Clinical trial results:
A PHASE III, MULTI-CENTER, OPEN-LABEL STUDY TO EVALUATE SAFETY AND EFFICACY OF MULTIHANCE® AT THE DOSE OF 0.10 mmol/kg IN MAGNETIC RESONANCE IMAGING OF THE CENTRAL NERVOUS SYSTEM IN PEDIATRIC PATIENTS.

Summary

EudraCT number	2005-004170-25
Trial protocol	DE BE IT
Global end of trial date	26 September 2008

Results information

Result version number	v1 (current)
This version publication date	31 December 2016
First version publication date	31 December 2016

Trial information

Trial identification

Sponsor protocol code	MH-110

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00323310
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bracco Diagnostics, Inc.
Sponsor organisation address	259 Prospect Plains Rd, Cranbury, United States, 08512
Public contact	Gianpaolo Pirovano, Executive Director, Corporate Medical Development, Bracco Diagnostics, Inc, (609) 514-2200,
Scientific contact	Gianpaolo Pirovano, Executive Director, Corporate Medical Development, Bracco Diagnostics, Inc, (609) 514-2200,

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 September 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 September 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of MULTIHANCE at a dose of 0.1 mmol/kg in MRI of the CNS in pediatric patients, in terms of by lesion changes from predose to pre + postdose with regard to the following co-primary visualization endpoints:
- Border delineation of lesions
- internal morphology of lesions
- Contrast enhancement of lesions

To assess the safety of MULTIHANCE at a dose of 0.1 mmol/kg in terms of adverse events and changes in vital signs, ECG findings and laboratory findings.

Protection of trial subjects:

If sedation and/or anesthesia are planned to be administered, the Investigator must carefully perform and monitor patients according to the approved local institution policies. Also obtain an additional predose vital signs series and ECG after sedation/anesthesia is started and immediately before the predose MRI.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 April 2006
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	China: 9
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	Poland: 18
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	United States: 36
Worldwide total number of subjects	94
EEA total number of subjects	48

Notes:

Subjects enrolled per age group

In utero	0

Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	55
Adolescents (12-17 years)	39
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study Initiation Date (first subject enrolled): April 4, 2006; Study completion date (last patient completed study related activities): Sept 26, 2006. The study was conducted at 17 investigational sites. Based on new sample size calculation and adequate distribution of disease/ages of patients, the study was terminated after 94 patients enrolled.

Pre-assignment

Screening details:

Male or female between 2 and 17 years old, inclusive; written informed consent obtained from the patient's parents or legal acceptable representative(s); assent from the patient when applicable; known or highly suspected disease of the CNS (brain/spine) and referred for cranial or spinal MR examination requiring an injection of MR contrast agent.

Period 1

Period 1 title	Predose
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Gadobenate Dimeglumine
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Gadobenate Dimeglumine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

A dose of 0.1 mmol/kg (i.e., 0.2 mL/kg) of 0.5 M MULTIHANCE was administered intravenously at a rate not exceeding 2 mL/sec followed by a saline flush that ensured adequate delivery of the investigational product to the patient.

Number of subjects in period 1	Gadobenate Dimeglumine
Started	94
Completed	92
Not completed	2
Equipment malfunction	1
Had emesis x1 prior to sedation/MRI cancelled	1

Period 2	
Period 2 title	Postdose
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms	
Arm title	Gadobenate Dimeglumine

Arm description:

Gadobenate Dimeglumine

Arm type	Experimental
Investigational medicinal product name	Gadobenate Dimeglumine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

A dose of 0.1 mmol/kg (i.e., 0.2 mL/kg) of 0.5 M MULTIHANCE was administered intravenously at a rate not exceeding 2 mL/sec followed by a saline flush that ensured adequate delivery of the investigational product to the patient.

Number of subjects in period 2	Gadobenate Dimeglumine
Started	92
Completed	89
Not completed	3
Consent withdrawn by subject	1
Did not complete the 24-hr follow up visit	1
A parent refused blood draw	1

Baseline characteristics

Reporting groups

Reporting group title	Gadobenate Dimeglumine

Reporting group description: -

Reporting group values	Gadobenate Dimeglumine	Total	
Number of subjects	94	94	
Age categorical Units: Subjects			
Children (2-11 years)	55	55	
Adolescents (12-17 years)	39	39	
Gender categorical Units: Subjects			
Female	48	48	
Male	46	46	

Subject analysis sets

Subject analysis set title	Subjects
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants

Subject analysis set title	Dummy set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Due to the system limitation with the EudraCT system, a Dummy set was created and used to as a comparison group.
EudraCT does not allow single arm/group statistical analysis. This is dummy set is a workaround to that limitation.
No subjects in this set.

Reporting group values	Subjects	Dummy set	
Number of subjects	92	1	
Age categorical Units: Subjects			
Children (2-11 years)	54	0	
Adolescents (12-17 years)	38	0	
Gender categorical Units: Subjects			
Female	47	0	
Male	45	0	

End points

End points reporting groups

Reporting group title	Gadobenate Dimeglumine
Reporting group description: -	
Reporting group title	Gadobenate Dimeglumine
Reporting group description: Gadobenate Dimeglumine	
Subject analysis set title	Subjects
Subject analysis set type	Intention-to-treat
Subject analysis set description: Participants	
Subject analysis set title	Dummy set
Subject analysis set type	Intention-to-treat
Subject analysis set description: Due to the system limitation with the EudraCT system, a Dummy set was created and used to as a comparison group. EudraCT does not allow single arm/group statistical analysis. This is dummy set is a workaround to that limitation. No subjects in this set.	

Primary: Delineation of Lesion Border(Change From Pre to Pre+Postdose) for Reader 1

End point title	Delineation of Lesion Border(Change From Pre to Pre+Postdose) for Reader 1
End point description:	
End point type	Primary
End point timeframe: pre-dose and immediately postdose	

End point values	Subjects	Dummy set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	92	1		
Units: Lesions				
number (not applicable)				
Lesions Analyzed	148	0		
Predose	1.7	0		
Predose (STD)	1.16	0		
Pre+Postdose	3	0		
Pre+Postdose (STD)	1.2	0		

Statistical analyses

Statistical analysis title	Change From Pre to Pre+Postdose for Reader 1
Statistical analysis description:	
Paired t-test to compare change from pre to pre+postdose	
Comparison groups	Subjects v Dummy set
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001 [2]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	1.5
Variability estimate	Standard deviation
Dispersion value	1.46

Notes:

[1] - Subjects in this analysis are 92

[2] - H0: udiff = 0; Ha: udiff not = 0

Primary: Delineation of Lesion Border (Change From Pre to Pre+Postdose) for Reader 2

End point title	Delineation of Lesion Border (Change From Pre to Pre+Postdose) for Reader 2
End point description:	
5-point scale (0=no delineation of lesion borders [lesion not identified in image, lesion borders not visible]; 1=poor border delineation [all borders poorly distinct, lesion not separated from surrounding tissues/structures/edema]; 2=moderate border delineation [border delineation fair/not complete, lesion not clearly separated]; 3=good border delineation [border delineation complete, lesion adequately separated]; 4=excellent border delineation [borders sharply/clearly distinct, lesion sharply separated]) paired assessment to compare the difference between pre to pre+postdose	
End point type	Primary
End point timeframe:	
pre-dose and immediately postdose	

End point values	Subjects	Dummy set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	92	1		
Units: Lesions				
number (not applicable)				
Lesions Analyzed	135	0		
Predose	1.9	0		
Predose (STD)	1.15	0		
Pre+Postdoes	3.1	0		
Pre+Postdose (STD)	1.11	0		

Statistical analyses

Statistical analysis title	Change From Pre to Pre+Postdose for Reader 2
Statistical analysis description:	
Paired t-test to compare change from pre to pre+postdose	
Comparison groups	Subjects v Dummy set
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.0001 [4]
Method	t-test, 2-sided
Parameter estimate	Median difference (final values)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.4
Variability estimate	Standard deviation
Dispersion value	1.45

Notes:

[3] - Subjects in this analysis are 92.

[4] - H0: udiff = 0; Ha: udiff not = 0

Primary: Delineation of Lesion Border (Change From Pre to Pre+Postdose) for Reader 3

End point title	Delineation of Lesion Border (Change From Pre to Pre+Postdose) for Reader 3
End point description:	
5-point scale (0=no delineation of lesion borders [lesion not identified in image, lesion borders not visible]; 1=poor border delineation [all borders poorly distinct, lesion not separated from surrounding tissues/structures/edema]; 2=moderate border delineation [border delineation fair/not complete, lesion not clearly separated]; 3=good border delineation [border delineation complete, lesion adequately separated]; 4=excellent border delineation [borders sharply/clearly distinct, lesion sharply separated]) paired assessment to compare the difference between pre to pre+postdose	
End point type	Primary
End point timeframe:	
pre-dose and immediately postdose	

End point values	Subjects	Dummy set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	92	1		
Units: Lesions				
number (not applicable)				
Lesions Analyzed	131	0		
Predose	1.7	0		
Predose (STD)	1.19	0		
Pre+Postdose	2.4	0		
Pre+Postdose (STD)	1.12	0		

Statistical analyses

Statistical analysis title	Change From Pre to Pre+Postdose for Reader 3
Statistical analysis description:	
Paired t-test to compare change from pre to pre+postdose	
Comparison groups	Subjects v Dummy set
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.0001 [6]
Method	t-test, 2-sided
Parameter estimate	Median difference (final values)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	0.9
Variability estimate	Standard deviation
Dispersion value	1.42

Notes:

[5] - Subjects in this analysis are 92

[6] - H0: udiff = 0; Ha: udiff not = 0

Primary: Visualization of Lesion Internal Morphology (Change From Pre to Pre+Postdose) for Reader 1

End point title	Visualization of Lesion Internal Morphology (Change From Pre to Pre+Postdose) for Reader 1
End point description:	
5-point scale (0=no visualization of lesion internal morphology (LIM) [lesion not identified in image, not visible]; 1=poor visualization of LIM [insufficiently depicted, intralesional features poorly identified]; 2=moderate visualization of LIM [not completely depicted, some intralesional features visible]; 3=good visualization of LIM [completely depicted, intralesional features adequately identified]; 4=excellent visualization of LIM [optimally depicted, intralesional features clearly identified and characterized]) paired assessment to compare the difference between pre to pre+postdose	
End point type	Primary
End point timeframe:	
pre-dose to immediately post dose	

End point values	Subjects	Dummy set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	92	1		
Units: Lesions				
number (not applicable)				
Lesions Analyzed	148	0		
Predose	1.9	0		
Predose (STD)	1.18	0		
Pre+Postdose	3.2	0		
Pre+Postdose (STD)	1.19	0		

Statistical analyses

Statistical analysis title	Change From Pre to Pre+Postdose for Reader 1
Statistical analysis description:	
Paired t-test to compare change from pre to pre+postdose	
Comparison groups	Subjects v Dummy set
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.001 [8]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	1.6
Variability estimate	Standard deviation
Dispersion value	1.56

Notes:

[7] - Subjects in this analysis are 92

[8] - H0: udiff = 0; Ha: udiff not = 0

Primary: Visualization of Lesion Internal Morphology (Change From Pre to Pre+Postdose) for Reader 2

End point title	Visualization of Lesion Internal Morphology (Change From Pre to Pre+Postdose) for Reader 2

End point description:

5-point scale (0=no visualization of lesion internal morphology (LIM) [lesion not identified in image, not visible]; 1=poor visualization of LIM [insufficiently depicted, intralesional features poorly identified]; 2=moderate visualization of LIM [not completely depicted, some intralesional features visible]; 3=good visualization of LIM [completely depicted, intralesional features adequately identified]; 4=excellent visualization of LIM [optimally depicted, intralesional features clearly identified and characterized]) paired assessment to compare the difference between pre to pre+postdose

End point type	Primary

End point timeframe:

pre-dose to immediately post dose

End point values	Subjects	Dummy set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	92	1		
Units: Lesions				
number (not applicable)				
Lesions Analyzed	135	0		
Predose	2.1	0		
Predose (STD)	1.17	0		
Pre+Postdose	3.2	0		
Pre+Postdose (STD)	1.13	0		

Statistical analyses

Statistical analysis title	Change From Pre to Pre+Postdose for Reader 2

Statistical analysis description:

Paired t-test to compare change from pre to pre+postdose

Comparison groups	Dummy set v Subjects
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	< 0.001 [10]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.4
Variability estimate	Standard deviation
Dispersion value	1.49

Notes:

[9] - Subjects in this analysis are 92

[10] - H0: udiff = 0; Ha: udiff not = 0

Primary: Visualization of Lesion Internal Morphology (Change From Pre to Pre+Postdose) for Reader 3

End point title	Visualization of Lesion Internal Morphology (Change From Pre to Pre+Postdose) for Reader 3

End point description:

5-point scale (0=no visualization of lesion internal morphology (LIM) [lesion not identified in image, not visible]; 1=poor visualization of LIM [insufficiently depicted, intralesional features poorly identified]; 2=moderate visualization of LIM [not completely depicted, some intralesional features visible]; 3=good visualization of LIM [completely depicted, intralesional features adequately identified]; 4=excellent visualization of LIM [optimally depicted, intralesional features clearly identified and characterized])

paired assessment to compare the difference between pre to pre+postdose

End point type	Primary

End point timeframe:

pre-dose to immediately postdose

End point values	Subjects	Dummy set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	92	1		
Units: Lesions				
number (not applicable)				
Lesions Analyzed	131	0		
Predose	1.4	0		
Predose (STD)	1.06	0		
Pre+Postdose	2	0		
Pre+Postdose (STD)	1.23	0		

Statistical analyses

Statistical analysis title	Change From Pre to Pre+Postdose for Reader 3

Statistical analysis description:

Paired t-test to compare change from pre to pre+postdose

Comparison groups	Subjects v Dummy set
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	< 0.0001 [12]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	0.8
Variability estimate	Standard deviation
Dispersion value	1.2

Notes:

[11] - Subjects in this analysis are 92.

[12] - H0: udiff = 0; Ha: udiff not = 0

Primary: Lesion Contrast Enhancement (CE) (Change From Pre to Pre+Postdose) for Reader 1

End point title	Lesion Contrast Enhancement (CE) (Change From Pre to Pre+Postdose) for Reader 1

End point description:

5-point scale (0=no lesion CE [lesion not identified in image, no contrast between lesion and surrounding normal brain/spine tissue]; 1=poor lesion CE [diff. in signal intensity (SI) poor, lesion

barely identified, not possible to evaluate/measure size]; 2=moderate lesion CE [diff. in SI fair, lesion identified, not possible to evaluate/measure size]; 3=good lesion CE [diff. in SI adequate, lesion identified, size evaluated/measured]; 4=excellent lesion CE [diff. in SI marked, lesion identified, size measured]) paired assessment to compare the diff. between pre to pre+postdose

End point type	Primary

End point timeframe:

pre-dose and immediately postdose

End point values	Subjects	Dummy set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	92	1		
Units: Lesions				
number (not applicable)				
Lesions Analyzed	148	0		
Predose	1.8	0		
Predose (STD)	1.16	0		
Pre+Postdose	3	0		
Pre+Postdose (STD)	1.19	0		

Statistical analyses

Statistical analysis title	Change From Pre to Pre+Postdose for Reader 1

Statistical analysis description:

Paired t-test to compare change from pre to pre+postdose

Comparison groups	Subjects v Dummy set
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	< 0.0001 [14]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	1.5
Variability estimate	Standard deviation
Dispersion value	1.57

Notes:

[13] - Subjects in this analysis are 92

[14] - H0: udiff = 0; Ha: udiff not = 0

Primary: Lesion Contrast Enhancement (CE) (Change From Pre to Pre+Postdose) for Reader 2

End point title	Lesion Contrast Enhancement (CE) (Change From Pre to Pre+Postdose) for Reader 2

End point description:

5-point scale (0=no lesion CE [lesion not identified in image, no contrast between lesion and surrounding normal brain/spine tissue]; 1=poor lesion CE [diff. in signal intensity (SI) poor, lesion barely identified, not possible to evaluate/measure size]; 2=moderate lesion CE [diff. in SI fair, lesion identified, not possible to evaluate/measure size]; 3=good lesion CE [diff. in SI adequate, lesion identified, size evaluated/measured]; 4=excellent lesion CE [diff. in SI marked, lesion identified, size measured]) paired assessment to compare the diff. between pre to pre+postdose

End point type	Primary

End point timeframe:

pre-dose to immediately postdose

End point values	Subjects	Dummy set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	92	1		
Units: Lesions				
number (not applicable)				
Lesions Analyzed	135	0		
Predose	2	0		
Predose (STD)	1.2	0		
Pre+Postdose	3.2	0		
Pre+Postdose (STD)	1.12	0		

Statistical analyses

Statistical analysis title	Change From Pre to Pre+Postdose for Reader 2

Statistical analysis description:

Paired t-test to compare change from pre to pre+postdose

Comparison groups	Subjects v Dummy set
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	< 0.0001 [16]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.4
Variability estimate	Standard deviation
Dispersion value	1.49

Notes:

[15] - Subjects in this analysis are 92

[16] - H0: udiff = 0; Ha: udiff not = 0

Primary: Lesion Contrast Enhancement (CE) (Change From Pre to Pre+Postdose) for Reader 3

End point title	Lesion Contrast Enhancement (CE) (Change From Pre to Pre+Postdose) for Reader 3

End point description:

5-point scale (0=no lesion CE [lesion not identified in image, no contrast between lesion and surrounding normal brain/spine tissue]; 1=poor lesion CE [diff. in signal intensity (SI) poor, lesion barely identified, not possible to evaluate/measure size]; 2=moderate lesion CE [diff. in SI fair, lesion identified, not possible to evaluate/measure size]; 3=good lesion CE [diff. in SI adequate, lesion identified, size evaluated/measured]; 4=excellent lesion CE [diff. in SI marked, lesion identified, size measured]) paired assessment to compare the diff. between pre to pre+postdose

End point type	Primary

End point timeframe:

pre-dose to immediately postdose

End point values	Subjects	Dummy set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	92	1		
Units: Lesions				
number (not applicable)				
Lesions Analyzed	131	0		
Predose	1.4	0		
Predose (STD)	0.96	0		
Pre+Postdose	2.2	0		
Pre+Postdose (STD)	1.41	0		

Statistical analyses

Statistical analysis title	Change From Pre to Pre+Postdose for Reader 3

Statistical analysis description:

Paired t-test to compare change from pre to pre+postdose

Comparison groups	Subjects v Dummy set
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority[17]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.1
Variability estimate	Standard deviation
Dispersion value	1.54

Notes:

[17] - Subjects in this analysis are 92.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: up to 72 hours post dose	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	10.1
Reporting groups	
Reporting group title	Safety Population

Reporting group description: -

Serious adverse events	Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 92 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

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

Non-serious adverse events	Safety Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 92 (8.70%)		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 92 (2.17%)		
occurrences (all)	2		
Somnolence			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences (all)	1		
Eye disorders			
Eyelid oedema			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences (all)	1		
Gastrointestinal disorders			

Abdominal discomfort subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 1 / 92 (1.09%) 1 1 / 92 (1.09%) 1 1 / 92 (1.09%) 1		
Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all)	 1 / 92 (1.09%) 1		
Infections and infestations Otitis media subjects affected / exposed occurrences (all)	 1 / 92 (1.09%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 January 2007	Changes in the Conduct of the Study The final date of the protocol was December 22, 2005. There was 1 amendment to the final protocol (Amendment 1 [January 15, 2007]): • As a proactive safety precaution, in response to recent reports of nephrogenic systemic fibrosis/nephrogenic fibrosing dermopathy (NSF/NFD), a rapidly-progressive fibrosis of unknown pathophysiology, occurring in some patients with severe renal impairment who received a gadolinium contrast agent, the exclusion of patients having moderate-to-severe renal impairment (GFR/eGFR < 60 mL/min) was added to provide a greater margin of safety.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported