

**Clinical trial results:**

Prospective non-randomized (pharmacoepidemiologic) cohort study (open-label, multicenter) to assess the magnitude of potential risk with the administration of Primovist/Eovist in patients with moderate to severe renal impairment for the development of nephrogenic systemic fibrosis (NSF) based on diagnostically specific clinical and histopathologic information.

Summary

EudraCT number	2008-005867-33
Trial protocol	DE AT GB
Global end of trial date	24 July 2013

Results information

Result version number	v2 (current)
This version publication date	02 September 2016
First version publication date	17 July 2015
Version creation reason	<ul style="list-style-type: none">• New data added to full data set• Correction of full data set Bayer sponsor contact information to be updated

Trial information**Trial identification**

Sponsor protocol code	BAY86-4873/13701
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00908596
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 November 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	24 July 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to assess the magnitude of the potential risk of developing NSF with the administration of Primovist/Eovist in patients with moderate to severe renal impairment, based on diagnostically specific clinical and histopathological information.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Only after the subject voluntarily signed the informed consent form was he/she able to enter the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 May 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 13
Country: Number of subjects enrolled	Germany: 57
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Italy: 43
Country: Number of subjects enrolled	Spain: 36
Country: Number of subjects enrolled	Korea, Republic of: 107
Country: Number of subjects enrolled	United States: 47
Country: Number of subjects enrolled	Thailand: 50
Country: Number of subjects enrolled	United Kingdom: 4
Worldwide total number of subjects	364
EEA total number of subjects	153

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	168
From 65 to 84 years	188
85 years and over	8

Subject disposition

Recruitment

Recruitment details:

The first subject's first visit was on 21 May 2009. Subjects were screened and enrolled in 35 study centers across Australia, Austria, Germany, Italy, Spain, South Korea, United Kingdom, United states, and Thailand, and undergone contrast enhanced (CE) magnetic resonance imaging (MRI) of liver with Primovist/Eovist within the approved indications.

Pre-assignment

Screening details:

A total of 364 subjects were enrolled. Of these, 4 were withdrawn prior to MRI already since they failed to meet the study entrance criteria, and 3 were withdrawn for other reasons. Subjects had to have moderate to severe renal impairment [estimated glomerular filtration rate (eGFR) 65 milliliter (mL)/minute (min)/1.73 square meter (m²) or less].

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Gadoxetic Acid Disodium - Mild Renal Impairment

Arm description:

Subjects with eGFR prior to Primovist/Eovist injection greater than (>) 65 mL/min/1.73 m². Subjects received Primovist/Eovist as part of their routine medical care.

Arm type	Experimental
Investigational medicinal product name	Primovist/Eovist
Investigational medicinal product code	BAY86-4873
Other name	Gadoxetate disodium
Pharmaceutical forms	Injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Subjects received Primovist/Eovist intravenously at a dose of 0.025 millimoles per kilogram (mmol/kg) body weight (BW).

Arm title	Gadoxetic Acid Disodium - Extended Moderate Renal Impairment
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Arm description:

Subjects with eGFR prior to Primovist/Eovist injection between > 59 and less than or equal to (\leq) 65 mL/min/1.73 m². Subjects received Primovist/Eovist as part of their routine medical care.

Arm type	Experimental
Investigational medicinal product name	Primovist/Eovist
Investigational medicinal product code	BAY86-4873
Other name	Gadoxetate disodium
Pharmaceutical forms	Injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Subjects received Primovist/Eovist intravenously at a dose of 0.025 mmol/kg BW.

Arm title	Gadoxetic Acid Disodium - Moderate Renal Impairment
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Arm description:

Subjects with eGFR prior to Primovist/Eovist injection between greater than or equal to (\geq) 30 and \leq 59 mL/min/1.73 m². Subjects received Primovist/Eovist as part of their routine medical care.

Arm type	Experimental
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Investigational medicinal product name	Primovist/Eovist
Investigational medicinal product code	BAY86-4873
Other name	Gadoxetate disodium
Pharmaceutical forms	Injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Subjects received Primovist/Eovist intravenously at a dose of 0.025 mmol/kg BW.

Arm title	Gadoxetic Acid Disodium - Severe Renal Impairment
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Arm description:

Subjects on dialysis or if not on dialysis with eGFR prior to Primovist/Eovist injection < 30 mL/min/1.73 m². Subjects received Primovist/Eovist as part of their routine medical care.

