Clinical trial results:
Prospective non-randomized (pharmacoepidemiologic) cohort study (open-label, multicenter) to assess the magnitude of potential risk with the administration of Gadovist 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	2008-004496-22
Trial protocol	DE AT FR
Global end of trial date	27 January 2015

Results information

Result version number	v2 (current)
This version publication date	02 September 2016
First version publication date	26 July 2015
Version creation reason	• New data added to full data set • Correction of full data set Bayer sponsor contact information to be updated

Trial information

Trial identification

Sponsor protocol code	BAY86-4875/13273

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00828737
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, D-51368, Leverkusen, Germany,
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	27 January 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to assess the magnitude of potential risk with the administration of Gadovist in subjects with moderate to severe renal impairment for the development of nephrogenic systemic fibrosis (NSF), 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. Before entering the study, the informed consent form was read by and explained to all subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 December 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 170
Country: Number of subjects enrolled	Australia: 17
Country: Number of subjects enrolled	Canada: 95
Country: Number of subjects enrolled	Germany: 277
Country: Number of subjects enrolled	Italy: 173
Country: Number of subjects enrolled	Korea, Republic of: 95
Country: Number of subjects enrolled	Spain: 47
Country: Number of subjects enrolled	Switzerland: 40
Country: Number of subjects enrolled	Thailand: 12
Worldwide total number of subjects	926
EEA total number of subjects	667

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)	337
From 65 to 84 years	552
85 years and over	37

Subject disposition

Recruitment

Recruitment details:

The study was conducted between 08 December 2008 (first subject first visit) and 27 January 2015 (last subject last visit).

Pre-assignment

Screening details:

Of 926 enrolled subjects, 907 were treated with study drug. The reasons for 19 subjects failure were withdrawal of consent, failed to meet entrance criteria and other reasons.

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?	Yes
Arm title	Mild Renal Impairment

Arm description:

Subjects with mild (estimated glomerular filtration rate [eGFR] greater than [>] 65 milliliter [mL]/minute/1.73 square meter [m^2]) renal impairment received single intravenous injection of Gadobutrol (Gadovist, BAY86-4875) at a dose range of 0.1 to 0.3 millimole (mmol)/kilogram (kg) body weight (1 mmol/kg=1 mL/kg).

Arm type	Experimental
Investigational medicinal product name	Gadobutrol
Investigational medicinal product code	BAY86-4875
Other name	Gadovist
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects with mild (eGFR >65 mL/minute/1.73 m^2) renal impairment received single intravenous injection of Gadobutrol (Gadovist, BAY86-4875) at a dose range of 0.1 to 0.3 mmol/kg body weight (1 mmol/kg=1 mL/kg).

Arm title	Extended Moderate Renal Impairment

Arm description:

Subjects with extended moderate (eGFR >59 and less than or equal to (<=) 65 mL/min/1.73 m^2) renal impairment received single intravenous injection of Gadobutrol (Gadovist, BAY86-4875) 0.1 to 0.3 mmol/kg body weight (1 mmol/kg=1 mL/kg).

Arm type	Experimental
Investigational medicinal product name	Gadobutrol
Investigational medicinal product code	BAY86-4875
Other name	Gadovist
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects with extended moderate (eGFR >59 and <=65 mL/min/1.73 m^2) renal impairment received single intravenous injection of Gadobutrol (Gadovist, BAY86-4875) 0.1 to 0.3 mmol/kg body weight (1 mmol/kg=1 mL/kg).

Arm title	Moderate Renal Impairment

Arm description:

Subjects with moderate (eGFR greater than or equal to (>=) 30 and <=59 mL/min/1.73 m^2) renal impairment received single intravenous injection of Gadobutrol (Gadovist, BAY86-4875) 0.1 to 0.3

mmol/kg body weight (1 mmol/kg=1 mL/kg).

Arm type	Experimental
Investigational medicinal product name	Gadobutrol
Investigational medicinal product code	BAY86- 4875
Other name	Gadovist
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects with moderate (eGFR >=30 and <=59 mL/min/1.73 m^2) renal impairment received single intravenous injection of Gadobutrol (Gadovist, BAY86-4875) 0.1 to 0.3 mmol/kg body weight (1 mmol/kg=1 mL/kg).

Arm title	Severe Renal Impairment

Arm description:

Subjects with severe (eGFR <30 mL/minute/1.73 m^2) renal impairment received single intravenous injection of Gadobutrol (Gadovist, BAY86-4875) 0.1 to 0.3 mmol/kg body weight (1 mmol/kg=1 mL/kg).

Arm type	Experimental
Investigational medicinal product name	Gadobutrol
Investigational medicinal product code	BAY86-4875
Other name	Gadovist
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects with severe (eGFR <30 mL/minute/1.73 m^2) renal impairment received single intravenous injection of Gadobutrol (Gadovist, BAY86-4875) 0.1 to 0.3 mmol/kg body weight (1 mmol/kg=1 mL/kg).

Arm title	Severe Renal Impairment Dialysis Dependent

Arm description:

Subjects with severe (eGFR <30 mL/minute/1.73 m^2) renal impairment and dependent on dialysis, received single intravenous injection of Gadobutrol (Gadovist, BAY86-4875) 0.1 to 0.3 mmol/kg body weight (1 mmol/kg=1 mL/kg).

Arm type	Experimental
Investigational medicinal product name	Gadobutrol
Investigational medicinal product code	BAY86-4875
Other name	Gadovist
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects with severe (eGFR <30 mL/minute/1.73 m^2) renal impairment and dependent on dialysis, received single intravenous injection of Gadobutrol (Gadovist, BAY86-4875) 0.1 to 0.3 mmol/kg body weight (1 mmol/kg=1 mL/kg).

Number of subjects in period 1[1]	Mild Renal Impairment	Extended Moderate Renal Impairment	Moderate Renal Impairment
Started	38	46	539
Completed	0	22	340
Not completed	38	24	199
Consent withdrawn by subject	-	3	24
Death	-	4	94
Unspecified	36	12	53
Lost to follow-up	-	2	27

Failed to meet entrance criteria	-	1	-
Protocol deviation	2	2	1

Number of subjects in period 1[1]	Severe Renal Impairment	Severe Renal Impairment Dialysis Dependent
Started	202	82
Completed	115	46
Not completed	87	36
Consent withdrawn by subject	10	6
Death	41	18
Unspecified	20	5
Lost to follow-up	16	7
Failed to meet entrance criteria	-	-
Protocol deviation	-	-

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 enrolled subjects were treated with study drug. 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	Mild Renal Impairment
Reporting group description:	
Subjects with mild (estimated glomerular filtration rate [eGFR] greater than [>] 65 milliliter [mL]/minute/1.73 square meter [m^2]) renal impairment received single intravenous injection of Gadobutrol (Gadovist, BAY86-4875) at a dose range of 0.1 to 0.3 millimole (mmol)/kilogram (kg) body weight (1 mmol/kg=1 mL/kg).	
Reporting group title	Extended Moderate Renal Impairment
Reporting group description:	
Subjects with extended moderate (eGFR >59 and less than or equal to (<=) 65 mL/min/1.73 m^2) renal impairment received single intravenous injection of Gadobutrol (Gadovist, BAY86-4875) 0.1 to 0.3 mmol/kg body weight (1 mmol/kg=1 mL/kg).	
Reporting group title	Moderate Renal Impairment
Reporting group description:	
Subjects with moderate (eGFR greater than or equal to (>=) 30 and <=59 mL/min/1.73 m^2) renal impairment received single intravenous injection of Gadobutrol (Gadovist, BAY86-4875) 0.1 to 0.3 mmol/kg body weight (1 mmol/kg=1 mL/kg).	
Reporting group title	Severe Renal Impairment
Reporting group description:	
Subjects with severe (eGFR <30 mL/minute/1.73 m^2) renal impairment received single intravenous injection of Gadobutrol (Gadovist, BAY86-4875) 0.1 to 0.3 mmol/kg body weight (1 mmol/kg=1 mL/kg).	
Reporting group title	Severe Renal Impairment Dialysis Dependent
Reporting group description:	
Subjects with severe (eGFR <30 mL/minute/1.73 m^2) renal impairment and dependent on dialysis, received single intravenous injection of Gadobutrol (Gadovist, BAY86-4875) 0.1 to 0.3 mmol/kg body weight (1 mmol/kg=1 mL/kg).	

Reporting group values	Mild Renal Impairment	Extended Moderate Renal Impairment	Moderate Renal Impairment
Number of subjects	38	46	539
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	61.8	67.2	68
standard deviation	± 13.91	± 11.6	± 12.02
Gender categorical			
Units: Subjects			
Female	14	18	179
Male	24	28	360

Reporting group values	Severe Renal Impairment	Severe Renal Impairment Dialysis Dependent	Total
Number of subjects	202	82	907
Age categorical			
Units: Subjects			

Age continuous Units: years			
arithmetic mean	66.8	59.8	
standard deviation	± 12.18	± 13.84	-
Gender categorical Units: Subjects			
Female	75	31	317
Male	127	51	590

End points

End points reporting groups

Reporting group title	Mild Renal Impairment

Reporting group description:

Subjects with mild (estimated glomerular filtration rate [eGFR] greater than [>] 65 milliliter [mL]/minute/1.73 square meter [m^2]) renal impairment received single intravenous injection of Gadobutrol (Gadovist, BAY86-4875) at a dose range of 0.1 to 0.3 millimole (mmol)/kilogram (kg) body weight (1 mmol/kg=1 mL/kg).

Reporting group title	Extended Moderate Renal Impairment

Reporting group description:

Subjects with extended moderate (eGFR >59 and less than or equal to (<=) 65 mL/min/1.73 m^2) renal impairment received single intravenous injection of Gadobutrol (Gadovist, BAY86-4875) 0.1 to 0.3 mmol/kg body weight (1 mmol/kg=1 mL/kg).

Reporting group title	Moderate Renal Impairment

Reporting group description:

Subjects with moderate (eGFR greater than or equal to (>=) 30 and <=59 mL/min/1.73 m^2) renal impairment received single intravenous injection of Gadobutrol (Gadovist, BAY86-4875) 0.1 to 0.3 mmol/kg body weight (1 mmol/kg=1 mL/kg).

Reporting group title	Severe Renal Impairment

Reporting group description:

Subjects with severe (eGFR <30 mL/minute/1.73 m^2) renal impairment received single intravenous injection of Gadobutrol (Gadovist, BAY86-4875) 0.1 to 0.3 mmol/kg body weight (1 mmol/kg=1 mL/kg).

Reporting group title	Severe Renal Impairment Dialysis Dependent

Reporting group description:

Subjects with severe (eGFR <30 mL/minute/1.73 m^2) renal impairment and dependent on dialysis, received single intravenous injection of Gadobutrol (Gadovist, BAY86-4875) 0.1 to 0.3 mmol/kg body weight (1 mmol/kg=1 mL/kg).

Subject analysis set title	Severe Renal Impairment-Combined
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Severe renal impairment-combined (N= 284) was classified or splitted into two groups one was severe renal imapairment (N= 202) and the other was severe renal impairment dialysis dependent (N= 82).

Subject analysis set title	Full Analysis Set (FAS) Population
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects who were enrolled into the study and received Gadovist were included in the FAS.

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

Subject analysis set description:

PPS included all subjects except the subjects with an eGFR greater than (>) 59 to less than or equal to (=<) 65 mL/min/1.73 m^2 as determined by the central laboratory, who were received a Gadolinium based contrast agent (GBCA) other than study drug in the 12 months prior to the magnetic resonance imaging (MRI) examination were not included.

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

End point title	Number of Subjects With Moderate to Severe Renal Impairment, who Develop Nephrogenic Systemic Fibrosis (NSF), Based on Diagnostically Specific Clinical and Histopathological Information[1][2]

End point description:

Clinicopathological definition of NSF requires both clinical symptoms and histopathological findings to make a confident diagnosis. Scores range of clinicopathological were 0 to 4, where 0= another diagnosis can be made, 1= inconsistent, 2= suggestive, 3= consistent, 4= highly consistent. A diagnosis of NSF was made to subjects in whom the clinicopathological score was at least consistent. 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:

From the time of MRI until the end of follow-up period (24 months)

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.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As the endpoint states "Subjects with Moderate and Severe Renal Impairment", subjects with mild renal impairment were not included. "Severe renal impairment" and "severe renal impairment dialysis dependent" reporting groups in the baseline period were combined in the subject analysis set "Severe Renal ImpairmentCombined" which was created to report the data for this endpoint. Hence, the end point is not reporting statistics for all the arms in the baseline period.

End point values	Extended Moderate Renal Impairment	Moderate Renal Impairment	Severe Renal Impairment-Combined	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	39[3]	516[4]	275[5]	
Units: Subjects	0	0	0	

Notes:

[3] - PPS

[4] - PPS

[5] - PPS

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 Nephrogenic Systemic Fibrosis (NSF) Based on Diagnostically Specific Clinical Information

End point title	Number of Subjects With Moderate to Severe Renal Impairment in Whom no Biopsy was Obtained who Develop Nephrogenic Systemic Fibrosis (NSF) Based on Diagnostically Specific Clinical Information[6]

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

End point timeframe:

From the time of MRI until the end of follow-up period (24 months)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As the endpoint states "Subjects with Moderate and Severe Renal Impairment", subjects with mild renal impairment were not included. "Severe renal impairment" and "severe renal impairment dialysis dependent" reporting groups in the baseline period were combined in the subject analysis set "Severe Renal ImpairmentCombined" which was created to report the data for this endpoint. Hence, the end point is not reporting statistics for all the arms in the baseline period.

End point values	Extended Moderate Renal Impairment	Moderate Renal Impairment	Severe Renal Impairment-Combined	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	39[7]	516[8]	275[9]	
Units: Subjects	0	0	0	

Notes:

[7] - PPS

[8] - PPS

[9] - PPS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Different Criteria of Diagnostic Confidence of the Investigator Based on the Gadovist-enhanced Magnetic Resonance Imaging (MRI)

End point title	Number of Subjects With Different Criteria of Diagnostic Confidence of the Investigator Based on the Gadovist-enhanced Magnetic Resonance Imaging (MRI)[10]

End point description:

The investigator was to record subjects confidence in making a diagnosis using a 4-point scale (Very high confidence, High confidence, Moderate, Low confidence). The number of subjects who reported different criteria of diagnostic confidence of the investigator based on the gadovist-enhanced MRI, were presented below.

End point type	Secondary

End point timeframe:

Immediately after Gadovist-enhanced MRI

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: "Severe renal impairment" and "severe renal impairment dialysis dependent" reporting groups in the baseline period were combined in the subject analysis set "Severe Renal ImpairmentCombined" which was created to report the data for this endpoint. Hence, the end point is not reporting statistics for all the arms in the baseline period.

End point values	Mild Renal Impairment	Extended Moderate Renal Impairment	Moderate Renal Impairment	Severe Renal Impairment-Combined
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	38[11]	46[12]	539[13]	284[14]
Units: Subjects				
Very High	23	31	251	150
High	14	11	250	110
Moderate	1	3	33	21
Low	0	0	5	3
Missing	0	1	0	0

Notes:

[11] - FAS population

[12] - FAS population

[13] - FAS population

[14] - FAS population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Image Quality Sufficient for Diagnosis

End point title	Number of Subjects With Image Quality Sufficient for

End point description:

The investigator was to record image quality of the Gadovist enhanced magnetic resonance (MR) image on qualitative assessment basis. The recordings were reported as 'yes', 'no' and 'missing'.

End point type	Secondary

End point timeframe:

Immediately after Gadovist-enhanced MRI

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: "Severe renal impairment" and "severe renal impairment dialysis dependent" reporting groups in the baseline period were combined in the subject analysis set "Severe Renal ImpairmentCombined" which was created to report the data for this endpoint. Hence, the end point is not reporting statistics for all the arms in the baseline period.

End point values	Mild Renal Impairment	Extended Moderate Renal Impairment	Moderate Renal Impairment	Severe Renal Impairment-Combined
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	38[16]	46[17]	539[18]	284[19]
Units: Subjects				
No	0	0	4	3
Yes	38	45	535	281
Missing	0	1	0	0

Notes:

[16] - FAS population

[17] - FAS population

[18] - FAS population

[19] - FAS population

Statistical analyses

No statistical analyses for this end point

Secondary: Evaluation of C-reactive Protein (CRP) in Subjects With Moderate and Severe Renal Impairment

End point title	Evaluation of C-reactive Protein (CRP) in Subjects With Moderate and Severe Renal Impairment[20]

End point description:

Specific cytokine CRP was evaluated and reported to characterize any potentially existing differences in subjects with moderate and severe renal impairment.

End point type	Secondary

End point timeframe:

Within 48 hours prior to the Gadovist administration

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As the endpoint states "Subjects with Moderate and Severe Renal Impairment", subjects

with mild renal impairment were not included. "Severe renal impairment" and "severe renal impairment dialysis dependent" reporting groups in the baseline period were combined in the subject analysis set "Severe Renal ImpairmentCombined" which was created to report the data for this endpoint. Hence, the end point is not reporting statistics for all the arms in the baseline period.

End point values	Extended Moderate Renal Impairment	Moderate Renal Impairment	Severe Renal Impairment	Severe Renal Impairment Dialysis Dependent
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18[21]	283[22]	133[23]	53[24]
Units: miligram per liter				
arithmetic mean (standard deviation)	32.42 (± 45.563)	31.31 (± 41.364)	41.84 (± 70.345)	34.95 (± 46.465)

Notes:

[21] - FAS population with subjects evaluable for this outcome.

[22] - FAS population with subjects evaluable for this outcome.

[23] - FAS population with subjects evaluable for this outcome.

[24] - FAS population with subjects evaluable for this outcome.

Statistical analyses

No statistical analyses for this end point

Secondary: Evaluation of Macrophage Inflammatory Proteins (MIP) and Monocyte Chemotactic Proteins (MCP) in Subjects With Moderate and Severe Renal Impairment

End point title	Evaluation of Macrophage Inflammatory Proteins (MIP) and Monocyte Chemotactic Proteins (MCP) in Subjects With Moderate and Severe Renal Impairment[25]

End point description:

MIPs (MIP-1 beta, MIP-2) and MCPs (MCP-1, MCP-3) were evaluated and reported to characterize any potentially existing differences in subjects with moderate and severe renal impairment. In the categories listed below, "N" signifies the number of subjects evaluable for the respective category.

End point type	Secondary

End point timeframe:

Within 48 hours prior to the Gadovist administration

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As the endpoint states "Subjects with Moderate and Severe Renal Impairment", subjects with mild renal impairment were not included. "Severe renal impairment" and "severe renal impairment dialysis dependent" reporting groups in the baseline period were combined in the subject analysis set "Severe Renal ImpairmentCombined" which was created to report the data for this endpoint. Hence, the end point is not reporting statistics for all the arms in the baseline period.

End point values	Extended Moderate Renal Impairment	Moderate Renal Impairment	Severe Renal Impairment	Severe Renal Impairment Dialysis Dependent
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	46[26]	539[27]	202[28]	82[29]
Units: picogram per milliliter				
arithmetic mean (standard deviation)				
MIP-1 beta (N= 44, 526, 198, 79)	311.89 (± 188.875)	363.28 (± 532.692)	396.79 (± 648.74)	791.21 (± 3814.956)

MIP-2 (N= 42, 525, 198, 79)	786.37 (± 776.666)	619.54 (± 588.275)	670.63 (± 598.305)	456.67 (± 330.863)
MCP-1 (N= 42, 526, 195, 78)	125.96 (± 61.889)	130.76 (± 189.794)	139.2 (± 142.496)	144.54 (± 83.585)
MCP-3 (N=25, 214, 95, 32)	31.47 (± 37.966)	33.84 (± 30.506)	46.83 (± 66.211)	36.02 (± 29.092)

Notes:

[26] - FAS population

[27] - FAS population

[28] - FAS population

[29] - FAS population

Statistical analyses

No statistical analyses for this end point

Secondary: Evaluation of Osteopontin and Tissue Inhibitor of Metallo Proteinase 1 (TIMP1) in Subjects With Moderate and Severe Renal Impairment

End point title	Evaluation of Osteopontin and Tissue Inhibitor of Metallo Proteinase 1 (TIMP1) in Subjects With Moderate and Severe Renal Impairment[30]

End point description:

Osteopontin and TIMP1 were evaluated and reported to characterize any potentially existing differences in subjects with moderate and severe renal impairment. In the categories listed below, "N" signifies the number of subjects evaluable for the respective category.

End point type	Secondary

End point timeframe:

Within 48 hours prior to the Gadovist administration

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As the endpoint states "Subjects with Moderate and Severe Renal Impairment", subjects with mild renal impairment were not included. "Severe renal impairment" and "severe renal impairment dialysis dependent" reporting groups in the baseline period were combined in the subject analysis set "Severe Renal ImpairmentCombined" which was created to report the data for this endpoint. Hence, the end point is not reporting statistics for all the arms in the baseline period.

End point values	Extended Moderate Renal Impairment	Moderate Renal Impairment	Severe Renal Impairment	Severe Renal Impairment Dialysis Dependent
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	44[31]	525[32]	198[33]	79[34]
Units: nanogram per milliliter				
arithmetic mean (standard deviation)				
Osteopontin	27.23 (± 15.899)	41.44 (± 61.48)	87.66 (± 112.252)	101.2 (± 76.857)
TIMP1	158.85 (± 59.179)	187.6 (± 99.455)	253.72 (± 237.127)	268.27 (± 99.728)

Notes:

[31] - FAS population with subjects evaluable for this outcome.

[32] - FAS population with subjects evaluable for this outcome.

[33] - FAS population with subjects evaluable for this outcome.

[34] - FAS population with subjects evaluable for this outcome.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs), Treatment-emergent Serious Adverse Event (TESAE), Drug-related Treatmentemergent Adverse Events (TEAEs) and Drug-related Treatment-emergent Serious Adverse Events (TESAEs)

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAEs), Treatment-emergent Serious Adverse Event (TESAE), Drug-related Treatmentemergent Adverse Events (TEAEs) and Drug-related Treatment-emergent Serious Adverse Events (TESAEs)[35]

End point description:

An adverse event (AE) is any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. A serious adverse event (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. A TEAE was defined as any AE arising or worsening after the start of study drug administration.

End point type	Secondary

End point timeframe:

From the time of MRI until the end of follow-up period (24 months)

Notes:

[35] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: "Severe renal impairment" and "severe renal impairment dialysis dependent" reporting groups in the baseline period were combined in the subject analysis set "Severe Renal ImpairmentCombined" which was created to report the data for this endpoint. Hence, the end point is not reporting statistics for all the arms in the baseline period.

End point values	Mild Renal Impairment	Extended Moderate Renal Impairment	Moderate Renal Impairment	Severe Renal Impairment-Combined
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	38[36]	46[37]	539[38]	284[39]
Units: Subjects				
At Least One TEAE	0	0	2	3
At Least One Serious TEAE	0	0	0	0
At Least One TEAE related to BAY86-4875	0	0	1	2
At Least One TEAE related to study conduct	0	0	1	0
At Least One Serious TEAE related to BAY86-4875	0	0	0	0

Notes:

[36] - FAS population

[37] - FAS population

[38] - FAS population

[39] - FAS population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time of study drug treatment until the end of follow-up period (24 months)

Adverse event reporting additional description:

A treatment-emergent adverse event was defined as any adverse event arising or worsening after the start of study drug administration.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Mild Renal Impairment

Reporting group description:

Subjects with mild (eGFR >65 mL/minute/1.73 m^2) renal impairment received single intravenous injection of Gadobutrol (Gadovist, BAY86-4875) at a dose range of 0.1 to 0.3 mmol/kg body weight (1 mmol/kg=1 mL/kg).

Reporting group title	Severe Renal Impairment-Combined

Reporting group description:

Subjects with severe (eGFR <30 mL/minute/1.73 m^2) renal impairment whether dialysis dependent or not, received single intravenous injection of Gadobutrol (Gadovist, BAY86-4875) 0.1 to 0.3 mmol/kg body weight (1 mmol/kg=1 mL/kg). This reporting group is a combined group of both 'severe renal impairment' and 'severe renal impairment dialysis dependent' reporting groups.

Reporting group title	Moderate Renal Impairment

Reporting group description:

Subjects with moderate (eGFR >=30 and <=59 mL/min/1.73 m^2) renal impairment received single intravenous injection of Gadobutrol (Gadovist, BAY86-4875) 0.1 to 0.3 mmol/kg body weight (1 mmol/kg=1 mL/kg).

Reporting group title	Extended Moderate Renal Impairment

Reporting group description:

Subjects with extended moderate (eGFR >59 and <=65 mL/min/1.73 m^2) renal impairment received single intravenous injection of Gadobutrol (Gadovist, BAY86-4875) 0.1 to 0.3 mmol/kg body weight (1 mmol/kg=1 mL/kg).

Serious adverse events	Mild Renal Impairment	Severe Renal Impairment-Combined	Moderate Renal Impairment
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 38 (0.00%)	0 / 284 (0.00%)	0 / 539 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Serious adverse events	Extended Moderate Renal Impairment		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 46 (0.00%)		
number of deaths (all causes)	0		

number of deaths resulting from adverse events			

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

Non-serious adverse events	Mild Renal Impairment	Severe Renal Impairment-Combined	Moderate Renal Impairment
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 38 (0.00%)	3 / 284 (1.06%)	2 / 539 (0.37%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 38 (0.00%)	0 / 284 (0.00%)	1 / 539 (0.19%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Retching			
subjects affected / exposed	0 / 38 (0.00%)	1 / 284 (0.35%)	0 / 539 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 38 (0.00%)	1 / 284 (0.35%)	0 / 539 (0.00%)
occurrences (all)	0	1	0
Urticaria			
subjects affected / exposed	0 / 38 (0.00%)	0 / 284 (0.00%)	1 / 539 (0.19%)
occurrences (all)	0	0	1
Infections and infestations			
Groin infection			
subjects affected / exposed	0 / 38 (0.00%)	1 / 284 (0.35%)	0 / 539 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Extended Moderate Renal Impairment		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 46 (0.00%)		
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			

Retching subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) Urticaria subjects affected / exposed occurrences (all)	 0 / 46 (0.00%) 0 0 / 46 (0.00%) 0		
Infections and infestations Groin infection subjects affected / exposed occurrences (all)	 0 / 46 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Since the final datasets are not yet available, the current results have been prepared using draft datasets. Therefore, data should be interpreted with caution. Decimal places were automatically truncated if last decimal equals zero.

Notes: