	0	1
Investigations			
Oxygen saturation decreased			
subjects affected / exposed	1 / 46 (2.17%)	0 / 44 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 46 (2.17%)	0 / 44 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
Head injury			
subjects affected / exposed	1 / 46 (2.17%)	0 / 44 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 46 (0.00%)	0 / 44 (0.00%)	1 / 48 (2.08%)
occurrences (all)	0	0	1
Dysgeusia			

subjects affected / exposed	0 / 46 (0.00%)	0 / 44 (0.00%)	2 / 48 (4.17%)
occurrences (all)	0	0	2
Headache			
subjects affected / exposed	0 / 46 (0.00%)	2 / 44 (4.55%)	2 / 48 (4.17%)
occurrences (all)	0	3	2
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	0 / 46 (0.00%)	1 / 44 (2.27%)	0 / 48 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 46 (2.17%)	1 / 44 (2.27%)	1 / 48 (2.08%)
occurrences (all)	1	1	1
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 46 (0.00%)	0 / 44 (0.00%)	1 / 48 (2.08%)
occurrences (all)	0	0	1
Abdominal pain			
subjects affected / exposed	0 / 46 (0.00%)	1 / 44 (2.27%)	0 / 48 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			
subjects affected / exposed	0 / 46 (0.00%)	0 / 44 (0.00%)	2 / 48 (4.17%)
occurrences (all)	0	0	2
Constipation			
subjects affected / exposed	0 / 46 (0.00%)	1 / 44 (2.27%)	0 / 48 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	0 / 46 (0.00%)	1 / 44 (2.27%)	0 / 48 (0.00%)
occurrences (all)	0	1	0
Enteritis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 44 (2.27%)	0 / 48 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	1 / 46 (2.17%)	1 / 44 (2.27%)	3 / 48 (6.25%)
occurrences (all)	1	1	3
Stomach discomfort			

subjects affected / exposed	0 / 46 (0.00%)	0 / 44 (0.00%)	2 / 48 (4.17%)
occurrences (all)	0	0	2
Vomiting			
subjects affected / exposed	2 / 46 (4.35%)	2 / 44 (4.55%)	1 / 48 (2.08%)
occurrences (all)	2	2	1
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	1 / 46 (2.17%)	0 / 44 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	0 / 46 (0.00%)	0 / 44 (0.00%)	1 / 48 (2.08%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	1 / 46 (2.17%)	0 / 44 (0.00%)	1 / 48 (2.08%)
occurrences (all)	1	0	1
Rash pruritic			
subjects affected / exposed	0 / 46 (0.00%)	1 / 44 (2.27%)	0 / 48 (0.00%)
occurrences (all)	0	1	0
Pruritus generalised			
subjects affected / exposed	0 / 46 (0.00%)	0 / 44 (0.00%)	1 / 48 (2.08%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 46 (0.00%)	0 / 44 (0.00%)	1 / 48 (2.08%)
occurrences (all)	0	0	1
Leukocyturia			
subjects affected / exposed	0 / 46 (0.00%)	0 / 44 (0.00%)	1 / 48 (2.08%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 46 (0.00%)	2 / 44 (4.55%)	1 / 48 (2.08%)
occurrences (all)	0	2	1
Pain in extremity			
subjects affected / exposed	0 / 46 (0.00%)	0 / 44 (0.00%)	1 / 48 (2.08%)
occurrences (all)	0	0	1
Infections and infestations			

Bronchitis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 44 (2.27%)	0 / 48 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis			
subjects affected / exposed	2 / 46 (4.35%)	1 / 44 (2.27%)	0 / 48 (0.00%)
occurrences (all)	2	1	0
Gastrointestinal infection			
subjects affected / exposed	1 / 46 (2.17%)	0 / 44 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 44 (2.27%)	1 / 48 (2.08%)
occurrences (all)	0	1	1
Otitis media			
subjects affected / exposed	1 / 46 (2.17%)	0 / 44 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 44 (2.27%)	1 / 48 (2.08%)
occurrences (all)	0	1	1
Upper respiratory tract infection			
subjects affected / exposed	1 / 46 (2.17%)	1 / 44 (2.27%)	0 / 48 (0.00%)
occurrences (all)	1	1	0
Central line infection			
subjects affected / exposed	1 / 46 (2.17%)	0 / 44 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0
Oral herpes			
subjects affected / exposed	1 / 46 (2.17%)	0 / 44 (0.00%)	0 / 48 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Gadobutrol - Age 2 to 17 Years		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 138 (35.51%)		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences (all)	1		
Feeling hot			

subjects affected / exposed	2 / 138 (1.45%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	5 / 138 (3.62%)		
occurrences (all)	5		
Respiratory, thoracic and mediastinal disorders			
Bronchial obstruction			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences (all)	1		
Pharyngolaryngeal pain			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences (all)	1		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences (all)	1		
Investigations			
Oxygen saturation decreased			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences (all)	1		
Head injury			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences (all)	1		
Dysgeusia			
subjects affected / exposed	2 / 138 (1.45%)		
occurrences (all)	2		
Headache			

subjects affected / exposed occurrences (all)	4 / 138 (2.90%) 5		
Blood and lymphatic system disorders Eosinophilia subjects affected / exposed occurrences (all)	 1 / 138 (0.72%) 1		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	 3 / 138 (2.17%) 3		
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Enteritis subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Stomach discomfort subjects affected / exposed occurrences (all) Vomiting	 1 / 138 (0.72%) 1 1 / 138 (0.72%) 1 2 / 138 (1.45%) 2 1 / 138 (0.72%) 1 1 / 138 (0.72%) 1 1 / 138 (0.72%) 1 5 / 138 (3.62%) 5 2 / 138 (1.45%) 2		

subjects affected / exposed	5 / 138 (3.62%)		
occurrences (all)	5		
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	2 / 138 (1.45%)		
occurrences (all)	2		
Rash pruritic			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences (all)	1		
Pruritus generalised			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences (all)	1		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences (all)	1		
Leukocyturia			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 138 (2.17%)		
occurrences (all)	3		
Pain in extremity			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences (all)	1		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences (all)	1		

Gastroenteritis			
subjects affected / exposed	3 / 138 (2.17%)		
occurrences (all)	3		
Gastrointestinal infection			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	2 / 138 (1.45%)		
occurrences (all)	2		
Otitis media			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	2 / 138 (1.45%)		
occurrences (all)	2		
Upper respiratory tract infection			
subjects affected / exposed	2 / 138 (1.45%)		
occurrences (all)	2		
Central line infection			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences (all)	1		
Oral herpes			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 June 2007	Rationale for the amendment was that in compliance with additional recommendations made on 27 March 2007 by The German Federal Institute for Drugs and Medical Devices (BfArM), the sections referring to the urine collection in children needed to be amended. The BfArM recommended that the urine collection should not only be performed in children aged at least 9 years but also in capable younger children. Provided that the children/parents were cooperating and that no additional strain was put on the children, it had to be endeavored to also gain data about the gadobutrol urine excretion in younger children - even in the youngest age group (2-6 years), if feasible.

Notes:

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.

Originally, urine was collected up to 6 hours post injection in subjects >9 years. This was amended to subjects of all age groups. As a result, urine was collected in 102 of 138 subjects with gadobutrol injection (lowest rate in subjects 2-6 years).

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/19858730