Arm type	Experimental
Investigational medicinal product name	Primovist/Eovist
Investigational medicinal product code	BAY86-4873
Other name	gadoxetate disodium
Pharmaceutical forms	Injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Subjects received Primovist/Eovist intravenously at a dose of 0.025 mmol/kg BW.

Number of subjects in period 1 ^[1]	Gadoxetic Acid Disodium - Mild Renal Impairment	Gadoxetic Acid Disodium - Extended Moderate Renal Impairment	Gadoxetic Acid Disodium - Moderate Renal Impairment
	Started	47	32
Completed	0	19	119
Not completed	47	13	74
Consent withdrawn by subject	-	1	3
Protocol violation	1	-	-
Death	-	5	57
Other reasons	46	6	2
Lost to follow-up	-	1	12

Number of subjects in period 1 ^[1]	Gadoxetic Acid Disodium - Severe Renal Impairment
Started	85
Completed	48
Not completed	37
Consent withdrawn by subject	1
Protocol violation	-
Death	32
Other reasons	-
Lost to follow-up	4

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Not all the enrolled subjects were treated with study drugs. As baseline included only treated subjects, the worldwide number enrolled in the trial differs with the number of subjects reported in the baseline period.

Baseline characteristics

Reporting groups

Reporting group title	Gadoxetic Acid Disodium - Mild Renal Impairment
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Reporting group description:

Subjects with eGFR prior to Primovist/Eovist injection greater than ($>$) 65 mL/min/1.73 m². Subjects received Primovist/Eovist as part of their routine medical care.

Reporting group title	Gadoxetic Acid Disodium - Extended Moderate Renal Impairment
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Reporting group description:

Subjects with eGFR prior to Primovist/Eovist injection between > 59 and less than or equal to (\leq) 65 mL/min/1.73 m². Subjects received Primovist/Eovist as part of their routine medical care.

Reporting group title	Gadoxetic Acid Disodium - Moderate Renal Impairment
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Reporting group description:

Subjects with eGFR prior to Primovist/Eovist injection between greater than or equal to (\geq) 30 and ≤ 59 mL/min/1.73 m². Subjects received Primovist/Eovist as part of their routine medical care.

Reporting group title	Gadoxetic Acid Disodium - Severe Renal Impairment
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Reporting group description:

Subjects on dialysis or if not on dialysis with eGFR prior to Primovist/Eovist injection < 30 mL/min/1.73 m². Subjects received Primovist/Eovist as part of their routine medical care.

Reporting group values	Gadoxetic Acid Disodium - Mild Renal Impairment	Gadoxetic Acid Disodium - Extended Moderate Renal Impairment	Gadoxetic Acid Disodium - Moderate Renal Impairment
Number of subjects	47	32	193
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	65.3	65.3	65.5
standard deviation	± 9.55	± 12.03	± 10.88
Gender categorical Units: Subjects			
Female	20	7	46
Male	27	25	147
Race/Ethnicity, Customized Units: Subjects			
Caucasian	15	9	101
Black	2	1	6
Hispanic	0	1	3
Asian	27	16	56
Other	3	5	27

Reporting group values	Gadoxetic Acid Disodium - Severe Renal Impairment	Total	
Number of subjects	85	357	
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	62.2 ± 13.83	-	
Gender categorical Units: Subjects			
Female	30	103	
Male	55	254	
Race/Ethnicity, Customized Units: Subjects			
Caucasian	63	188	
Black	2	11	
Hispanic	0	4	
Asian	8	107	
Other	12	47	

End points

End points reporting groups

Reporting group title	Gadoxetic Acid Disodium - Mild Renal Impairment
Reporting group description: Subjects with eGFR prior to Primovist/Eovist injection greater than (>) 65 mL/min/1.73 m ² . Subjects received Primovist/Eovist as part of their routine medical care.	
Reporting group title	Gadoxetic Acid Disodium - Extended Moderate Renal Impairment
Reporting group description: Subjects with eGFR prior to Primovist/Eovist injection between > 59 and less than or equal to (≤) 65 mL/min/1.73 m ² . Subjects received Primovist/Eovist as part of their routine medical care.	
Reporting group title	Gadoxetic Acid Disodium - Moderate Renal Impairment
Reporting group description: Subjects with eGFR prior to Primovist/Eovist injection between greater than or equal to (≥) 30 and ≤ 59 mL/min/1.73 m ² . Subjects received Primovist/Eovist as part of their routine medical care.	
Reporting group title	Gadoxetic Acid Disodium - Severe Renal Impairment
Reporting group description: Subjects on dialysis or if not on dialysis with eGFR prior to Primovist/Eovist injection < 30 mL/min/1.73 m ² . Subjects received Primovist/Eovist as part of their routine medical care.	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description: FAS (N=357) included all subjects who were enrolled and received Primovist/Eovist.	

Primary: Number of Subjects With Moderate to Severe Renal Impairment, Who Develop NSF (Nephrogenic Systemic Fibrosis), Based on Diagnostically Specific Clinical and Histopathological Information

End point title	Number of Subjects With Moderate to Severe Renal Impairment, Who Develop NSF (Nephrogenic Systemic Fibrosis), Based on Diagnostically Specific Clinical and Histopathological Information ^[1]
End point description: A diagnosis of NSF was assumed for subjects with a minimum combined clinical (scale: 0-other diagnosis, 1-inconsistent, 2-suggestive, 3-consistent, 4-highly consistent) and histopathological score (same scale as clinical score). Either the clinical score or the histopathology score had to be at least 2, and the other at least 3.	
End point type	Primary
End point timeframe: Up to 24 months following the administration of Primovist/Eovist	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Gadoxetic Acid Disodium - Mild Renal Impairment	Gadoxetic Acid Disodium - Extended Moderate Renal Impairment	Gadoxetic Acid Disodium - Moderate Renal Impairment	Gadoxetic Acid Disodium - Severe Renal Impairment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	47 ^[2]	32 ^[3]	193 ^[4]	85 ^[5]
Units: subjects	0	0	0	0

Notes:

[2] - FAS

[3] - FAS

[4] - FAS

[5] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Moderate to Severe Renal Impairment in Whom no Biopsy Was Obtained Who Develop NSF-like Symptoms Based on Diagnostically Specific Clinical Information Summarized by Clinical Score

End point title	Number of Subjects With Moderate to Severe Renal Impairment in Whom no Biopsy Was Obtained Who Develop NSF-like Symptoms Based on Diagnostically Specific Clinical Information Summarized by Clinical Score
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End point description:

Subjects in whom no biopsy was obtained with a clinical score of 4 on a scale comprising 0-other diagnosis, 1-inconsistent, 2-suggestive, 3-consistent, 4-highly consistent.

End point type	Secondary
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End point timeframe:

Up to 24 months following the administration of Primovist/Eovist

End point values	Gadoxetic Acid Disodium - Mild Renal Impairment	Gadoxetic Acid Disodium - Extended Moderate Renal Impairment	Gadoxetic Acid Disodium - Moderate Renal Impairment	Gadoxetic Acid Disodium - Severe Renal Impairment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	47 ^[6]	32 ^[7]	193 ^[8]	85 ^[9]
Units: subjects	0	0	0	0

Notes:

[6] - FAS

[7] - FAS

[8] - FAS

[9] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Confidence of the Investigator to Make a Diagnosis Based on the Primovist/Eovist Enhanced MRI (Magnetic Resonance Imaging)

End point title	Confidence of the Investigator to Make a Diagnosis Based on the Primovist/Eovist Enhanced MRI (Magnetic Resonance Imaging)
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End point description:

The investigator was to record his/her confidence in making a diagnosis using a 4 point scale (Very high confidence / High confidence / Moderate / Low confidence). For some subjects, the values were not collected.

End point type	Secondary
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End point timeframe:

Immediately after Primovist/Eovist-enhanced MRI

End point values	Gadoxetic Acid Disodium - Mild Renal Impairment	Gadoxetic Acid Disodium - Extended Moderate Renal Impairment	Gadoxetic Acid Disodium - Moderate Renal Impairment	Gadoxetic Acid Disodium - Severe Renal Impairment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	47 ^[10]	32 ^[11]	193 ^[12]	85 ^[13]
Units: subjects				
Very high	26	16	98	33
High	15	13	80	38
Moderate	5	3	12	4
Low	1	0	2	1

Notes:

[10] - FAS

[11] - FAS

[12] - FAS

[13] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With "Excellent / Good / Adequate / Insufficient" Scores for Lesion Detection

End point title	Number of Subjects With "Excellent / Good / Adequate / Insufficient" Scores for Lesion Detection
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End point description:

The investigator was to record the imaging efficacy by evaluation of lesion detection using a 4 point scale (Excellent / Good / Adequate / Insufficient). For some subjects, the values were not collected.

End point type	Secondary
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End point timeframe:

Immediately after Primovist/Eovist-enhanced MRI

End point values	Gadoxetic Acid Disodium - Mild Renal Impairment	Gadoxetic Acid Disodium - Extended Moderate Renal Impairment	Gadoxetic Acid Disodium - Moderate Renal Impairment	Gadoxetic Acid Disodium - Severe Renal Impairment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	47 ^[14]	32 ^[15]	193 ^[16]	85 ^[17]
Units: subjects				
Excellent	29	20	99	34
Good	15	12	74	29
Adequate	1	0	15	8
Insufficient	0	0	1	2

Notes:

[14] - FAS

[15] - FAS

[16] - FAS

[17] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With "Excellent / Good / Adequate / Insufficient" Scores for Lesion Delineation

End point title	Number of Subjects With "Excellent / Good / Adequate / Insufficient" Scores for Lesion Delineation
End point description: The investigator was to record the imaging efficacy by evaluation of lesion delineation using a 4 point scale (Excellent / Good / Adequate / Insufficient). For some subjects, the values were not collected.	
End point type	Secondary
End point timeframe: Immediately after Primovist/Eovist-enhanced MRI	

End point values	Gadoxetic Acid Disodium - Mild Renal Impairment	Gadoxetic Acid Disodium - Extended Moderate Renal Impairment	Gadoxetic Acid Disodium - Moderate Renal Impairment	Gadoxetic Acid Disodium - Severe Renal Impairment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	47 ^[18]	32 ^[19]	193 ^[20]	85 ^[21]
Units: subjects				
Excellent	27	16	94	31
Good	15	16	77	34
Adequate	3	0	16	6
Insufficient	0	0	1	3

Notes:

[18] - FAS

[19] - FAS

[20] - FAS

[21] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With "Excellent / Good / Adequate / Insufficient" Scores for Lesion Characterization

End point title	Number of Subjects With "Excellent / Good / Adequate / Insufficient" Scores for Lesion Characterization
End point description: The investigator was to record the imaging efficacy by evaluation of lesion characterization using a 4 point scale (Excellent / Good / Adequate / Insufficient). For some subjects, the values were not collected.	

End point type	Secondary
End point timeframe:	
Immediately after Primovist/Eovist-enhanced MRI	

End point values	Gadoxetic Acid Disodium - Mild Renal Impairment	Gadoxetic Acid Disodium - Extended Moderate Renal Impairment	Gadoxetic Acid Disodium - Moderate Renal Impairment	Gadoxetic Acid Disodium - Severe Renal Impairment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	47 ^[22]	32 ^[23]	193 ^[24]	85 ^[25]
Units: subjects				
Excellent	30	13	93	33
Good	12	16	79	34
Adequate	2	3	14	5
Insufficient	1	0	2	2

Notes:

[22] - FAS

[23] - FAS

[24] - FAS

[25] - FAS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 24 months following the administration of Primovist/Eovist

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.0
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Reporting groups

Reporting group title	Gadoxetic Acid Disodium - Mild Renal Impairment
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Reporting group description:

Subjects with eGFR prior to Primovist/Eovist injection >65 mL/min/1.73 m². Subjects received Primovist/Eovist as part of their routine medical care.

Reporting group title	Gadoxetic Acid Disodium - Moderate Renal Impairment
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Reporting group description:

Subjects with eGFR prior to Primovist/Eovist injection between ≥30 and ≤59 mL/min/1.73 m². Subjects received Primovist/Eovist as part of their routine medical care.

Reporting group title	Gadoxetic Acid Disodium - Severe Renal Impairment
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Reporting group description:

Subjects on dialysis or if not on dialysis with eGFR prior to Primovist/Eovist injection <30 mL/min/1.73 m². Subjects received Primovist/Eovist as part of their routine medical care.

Reporting group title	Gadoxetic Acid Disodium - Extended Moderate Renal Impairment
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Reporting group description:

Subjects with eGFR prior to Primovist/Eovist injection between >59 and ≤65 mL/min/1.73 m². Subjects received Primovist/Eovist as part of their routine medical care.

Serious adverse events	Gadoxetic Acid Disodium - Mild Renal Impairment	Gadoxetic Acid Disodium - Moderate Renal Impairment	Gadoxetic Acid Disodium - Severe Renal Impairment
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 47 (0.00%)	0 / 193 (0.00%)	1 / 85 (1.18%)
number of deaths (all causes)	0	57	32
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 47 (0.00%)	0 / 193 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Gadoxetic Acid Disodium - Extended Moderate Renal Impairment		
Total subjects affected by serious adverse events			

subjects affected / exposed	0 / 32 (0.00%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Gadoxetic Acid Disodium - Mild Renal Impairment	Gadoxetic Acid Disodium - Moderate Renal Impairment	Gadoxetic Acid Disodium - Severe Renal Impairment
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 47 (0.00%)	7 / 193 (3.63%)	6 / 85 (7.06%)
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 47 (0.00%)	0 / 193 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Respiratory distress			
subjects affected / exposed	0 / 47 (0.00%)	0 / 193 (0.00%)	0 / 85 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Dermal cyst			
subjects affected / exposed	0 / 47 (0.00%)	0 / 193 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	0	1
Dry skin			
subjects affected / exposed	0 / 47 (0.00%)	0 / 193 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	0 / 47 (0.00%)	4 / 193 (2.07%)	2 / 85 (2.35%)
occurrences (all)	0	4	2
Rash papular			
subjects affected / exposed	0 / 47 (0.00%)	0 / 193 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	0	1
Pruritus generalised			

subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	0 / 193 (0.00%) 0	0 / 85 (0.00%) 0
Skin ulcer subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	0 / 193 (0.00%) 0	1 / 85 (1.18%) 1
Musculoskeletal and connective tissue disorders Extremity contracture subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	0 / 193 (0.00%) 0	1 / 85 (1.18%) 1
Infections and infestations Erysipelas subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	0 / 193 (0.00%) 0	1 / 85 (1.18%) 1
Cellulitis subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	2 / 193 (1.04%) 2	0 / 85 (0.00%) 0
Rash pustular subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	1 / 193 (0.52%) 1	1 / 85 (1.18%) 1

Non-serious adverse events	Gadoxetic Acid Disodium - Extended Moderate Renal Impairment		
Total subjects affected by non-serious adverse events subjects affected / exposed	1 / 32 (3.13%)		
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Respiratory distress subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1		
Skin and subcutaneous tissue disorders Dermal cyst subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0		
Dry skin			

<p>subjects affected / exposed occurrences (all)</p> <p>Pruritus</p> <p>subjects affected / exposed occurrences (all)</p> <p>Rash papular</p> <p>subjects affected / exposed occurrences (all)</p> <p>Pruritus generalised</p> <p>subjects affected / exposed occurrences (all)</p> <p>Skin ulcer</p> <p>subjects affected / exposed occurrences (all)</p>	<p>0 / 32 (0.00%) 0</p> <p>0 / 32 (0.00%) 0</p> <p>0 / 32 (0.00%) 0</p> <p>1 / 32 (3.13%) 1</p> <p>0 / 32 (0.00%) 0</p>		
<p>Musculoskeletal and connective tissue disorders</p> <p>Extremity contracture</p> <p>subjects affected / exposed occurrences (all)</p>	<p>0 / 32 (0.00%) 0</p>		
<p>Infections and infestations</p> <p>Erysipelas</p> <p>subjects affected / exposed occurrences (all)</p> <p>Cellulitis</p> <p>subjects affected / exposed occurrences (all)</p> <p>Rash pustular</p> <p>subjects affected / exposed occurrences (all)</p>	<p>0 / 32 (0.00%) 0</p> <p>0 / 32 (0.00%) 0</p> <p>0 / 32 (0.00%) 0</p>		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 July 2010	Global protocol amendment 4 contained a change in list of participating countries, change of exclusion criteria (to allow for inclusion of subjects who had prior exposure to Primovist/Eovist), additional definition of per protocol set for analysis, update of procedures for subject identification numbers, extension of subject population to be included in the safety follow-up, correction of mistake with regard to cytokine evaluation and clarification of time point for blood sample at baseline, correction of mistake in wording of explanatory text for inclusion criterion, and correction of mistake regarding baseline blood sample. At the express request of the Korean authority, the integrated protocol for global protocol amendment 4 , also contained the changes introduced by local amendments 1 (Austria) and 2 (Korea). Unless otherwise specified, it did not contain the changes introduced by local amendment 3 (United Kingdom).
10 August 2011	Global protocol amendment 5 contained an update to reflect changes in study personnel, removal of the planned study schedule from synopsis, addition of risk categories defined by the European Medicines Agency, clarification of responsibility for the physical examination, addition of a definition for pre-treatment adverse events (AEs), update of expected AEs, clarification of process for reporting serious adverse events clarification regarding direct data entry in case report forms (CRFs), update of archiving requirements, and the correction of mistake with regard to labeling of CRF pages.

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.

The study was stopped early since Food and Drug Administration (FDA) released the sponsor from completing enrollment because the NSF incidence estimate was lower than the original literature-based estimate, and enrollment quota was not feasible.

Notes: