



## Clinical trial results:

**Multicenter, open-label study to evaluate the safety and efficacy (by blinded reading) of Gadobutrol-enhanced magnetic resonance angiography (MRA) after a single injection of 0.1 mmol/kg of Gadobutrol in subjects with known or suspected renal artery disease**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2010-023002-13 |
| Trial protocol           | CZ DE AT       |
| Global end of trial date | 06 July 2012   |

### Results information

|                                   |                                                     |
|-----------------------------------|-----------------------------------------------------|
| Result version number             | v2                                                  |
| This version publication date     | 12 July 2016                                        |
| First version publication date    | 09 November 2014                                    |
| Version creation reason           |                                                     |
| Summary attachment (see zip file) | Bayer Study Synopsis (91759_Study Synopsis_CTP.pdf) |

### Trial information

#### Trial identification

|                       |                   |
|-----------------------|-------------------|
| Sponsor protocol code | BAY 86-4875/91759 |
|-----------------------|-------------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01344460 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

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

Notes:

### Paediatric regulatory details

|                                                                      |    |
|----------------------------------------------------------------------|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | 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                       | 06 July 2012 |
| Is this the analysis of the primary completion data? | No           |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 06 July 2012 |
| Was the trial ended prematurely?                     | No           |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy of gadobutrol-enhanced magnetic resonance angiography (MRA) over two dimensional-Time of Flight (2D-ToF) MRA in subjects with known or suspected renal artery disease, as verified by:

- superiority for structural delineation,
- non-inferiority for the detection of clinically significant vascular disease,
- non-inferiority for the exclusion of clinically significant vascular disease,
- minimum performance for gadobutrol detection of clinically significant vascular disease, and
- minimum performance for gadobutrol exclusion of clinically significant vascular disease

using computed tomographic angiography (CTA) as the standard of reference (SoR) excluding the first objective, structural delineation.

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 and/or their legally authorized representative. 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                          | 16 May 2011 |
| 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 | Poland: 35         |
| Country: Number of subjects enrolled | Czech Republic: 15 |
| Country: Number of subjects enrolled | France: 31         |
| Country: Number of subjects enrolled | Germany: 11        |
| Country: Number of subjects enrolled | Argentina: 37      |
| Country: Number of subjects enrolled | Brazil: 31         |
| Country: Number of subjects enrolled | Switzerland: 4     |
| Country: Number of subjects enrolled | Colombia: 15       |

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Korea, Republic of: 58 |
| Country: Number of subjects enrolled | Turkey: 13             |
| Country: Number of subjects enrolled | Taiwan: 7              |
| Country: Number of subjects enrolled | United States: 52      |
| Worldwide total number of subjects   | 315                    |
| EEA total number of subjects         | 98                     |

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)                      | 203 |
| From 65 to 84 years                       | 109 |
| 85 years and over                         | 3   |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 55 study centers in 13 countries, between 16 May 2011 (first subject first visit) and 06 July 2012 (last subject last visit).

### Pre-assignment

Screening details:

A total of 338 subjects were screened, of which 317 were enrolled and 315 received the study drug. The 23 subjects who did not receive the study drug included 9 screen failures and 12 premature discontinuations (10 subjects withdrew consent and 2 subjects for other reasons) and 2 subjects never received the study drug.

### Period 1

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

### Arms

|           |                                    |
|-----------|------------------------------------|
| Arm title | Gadobutrol (Gadavist, BAY 86-4875) |
|-----------|------------------------------------|

Arm description:

Gadobutrol was administered to all subjects receiving study drug at the standard dose of 0.1 millimole per kilogram (mmol/kg) body weight (BW) by single intravenous (IV) bolus injection. During the course of the study, non-contrast MRA images were obtained before the administration of gadobutrol, and gadobutrol-enhanced MRA images were obtained after injection.

|                                        |                        |
|----------------------------------------|------------------------|
| Arm type                               | Experimental           |
| Investigational medicinal product name | Gadobutrol             |
| Investigational medicinal product code | BAY 86-4875            |
| Other name                             | Gadovist, Gadavist     |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravenous bolus use  |

Dosage and administration details:

Gadobutrol was administered to all subjects receiving study drug at the standard dose of 0.1 mmol/kg BW by single IV bolus injection.

| Number of subjects in period 1 | Gadobutrol<br>(Gadavist, BAY 86-4875) |
|--------------------------------|---------------------------------------|
| Started                        | 315                                   |
| Completed                      | 312                                   |
| Not completed                  | 3                                     |
| Consent withdrawn by subject   | 1                                     |
| Lost to follow-up              | 2                                     |

## Baseline characteristics

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | Overall Trial |
|-----------------------|---------------|

Reporting group description:

Gadobutrol was administered to all subjects receiving study drug at the standard dose of 0.1 mmol/kg BW by single IV bolus injection. During the course of the study, non-contrast MRA images were obtained before the administration of gadobutrol, and Gadobutrol-enhanced MRA images were obtained after injection.

| Reporting group values | Overall Trial | Total |  |
|------------------------|---------------|-------|--|
| Number of subjects     | 315           | 315   |  |
| Age categorical        |               |       |  |
| Units: Subjects        |               |       |  |
| < 45 years             | 92            | 92    |  |
| 45 - 64 years          | 111           | 111   |  |
| >= 65 years            | 112           | 112   |  |
| Age continuous         |               |       |  |
| Units: years           |               |       |  |
| arithmetic mean        | 54.9          |       |  |
| standard deviation     | ± 16.9        | -     |  |
| Gender categorical     |               |       |  |
| Units: Subjects        |               |       |  |
| Female                 | 145           | 145   |  |
| Male                   | 170           | 170   |  |
| Baseline Weight        |               |       |  |
| Units: kilogram(s)     |               |       |  |
| arithmetic mean        | 77.5          |       |  |
| standard deviation     | ± 16.9        | -     |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                             |                                                       |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                       | Gadobutrol (Gadavist, BAY 86-4875)                    |
| Reporting group description:<br>Gadobutrol was administered to all subjects receiving study drug at the standard dose of 0.1 millimole per kilogram (mmol/kg) body weight (BW) by single intravenous (IV) bolus injection. During the course of the study, non-contrast MRA images were obtained before the administration of gadobutrol, and gadobutrol-enhanced MRA images were obtained after injection. |                                                       |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                  | Unenhanced MRA                                        |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                   | Sub-group analysis                                    |
| Subject analysis set description:<br>Unenhanced MRA set included those subjects in FAS who showed only unenhanced MRA image sets.                                                                                                                                                                                                                                                                           |                                                       |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                  | Safety analysis set (SAF)                             |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                   | Safety analysis                                       |
| Subject analysis set description:<br>SAF included all subjects administered gadobutrol, including any subjects used for blinded reader training.                                                                                                                                                                                                                                                            |                                                       |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                  | Gadobutrol-Enhanced MRA set                           |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                   | Sub-group analysis                                    |
| Subject analysis set description:<br>Gadobutrol-Enhanced MRA set included those subjects in Full analysis set (FAS) who showed only Gadobutrol enhanced MRA image sets.                                                                                                                                                                                                                                     |                                                       |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                  | Full analysis set (FAS)                               |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                   | Full analysis                                         |
| Subject analysis set description:<br>FAS included all subjects who have both gadobutrol-enhanced and non-contrast (unenhanced) MRA image sets, and the SoR diagnosis were available (CTA was required to be interpretable and without technical problems). FAS excluded those subjects for who images were used for blinded reader training.                                                                |                                                       |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                  | Computed Tomographic Angiography (CTA)                |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                   | Sub-group analysis                                    |
| Subject analysis set description:<br>CTA included those subjects in FAS who showed only CTA scan image sets.                                                                                                                                                                                                                                                                                                |                                                       |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                  | CTA minus Unenhanced MRA for blinded reading          |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                   | Sub-group analysis                                    |
| Subject analysis set description:<br>Subjects with CTA scan images minus unenhanced MRA images for blinded reading included in this set.                                                                                                                                                                                                                                                                    |                                                       |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                  | CTA minus gadobutrol-enhanced MRA for blinded reading |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                   | Sub-group analysis                                    |
| Subject analysis set description:<br>Subjects with CTA scan images minus gadobutrol-enhanced MRA images for blinded reading included in this set.                                                                                                                                                                                                                                                           |                                                       |

### Primary: Percentage of Assessable Vascular Segments Using Gadobutrol-Enhanced MRA and Unenhanced MRA

|                 |                                                                                                            |
|-----------------|------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Assessable Vascular Segments Using Gadobutrol-Enhanced MRA and Unenhanced MRA <sup>[1]</sup> |
|-----------------|------------------------------------------------------------------------------------------------------------|

#### End point description:

Each vascular segment was visualized using unenhanced MRA and gadobutrol-enhanced MRA, characterized by the on-site investigators, three independent blinded readers (reader 1, 2 and 3) and majority readers (the outcome determined by at least two of the blinded readers). The segments were predefined to standardize the blinded reader evaluations.

A segment was assessable if it was visualized along its entire length and if any region of stenosis, was measured reliably. There were 6 segments assessed per subject (3 segments in the right renal artery and 3 segments in the left renal artery) and up to 9 segments in subjects with renal transplant.

In below table, "n/n" signifies the number of subjects/segments that were evaluable in specified category of each group.

|                                                    |         |
|----------------------------------------------------|---------|
| End point type                                     | Primary |
| End point timeframe:                               |         |
| Images were taken pre-injection and post-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: EudraCT format does auto-adding of number of subjects analysed while reporting an explorative analysis of two treatment groups. Due to this format constrains, we have uploaded charts with the accurate details of statistical analyses for this endpoint. Please find the statistical analyses in the attachment below.

| End point values                    | Unenhanced MRA       | Gadobutrol-Enhanced MRA set |  |  |
|-------------------------------------|----------------------|-----------------------------|--|--|
| Subject group type                  | Subject analysis set | Subject analysis set        |  |  |
| Number of subjects analysed         | 292 <sup>[2]</sup>   | 292 <sup>[3]</sup>          |  |  |
| Units: Percentage of segments       |                      |                             |  |  |
| number (not applicable)             |                      |                             |  |  |
| Majority reader (n=292/1752)        | 77.6                 | 95.9                        |  |  |
| Blinded reader 1 (n=292/1746)       | 81.7                 | 98.1                        |  |  |
| Blinded reader 2 (n=292/1752)       | 71.5                 | 95.5                        |  |  |
| Blinded reader 3 (n=292/1734)       | 78.1                 | 95.5                        |  |  |
| Clinical investigators (n=292/1764) | 68.9                 | 94.4                        |  |  |

Notes:

[2] - FAS

[3] - FAS

|                                   |                                                          |
|-----------------------------------|----------------------------------------------------------|
| <b>Attachments (see zip file)</b> | 91759_Statistical Analyses_Primary OM_Assessability.docx |
|-----------------------------------|----------------------------------------------------------|

## Statistical analyses

No statistical analyses for this end point

## Primary: Sensitivity for Detection of Clinically Significant Disease Using Gadobutrol-Enhanced MRA and Unenhanced MRA

|                 |                                                                                                                             |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------|
| End point title | Sensitivity for Detection of Clinically Significant Disease Using Gadobutrol-Enhanced MRA and Unenhanced MRA <sup>[4]</sup> |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------|

End point description:

Clinically significant disease was defined as 50 to 99 percent (%) stenosis of a segment, but not occluded as assessed by the SoR. For each segment, the most severe stenosis/narrowing was identified and considered for the evaluation of clinically significant disease. In the below table, "n" signifies subjects who were evaluable for the specified parameter for each arm, respectively.

In below table, "n/n" signifies the number of subjects/segments that were evaluable in specified category of each group

|                                                    |         |
|----------------------------------------------------|---------|
| End point type                                     | Primary |
| End point timeframe:                               |         |
| Images were taken pre-injection and post-injection |         |

Notes:

[4] - 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: EudraCT format does auto-adding of number of subjects analysed while reporting an explorative analysis of two treatment groups. Due to this format constrains, we have uploaded charts with the accurate details of statistical analyses for this endpoint. Please find the statistical analyses in the attachment below.

| End point values                   | Unenhanced<br>MRA    | Gadobutrol-<br>Enhanced MRA<br>set |  |  |
|------------------------------------|----------------------|------------------------------------|--|--|
| Subject group type                 | Subject analysis set | Subject analysis set               |  |  |
| Number of subjects analysed        | 292 <sup>[5]</sup>   | 292 <sup>[6]</sup>                 |  |  |
| Units: percentage of Sensitivity   |                      |                                    |  |  |
| number (not applicable)            |                      |                                    |  |  |
| Majority reader (n=93/133)         | 46.6                 | 53.4                               |  |  |
| Blinded reader 1 (n=93/133)        | 51.1                 | 51.9                               |  |  |
| Blinded reader 2 (n=93/133)        | 39.1                 | 54.1                               |  |  |
| Blinded reader 3 (n=93/133)        | 50.4                 | 52.6                               |  |  |
| Clinical investigators (n=113/140) | 50                   | 69.3                               |  |  |

Notes:

[5] - FAS

[6] - FAS

|                                   |                                                        |
|-----------------------------------|--------------------------------------------------------|
| <b>Attachments (see zip file)</b> | 91759_Statistical Analysis_Primary OM_Sensitivity.docx |
|-----------------------------------|--------------------------------------------------------|

### Statistical analyses

No statistical analyses for this end point

### Primary: Specificity for Exclusion of Clinically Significant Disease Using Gadobutrol-Enhanced MRA and Unenhanced MRA

|                 |                                                                                                                             |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------|
| End point title | Specificity for Exclusion of Clinically Significant Disease Using Gadobutrol-Enhanced MRA and Unenhanced MRA <sup>[7]</sup> |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------|

End point description:

Clinically significant disease (stenosis) was defined as 50 to 99 percent (%) stenosis of a segment, but not occluded as assessed by the SoR. For each segment, the most severe stenosis/narrowing was identified and considered for the evaluation of clinically significant disease.

Specificity = percentage of subjects for which the imaging modalities (unenhanced or gadobutrol-enhanced) in the detection and exclusion of clinically significant stenosis.

In below table, "n/n" signifies the number of subjects/segments that were evaluable in specified category of each group.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Images were taken pre-injection and post-injection

Notes:

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

Justification: EudraCT format does auto-adding of number of subjects analysed while reporting an explorative analysis of two treatment groups. Due to this format constrains, we have uploaded charts with the accurate details of statistical analyses for this endpoint. Please find the statistical analyses in the attachment below.

| End point values                 | Unenhanced<br>MRA    | Gadobutrol-<br>Enhanced MRA<br>set |  |  |
|----------------------------------|----------------------|------------------------------------|--|--|
| Subject group type               | Subject analysis set | Subject analysis set               |  |  |
| Number of subjects analysed      | 292 <sup>[8]</sup>   | 292 <sup>[9]</sup>                 |  |  |
| Units: Percentage of Specificity |                      |                                    |  |  |
| number (not applicable)          |                      |                                    |  |  |
| Majority reader (n=292/1605)     | 85.7                 | 94.8                               |  |  |
| Blinded reader 1 (n=292/1605)    | 83.1                 | 94.4                               |  |  |
| Blinded reader 2 (n=292/1605)    | 85                   | 94.8                               |  |  |
| Blinded reader 3 (n=292/1605)    | 80.7                 | 94                                 |  |  |



|                                     |      |      |  |  |
|-------------------------------------|------|------|--|--|
| Clinical investigators (n=292/1598) | 83.5 | 96.5 |  |  |
|-------------------------------------|------|------|--|--|

Notes:

[8] - Evaluable subjects in FAS

[9] - Evaluable subjects in FAS

|                                   |                                                        |
|-----------------------------------|--------------------------------------------------------|
| <b>Attachments (see zip file)</b> | 91759_Statistical Analysis_Primary OM_Specificity.docx |
|-----------------------------------|--------------------------------------------------------|

## Statistical analyses

No statistical analyses for this end point

## Primary: Minimum Gadobutrol Performance for Sensitivity: Sensitivity > 50%

|                 |                                                                                   |
|-----------------|-----------------------------------------------------------------------------------|
| End point title | Minimum Gadobutrol Performance for Sensitivity: Sensitivity > 50% <sup>[10]</sup> |
|-----------------|-----------------------------------------------------------------------------------|

End point description:

Clinically significant disease was defined as >50% stenosis of a segment, but not occluded as assessed by the SoR. For each segment, the most severe stenosis/narrowing was identified and considered for the evaluation of clinically significant disease. Gadobutrol minimum performance criteria was based on a stenosis of 50% calculated from the native vessel diameter. In the below table, "n" signifies subjects who were evaluable for the specified parameter for each arm, respectively.

In below table, "n/n" signifies the number of subjects/segments that were evaluable in specified category.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Images were taken pre-injection and post-injection

Notes:

[10] - 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: EudraCT format does auto-adding of number of subjects analysed while reporting an explorative analysis of two treatment groups. Due to this format constrains, we have uploaded charts with the accurate details of statistical analyses for this endpoint. Please find the statistical analyses in the attachment below.

| End point values                   | Gadobutrol-Enhanced MRA set |  |  |  |
|------------------------------------|-----------------------------|--|--|--|
| Subject group type                 | Subject analysis set        |  |  |  |
| Number of subjects analysed        | 292 <sup>[11]</sup>         |  |  |  |
| Units: Percentage of sensitivity   |                             |  |  |  |
| number (not applicable)            |                             |  |  |  |
| Majority reader (n=84/119)         | 54.6                        |  |  |  |
| Blinded reader 1 (n=91/128)        | 51.6                        |  |  |  |
| Blinded reader 2 (n=82/114)        | 54.4                        |  |  |  |
| Blinded reader 3 (n=83/118)        | 53.4                        |  |  |  |
| Clinical investigators (n=108/129) | 71.3                        |  |  |  |

Notes:

[11] - FAS

|                                   |                                                           |
|-----------------------------------|-----------------------------------------------------------|
| <b>Attachments (see zip file)</b> | 91759_Statistical Analysis_Primary OM_Sensitivity_50.docx |
|-----------------------------------|-----------------------------------------------------------|

## Statistical analyses

No statistical analyses for this end point

### Primary: Minimum Gadobutrol Performance for Specificity: Specificity > 50%

|                 |                                                                                   |
|-----------------|-----------------------------------------------------------------------------------|
| End point title | Minimum Gadobutrol Performance for Specificity: Specificity > 50% <sup>[12]</sup> |
|-----------------|-----------------------------------------------------------------------------------|

End point description:

Clinically significant disease (stenosis) was defined as >50% stenosis of a segment, but not occluded as assessed by the SoR. For each segment, the most severe stenosis/narrowing was identified and considered for the evaluation of clinically significant disease. Gadobutrol minimum performance criteria was based on a stenosis of 50% calculated from the native vessel diameter.

In the below table, "n" signifies subjects who were evaluable for the specified parameter for each arm, respectively.

In below table, "n/n" signifies the number of subjects/segments that were evaluable in specified category.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Images were taken pre-injection and post-injection

Notes:

[12] - 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: EudraCT format does auto-adding of number of subjects analysed while reporting an explorative analysis of two treatment groups. Due to this format constrains, we have uploaded charts with the accurate details of statistical analyses for this endpoint. Please find the statistical analyses in the attachment below.

| End point values                    | Gadobutrol-Enhanced MRA set |  |  |  |
|-------------------------------------|-----------------------------|--|--|--|
| Subject group type                  | Subject analysis set        |  |  |  |
| Number of subjects analysed         | 292 <sup>[13]</sup>         |  |  |  |
| Units: Percentage of specificity    |                             |  |  |  |
| number (not applicable)             |                             |  |  |  |
| Majority reader (n=291/1555)        | 95.9                        |  |  |  |
| Blinded reader 1 (n=292/1585)       | 95                          |  |  |  |
| Blinded reader 2 (n=291/1554)       | 96.2                        |  |  |  |
| Blinded reader 3 (n=290/1544)       | 95.8                        |  |  |  |
| Clinical investigators (n=289/1535) | 98.4                        |  |  |  |

Notes:

[13] - FAS

|                            |                                                           |
|----------------------------|-----------------------------------------------------------|
| Attachments (see zip file) | 91759_Statistical Analysis_Primary OM_Specificity_50.docx |
|----------------------------|-----------------------------------------------------------|

### Statistical analyses

No statistical analyses for this end point

### Secondary: Length of the right and left renal arteries assessed by gadobutrol-enhanced MRA and unenhanced MRA - Blinded reader

|                 |                                                                                                                     |
|-----------------|---------------------------------------------------------------------------------------------------------------------|
| End point title | Length of the right and left renal arteries assessed by gadobutrol-enhanced MRA and unenhanced MRA - Blinded reader |
|-----------------|---------------------------------------------------------------------------------------------------------------------|

End point description:

The length of the left and right renal arteries were measured from the origin at the aorta to the bifurcation into the upper and lower pole arteries or the most distal point of the renal artery which could be visualized. This distal margin was the point where the diameter was still assessable. If there were more than 2 distal branches then the first large branch that was the dominant supply to a renal pole was

used as the distal point.

|                                                    |           |
|----------------------------------------------------|-----------|
| End point type                                     | Secondary |
| End point timeframe:                               |           |
| Images were taken pre-injection and post-injection |           |

| End point values                     | Unenhanced MRA       | Gadobutrol-Enhanced MRA set |  |  |
|--------------------------------------|----------------------|-----------------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set        |  |  |
| Number of subjects analysed          | 292 <sup>[14]</sup>  | 292 <sup>[15]</sup>         |  |  |
| Units: millimeter(s) (mm)            |                      |                             |  |  |
| arithmetic mean (standard deviation) |                      |                             |  |  |
| Left renal artery- Blind reader 1    | 32.25 (± 11.32)      | 35.07 (± 11.76)             |  |  |
| Right renal artery - Blind reader 1  | 43.05 (± 14.34)      | 46.23 (± 14.01)             |  |  |
| Left renal artery- Blind reader 2    | 32.15 (± 11.35)      | 35.07 (± 11.76)             |  |  |
| Right renal artery - Blind reader 2  | 42.95 (± 14.42)      | 46.27 (± 14.01)             |  |  |
| Left renal artery- Blind reader 3    | 32.64 (± 12.74)      | 35.07 (± 11.76)             |  |  |
| Right renal artery - Blind reader 3  | 43.05 (± 14.34)      | 46.23 (± 14)                |  |  |

Notes:

[14] - Evaluable subjects in FAS

[15] - Evaluable subjects in FAS

## Statistical analyses

No statistical analyses for this end point

## Secondary: Length of the right and left renal arteries assessed by computed tomographic angiography (CTA) - blinded reader

|                 |                                                                                                                 |
|-----------------|-----------------------------------------------------------------------------------------------------------------|
| End point title | Length of the right and left renal arteries assessed by computed tomographic angiography (CTA) - blinded reader |
|-----------------|-----------------------------------------------------------------------------------------------------------------|

End point description:

The length of the left and right renal arteries were measured from the origin at the aorta to the bifurcation into the upper and lower pole arteries or the most distal point of the renal artery which could be visualized. This distal margin was the point where the diameter was still assessable. If there were more than 2 distal branches then the first large branch that was the dominant supply to a renal pole was used as the distal point.

|                                                    |           |
|----------------------------------------------------|-----------|
| End point type                                     | Secondary |
| End point timeframe:                               |           |
| Images were taken pre-injection and post-injection |           |

| End point values                        | Computed Tomographic Angiography (CTA) |  |  |  |
|-----------------------------------------|----------------------------------------|--|--|--|
| Subject group type                      | Subject analysis set                   |  |  |  |
| Number of subjects analysed             | 292 <sup>[16]</sup>                    |  |  |  |
| Units: millimeter(s) (mm)               |                                        |  |  |  |
| arithmetic mean (standard deviation)    |                                        |  |  |  |
| Left renal artery- CTA Blind reader 4   | 36.59 (± 12.14)                        |  |  |  |
| Right renal artery - CTA Blind reader 4 | 48.44 (± 14.51)                        |  |  |  |
| Left renal artery- CTA Blind reader 5   | 36.59 (± 12.14)                        |  |  |  |
| Right renal artery - CTA Blind reader 5 | 48.44 (± 14.5)                         |  |  |  |
| Left renal artery- CTA Blind reader 6   | 36.59 (± 12.14)                        |  |  |  |
| Right renal artery - CTA Blind reader 6 | 48.45 (± 14.5)                         |  |  |  |

Notes:

[16] - Evaluable subjects in FAS

## Statistical analyses

No statistical analyses for this end point

## Secondary: Mean Difference in Vessel Diameter (millimeter [mm]) at Normal and Narrowest point assessed by gadobutrol-enhanced MRA and unenhanced MRA compared to CTA

|                 |                                                                                                                                                           |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Mean Difference in Vessel Diameter (millimeter [mm]) at Normal and Narrowest point assessed by gadobutrol-enhanced MRA and unenhanced MRA compared to CTA |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The segment evaluated to have a reduction in diameter of greater than 10% was considered abnormal and measured. The diameter of each of these abnormal segments was measured using electronic calipers (perpendicular to the long axis of the vessel) at the point of most severe stenosis within each segment. The mean of vessel diameters was calculated by segment across readers separately for CTA and MRA readers.

In below table, "n" signifies the number of segments that were evaluable in specified category.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Images were taken pre-injection and post-injection

| End point values                                | CTA minus Unenhanced MRA for blinded reading | CTA minus gadobutrol-enhanced MRA for blinded reading |  |  |
|-------------------------------------------------|----------------------------------------------|-------------------------------------------------------|--|--|
| Subject group type                              | Subject analysis set                         | Subject analysis set                                  |  |  |
| Number of subjects analysed                     | 292 <sup>[17]</sup>                          | 292 <sup>[18]</sup>                                   |  |  |
| Units: millimeter                               |                                              |                                                       |  |  |
| arithmetic mean (standard deviation)            |                                              |                                                       |  |  |
| Vessel DIA at normal point: BRs (n=298; 320)    | 0.17 (± 1.28)                                | -0.09 (± 1.14)                                        |  |  |
| Vessel DIA at narrowest point: BRs (n=298; 320) | 0.41 (± 1.15)                                | -0.15 (± 1.01)                                        |  |  |

Notes:

[17] - Evaluable subjects in FAS

[18] - Evaluable subjects in FAS

## Statistical analyses

No statistical analyses for this end point

### Secondary: The Percentage of Location of Stenosis $\geq 50\%$ (Within and Beyond 5 millimeter From the Aorta) in the Proximal Segments Assessed by Gadobutrol-Enhanced MRA and Unenhanced MRA

|                 |                                                                                                                                                                                    |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | The Percentage of Location of Stenosis $\geq 50\%$ (Within and Beyond 5 millimeter From the Aorta) in the Proximal Segments Assessed by Gadobutrol-Enhanced MRA and Unenhanced MRA |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Location within the right and left proximal segment was based on the point of greatest stenosis and was recorded for stenosis  $\geq 50\%$  as:

- Within 5 mm of the aorta (or occlusion proximal to the origin of the segment)
- Beyond 5 mm from the aorta.

In below table, "n" signifies the number of segments that were evaluable in specified category of each group.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Images were taken pre-injection and post-injection

| End point values                             | Unenhanced MRA       | Gadobutrol-Enhanced MRA set |  |  |
|----------------------------------------------|----------------------|-----------------------------|--|--|
| Subject group type                           | Subject analysis set | Subject analysis set        |  |  |
| Number of subjects analysed                  | 292 <sup>[19]</sup>  | 292 <sup>[20]</sup>         |  |  |
| Units: Percentage of location                |                      |                             |  |  |
| number (not applicable)                      |                      |                             |  |  |
| Within 5 mm of the aorta BR 1 (n=105; 110)   | 22.9                 | 26.4                        |  |  |
| Within 5 mm of the aorta BR 2 (n=39; 83)     | 71.8                 | 73.5                        |  |  |
| Within 5 mm of the aorta BR 3 (n=87; 83)     | 21.8                 | 25.3                        |  |  |
| Beyond 5 mm from the aorta BR 1 (n=105; 110) | 77.1                 | 73.6                        |  |  |
| Beyond 5 mm from the aorta BR 2 (n=39; 83)   | 28.2                 | 26.5                        |  |  |
| Beyond 5 mm from the aorta BR 3 (n=87; 83)   | 78.2                 | 74.7                        |  |  |

Notes:

[19] - Evaluable subjects in FAS

[20] - Evaluable subjects in FAS

## Statistical analyses

No statistical analyses for this end point

## Secondary: The Percentage of Segments With Artifacts Presence

|                 |                                                    |
|-----------------|----------------------------------------------------|
| End point title | The Percentage of Segments With Artifacts Presence |
|-----------------|----------------------------------------------------|

End point description:

Artifacts were collected for the MRA images on a segmental basis. In the below table, "n" signifies number of subjects that were evaluable for the specified category.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Images were taken pre-injection and post-injection

| End point values              | Unenhanced MRA       | Gadobutrol-Enhanced MRA set |  |  |
|-------------------------------|----------------------|-----------------------------|--|--|
| Subject group type            | Subject analysis set | Subject analysis set        |  |  |
| Number of subjects analysed   | 292 <sup>[21]</sup>  | 292 <sup>[22]</sup>         |  |  |
| Units: percentage of subjects |                      |                             |  |  |
| number (not applicable)       |                      |                             |  |  |
| Blinded Reader 1              | 92.3                 | 97.4                        |  |  |
| Blinded Reader 2              | 80.4                 | 22.1                        |  |  |
| Blinded Reader 3              | 97.4                 | 41.5                        |  |  |

Notes:

[21] - Evaluable subjects in FAS

[22] - Evaluable subjects in FAS

## Statistical analyses

No statistical analyses for this end point

## Secondary: Types of Artifacts Assessed by Gadobutrol-enhanced MRA and Unenhanced MRA by Blinded Reader 1

|                 |                                                                                               |
|-----------------|-----------------------------------------------------------------------------------------------|
| End point title | Types of Artifacts Assessed by Gadobutrol-enhanced MRA and Unenhanced MRA by Blinded Reader 1 |
|-----------------|-----------------------------------------------------------------------------------------------|

End point description:

The following types of artifacts were considered: Motion artifact (including pulsatility, breathing, swallowing), venous opacification, saturation artifact (for example [eg], in-plane flow, turbulence, dephasing, saturation band), susceptibility artifacts (including devices, eg, stents), ringing artifact (eg, bands), bolus timing error, and other (artifact not specified above or no artifact).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Images were taken pre-injection and post-injection

| End point values              | Unenhanced MRA       | Gadobutrol-Enhanced MRA set |  |  |
|-------------------------------|----------------------|-----------------------------|--|--|
| Subject group type            | Subject analysis set | Subject analysis set        |  |  |
| Number of subjects analysed   | 292 <sup>[23]</sup>  | 292 <sup>[24]</sup>         |  |  |
| Units: Percentage of segments |                      |                             |  |  |
| number (not applicable)       |                      |                             |  |  |
| Motion artifact               | 81.4                 | 17.5                        |  |  |
| Venous opacification          | 15.1                 | 4.8                         |  |  |

|                          |     |     |  |  |
|--------------------------|-----|-----|--|--|
| Saturation artifact      | 0.4 | 0.2 |  |  |
| Susceptibility artifacts | 0.1 | 0   |  |  |
| Other                    | 7.2 | 5   |  |  |

Notes:

[23] - Subjects in FAS with artifacts presence.

[24] - Subjects in FAS with artifacts presence.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Types of Artifacts Assessed by Gadobutrol-Enhanced MRA and Unenhanced MRA by Blinded Reader 2

|                 |                                                                                               |
|-----------------|-----------------------------------------------------------------------------------------------|
| End point title | Types of Artifacts Assessed by Gadobutrol-Enhanced MRA and Unenhanced MRA by Blinded Reader 2 |
|-----------------|-----------------------------------------------------------------------------------------------|

End point description:

The following types of artifacts were considered: Motion artifact (including pulsatility, breathing, swallowing), venous opacification, saturation artifact (eg, in-plane flow, turbulence, dephasing, saturation band), susceptibility artifacts (including devices, eg, stents), ringing artifact (eg, bands), bolus timing error, and other (artifact not specified above or no artifact).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Images were taken pre-injection and post-injection

| End point values              | Unenhanced MRA       | Gadobutrol-Enhanced MRA set |  |  |
|-------------------------------|----------------------|-----------------------------|--|--|
| Subject group type            | Subject analysis set | Subject analysis set        |  |  |
| Number of subjects analysed   | 292 <sup>[25]</sup>  | 292 <sup>[26]</sup>         |  |  |
| Units: Percentage of segments |                      |                             |  |  |
| number (not applicable)       |                      |                             |  |  |
| Motion artifact               | 57.1                 | 5.4                         |  |  |
| Venous opacification          | 9.6                  | 12                          |  |  |
| Saturation artifact           | 24.4                 | 0.2                         |  |  |
| Susceptibility artifacts      | 6                    | 3.6                         |  |  |
| Ringing artifact              | 1.4                  | 0.6                         |  |  |
| Bolus timing error            | 1.4                  | 1.7                         |  |  |
| Other                         | 6.5                  | 1.7                         |  |  |

Notes:

[25] - Subjects in FAS with artifacts presence.

[26] - Subjects in FAS with artifacts presence.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Types of Artifacts Assessed by Gadobutrol-Enhanced MRA and Unenhanced MRA by Blinded Reader 3

|                 |                                                                                               |
|-----------------|-----------------------------------------------------------------------------------------------|
| End point title | Types of Artifacts Assessed by Gadobutrol-Enhanced MRA and Unenhanced MRA by Blinded Reader 3 |
|-----------------|-----------------------------------------------------------------------------------------------|

End point description:

The following types of artifacts were considered: Motion artifact (including pulsatility, breathing,

swallowing), venous opacification, saturation artifact (eg, in-plane flow, turbulence, dephasing, saturation band), susceptibility artifacts (including devices, eg, stents), ringing artifact (eg, bands), bolus timing error, and other (artifact not specified above or no artifact).

|                                                    |           |
|----------------------------------------------------|-----------|
| End point type                                     | Secondary |
| End point timeframe:                               |           |
| Images were taken pre-injection and post-injection |           |

| End point values              | Unenhanced MRA       | Gadobutrol-Enhanced MRA set |  |  |
|-------------------------------|----------------------|-----------------------------|--|--|
| Subject group type            | Subject analysis set | Subject analysis set        |  |  |
| Number of subjects analysed   | 292 <sup>[27]</sup>  | 292 <sup>[28]</sup>         |  |  |
| Units: Percentage of segments |                      |                             |  |  |
| number (not applicable)       |                      |                             |  |  |
| Motion artifact               | 96.2                 | 32.8                        |  |  |
| Venous opacification          | 34.5                 | 14.2                        |  |  |
| Saturation artifact           | 56                   | 3                           |  |  |
| Susceptibility artifacts      | 7                    | 4                           |  |  |
| Ringing artifact              | 7                    | 6.7                         |  |  |
| Bolus timing error            | 1.5                  | 0.3                         |  |  |
| Other                         | 0.2                  | 0.7                         |  |  |

Notes:

[27] - Subjects in FAS with artifacts presence.

[28] - Subjects in FAS with artifacts presence.

## Statistical analyses

No statistical analyses for this end point

## Secondary: The Percentage of Accessory (Non-dominant) Renal Artery Presence Assessed by Gadobutrol-Enhanced MRA and Unenhanced MRA

|                 |                                                                                                                         |
|-----------------|-------------------------------------------------------------------------------------------------------------------------|
| End point title | The Percentage of Accessory (Non-dominant) Renal Artery Presence Assessed by Gadobutrol-Enhanced MRA and Unenhanced MRA |
|-----------------|-------------------------------------------------------------------------------------------------------------------------|

End point description:

An accessory renal artery was defined as an additional, non-dominant, renal artery typically emanating from the aorta and anastomosing distal to the proximal third, segment of that renal artery. It was recorded only as present or absent on the right and left, regardless of how many accessory renal arteries were present.

|                                                    |           |
|----------------------------------------------------|-----------|
| End point type                                     | Secondary |
| End point timeframe:                               |           |
| Images were taken pre-injection and post-injection |           |



| End point values                                          | Unenhanced<br>MRA    | Gadobutrol-<br>Enhanced MRA<br>set |  |  |
|-----------------------------------------------------------|----------------------|------------------------------------|--|--|
| Subject group type                                        | Subject analysis set | Subject analysis set               |  |  |
| Number of subjects analysed                               | 292 <sup>[29]</sup>  | 292 <sup>[30]</sup>                |  |  |
| Units: Percentage of accessory<br>number (not applicable) |                      |                                    |  |  |
| Left side: Reader 1                                       | 0.7                  | 7.2                                |  |  |
| Right side: Reader 1                                      | 1.4                  | 9.2                                |  |  |
| Left side: Reader 2                                       | 2.7                  | 15.4                               |  |  |
| Right side: Reader 2                                      | 3.1                  | 17.8                               |  |  |
| Left side: Reader 3                                       | 5.8                  | 13.4                               |  |  |
| Right side: Reader 3                                      | 4.5                  | 16.4                               |  |  |
| Left side: Clinical investigators                         | 11.6                 | 18.2                               |  |  |
| Right side: Clinical investigators                        | 12.7                 | 19.2                               |  |  |

Notes:

[29] - FAS

[30] - FAS

### Statistical analyses

No statistical analyses for this end point

### Secondary: The Presence of any Aneurysmal Dilatation in Each Segment (Proximal, Mid- and Distal) in the Right and the Left Renal Arteries Assessed by Gadobutrol-Enhanced MRA and Unenhanced MRA

|                 |                                                                                                                                                                                       |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | The Presence of any Aneurysmal Dilatation in Each Segment (Proximal, Mid- and Distal) in the Right and the Left Renal Arteries Assessed by Gadobutrol-Enhanced MRA and Unenhanced MRA |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Any focal dilatation (aneurysmal dilatation) of a segment was recorded. The diameter at the widest point was measured with the electronic calipers if a dilatation was present in any segment. The number of subjects with an aneurysmal dilatation in each segment (proximal, mid- and distal) in the right and the left renal arteries assessed by gadobutrol-enhanced MRA and unenhanced MRA were reported.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Images were taken pre-injection and post-injection

| End point values                                         | Unenhanced<br>MRA    | Gadobutrol-<br>Enhanced MRA<br>set |  |  |
|----------------------------------------------------------|----------------------|------------------------------------|--|--|
| Subject group type                                       | Subject analysis set | Subject analysis set               |  |  |
| Number of subjects analysed                              | 292 <sup>[31]</sup>  | 292 <sup>[32]</sup>                |  |  |
| Units: Percentage of subjects<br>number (not applicable) |                      |                                    |  |  |
| Right : Proximal                                         | 0                    | 0.3                                |  |  |
| Right : Mid                                              | 0                    | 1                                  |  |  |
| Right : Distal                                           | 0                    | 1.4                                |  |  |
| Left : Proximal                                          | 0                    | 0                                  |  |  |
| Left : Mid                                               | 0.3                  | 0.3                                |  |  |
| Left : Distal                                            | 0.3                  | 0.7                                |  |  |

Notes:

[31] - FAS

[32] - FAS

## Statistical analyses

No statistical analyses for this end point

### Secondary: The Percentage of Subjects With Diagnosis of Fibromuscular Dysplasia and Arteriosclerosis Assessed by Gadobutrol-Enhanced MRA and Unenhanced MRA

|                 |                                                                                                                                                  |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | The Percentage of Subjects With Diagnosis of Fibromuscular Dysplasia and Arteriosclerosis Assessed by Gadobutrol-Enhanced MRA and Unenhanced MRA |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Any focal dilatation (aneurysmal dilatation) of a segment was recorded. The diameter at the widest point was measured with the electronic calipers if a dilatation was present in any segment. The number of participants with an aneurysmal dilatation in each segment (proximal, mid- and distal) in the right and the left renal arteries assessed by gadobutrol-enhanced MRA and unenhanced MRA were reported.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Images were taken pre-injection and post-injection

| End point values                   | Unenhanced MRA       | Gadobutrol-Enhanced MRA set |  |  |
|------------------------------------|----------------------|-----------------------------|--|--|
| Subject group type                 | Subject analysis set | Subject analysis set        |  |  |
| Number of subjects analysed        | 292 <sup>[33]</sup>  | 292 <sup>[34]</sup>         |  |  |
| Units: Percentage of subjects      |                      |                             |  |  |
| number (not applicable)            |                      |                             |  |  |
| Fibromuscular dysplasia : reader 1 | 0.7                  | 2.7                         |  |  |
| Arteriosclerotic : reader 1        | 12                   | 16.4                        |  |  |
| Fibromuscular dysplasia : reader 2 | 0                    | 4.1                         |  |  |
| Arteriosclerotic : reader 2        | 18.8                 | 38.4                        |  |  |
| Fibromuscular dysplasia : reader 3 | 0.7                  | 6.2                         |  |  |
| Arteriosclerotic : reader 3        | 54.5                 | 41.1                        |  |  |

Notes:

[33] - FAS

[34] - FAS

## Statistical analyses

No statistical analyses for this end point

### Secondary: Diagnostic Confidence by the Blinded Readers Using Gadobutrol-Enhanced MRA and Unenhanced MRA

|                 |                                                                                               |
|-----------------|-----------------------------------------------------------------------------------------------|
| End point title | Diagnostic Confidence by the Blinded Readers Using Gadobutrol-Enhanced MRA and Unenhanced MRA |
|-----------------|-----------------------------------------------------------------------------------------------|

End point description:

Diagnostic confidence was evaluated to determine the level of certainty that the blinded readers assigned to a diagnosis for each segment. This was defined as the degree of confidence that the information on the MRA images represented the true and complete clinical picture of a particular segment.

The degree of confidence was rated on a 4-point scale: 1 = Not confident, 2 = Somewhat confident, 3 = Confident, and 4 = Very confident.

In the below table, "n" signifies the number of segments that were evaluable in specified category of each group.

|                                                    |           |
|----------------------------------------------------|-----------|
| End point type                                     | Secondary |
| End point timeframe:                               |           |
| Images were taken pre-injection and post-injection |           |

| End point values                     | Unenhanced MRA       | Gadobutrol-Enhanced MRA set |  |  |
|--------------------------------------|----------------------|-----------------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set        |  |  |
| Number of subjects analysed          | 292 <sup>[35]</sup>  | 292 <sup>[36]</sup>         |  |  |
| Units: Units on scale                |                      |                             |  |  |
| arithmetic mean (standard deviation) |                      |                             |  |  |
| Blinded reader 1 (n=1728, 1745)      | 1.9 (± 0.7)          | 3 (± 0.8)                   |  |  |
| Blinded reader 2 (n=1729, 1745)      | 2.1 (± 1)            | 3.5 (± 0.8)                 |  |  |
| Blinded reader 3 (n=1737, 1749)      | 2.2 (± 0.9)          | 3.5 (± 0.8)                 |  |  |

Notes:

[35] - Evaluable subjects in FAS

[36] - Evaluable subjects in FAS

## Statistical analyses

No statistical analyses for this end point

## Secondary: The Percentage of Subjects With Additional Imaging Studies Recommended by the Blinded Readers and the Clinical Investigator After Evaluation of the Gadobutrol-Enhanced and Unenhanced MRA Images

|                 |                                                                                                                                                                                                   |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | The Percentage of Subjects With Additional Imaging Studies Recommended by the Blinded Readers and the Clinical Investigator After Evaluation of the Gadobutrol-Enhanced and Unenhanced MRA Images |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

A measure of diagnostic value was the reduction in the number of additional diagnostic imaging studies recommended/ordered. The clinical investigators and the blinded readers were asked if they had recommended an additional imaging study for each subject, and the data were recorded.

|                                                    |           |
|----------------------------------------------------|-----------|
| End point type                                     | Secondary |
| End point timeframe:                               |           |
| Images were taken pre-injection and post-injection |           |

| End point values              | Unenhanced MRA       | Gadobutrol-Enhanced MRA set |  |  |
|-------------------------------|----------------------|-----------------------------|--|--|
| Subject group type            | Subject analysis set | Subject analysis set        |  |  |
| Number of subjects analysed   | 292 <sup>[37]</sup>  | 292 <sup>[38]</sup>         |  |  |
| Units: Percentage of subjects |                      |                             |  |  |
| number (not applicable)       |                      |                             |  |  |
| Reader: 1                     | 96.6                 | 41.4                        |  |  |
| Reader: 2                     | 77.1                 | 14                          |  |  |
| Reader: 3                     | 44.9                 | 8.6                         |  |  |
| Clinical investigators        | 43.5                 | 18.8                        |  |  |

Notes:

[37] - FAS

[38] - FAS

## Statistical analyses

No statistical analyses for this end point

## Secondary: Types of Additional Imaging Studies Recommended by the Blinded Readers After Evaluation of the Gadobutrol-Enhanced and Unenhanced MRA images – Blinded Reader 1

|                 |                                                                                                                                                                 |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Types of Additional Imaging Studies Recommended by the Blinded Readers After Evaluation of the Gadobutrol-Enhanced and Unenhanced MRA images – Blinded Reader 1 |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

An additional imaging study recommended was specified from the following list: Non-contrast MRA, Contrast-enhanced MRA, CTA, Ultrasound, Digital subtraction catheter angiogram (DSCA), and Nuclear medicine study.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Images were taken pre-injection and post-injection

| End point values            | Unenhanced MRA       | Gadobutrol-Enhanced MRA set |  |  |
|-----------------------------|----------------------|-----------------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set        |  |  |
| Number of subjects analysed | 282 <sup>[39]</sup>  | 121 <sup>[40]</sup>         |  |  |
| Units: Subjects             |                      |                             |  |  |
| Non-contrast MRA            | 2                    | 0                           |  |  |
| Contrast-enhanced MRA       | 0                    | 1                           |  |  |
| CTA                         | 280                  | 120                         |  |  |
| Ultrasound                  | 0                    | 0                           |  |  |
| DSCA                        | 0                    | 0                           |  |  |
| Nuclear medicine study      | 0                    | 0                           |  |  |

Notes:

[39] - FAS with subjects who were recommended for additional imaging studies.

[40] - FAS with subjects who were recommended for additional imaging studies.

## Statistical analyses

No statistical analyses for this end point

---

**Secondary: Types of Additional Imaging Studies Recommended by the Blinded Readers After Evaluation of the Gadobutrol-Enhanced and Unenhanced MRA images – Blinded Reader 2**

---

|                 |                                                                                                                                                                 |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Types of Additional Imaging Studies Recommended by the Blinded Readers After Evaluation of the Gadobutrol-Enhanced and Unenhanced MRA images – Blinded Reader 2 |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

An additional imaging study recommended was specified from the following list: Non-contrast MRA, Contrast-enhanced MRA, CTA, Ultrasound, DSCA, and Nuclear medicine study.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Images were taken pre-injection and post-injection

---

| End point values            | Unenhanced MRA       | Gadobutrol-Enhanced MRA set |  |  |
|-----------------------------|----------------------|-----------------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set        |  |  |
| Number of subjects analysed | 225 <sup>[41]</sup>  | 41 <sup>[42]</sup>          |  |  |
| Units: Subjects             |                      |                             |  |  |
| Non-contrast MRA            | 0                    | 0                           |  |  |
| Contrast-enhanced MRA       | 114                  | 0                           |  |  |
| CTA                         | 110                  | 39                          |  |  |
| Ultrasound                  | 1                    | 1                           |  |  |
| DSCA                        | 0                    | 1                           |  |  |
| Nuclear medicine study      | 0                    | 0                           |  |  |

Notes:

[41] - FAS with subjects who were recommended for additional imaging studies.

[42] - FAS with subjects who were recommended for additional imaging studies.

---

**Statistical analyses**

---

No statistical analyses for this end point

---

**Secondary: Types of Additional Imaging Studies Recommended by the Blinded Readers After Evaluation of the Gadobutrol-Enhanced and Unenhanced MRA images – Blinded Reader 3**

---

|                 |                                                                                                                                                                 |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Types of Additional Imaging Studies Recommended by the Blinded Readers After Evaluation of the Gadobutrol-Enhanced and Unenhanced MRA images – Blinded Reader 3 |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

An additional imaging study recommended was specified from the following list: Non-contrast MRA, Contrast-enhanced MRA, CTA, Ultrasound, DSCA, and Nuclear medicine study.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Images were taken pre-injection and post-injection

---

| End point values            | Unenhanced MRA       | Gadobutrol-Enhanced MRA set |  |  |
|-----------------------------|----------------------|-----------------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set        |  |  |
| Number of subjects analysed | 131 <sup>[43]</sup>  | 25 <sup>[44]</sup>          |  |  |
| Units: Subjects             |                      |                             |  |  |
| Non-contrast MRA            | 1                    | 0                           |  |  |
| Contrast-enhanced MRA       | 14                   | 1                           |  |  |
| CTA                         | 116                  | 22                          |  |  |
| Ultrasound                  | 0                    | 0                           |  |  |
| DSCA                        | 0                    | 2                           |  |  |
| Nuclear medicine study      | 0                    | 0                           |  |  |

Notes:

[43] - FAS with subjects who were recommended for additional imaging studies.

[44] - FAS with subjects who were recommended for additional imaging studies.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Types of Additional Imaging Studies Recommended by the Clinical Investigator After Evaluation of the Unenhanced and Gadobutrol-Enhanced MRA Images

|                 |                                                                                                                                                    |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Types of Additional Imaging Studies Recommended by the Clinical Investigator After Evaluation of the Unenhanced and Gadobutrol-Enhanced MRA Images |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

An additional imaging study recommended was specified from the following list: Non-contrast MRA, Contrast-enhanced MRA, CTA, Ultrasound, DSCA, and Nuclear medicine study.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Images were taken pre-injection and post-injection

| End point values            | Unenhanced MRA       | Gadobutrol-Enhanced MRA set |  |  |
|-----------------------------|----------------------|-----------------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set        |  |  |
| Number of subjects analysed | 127 <sup>[45]</sup>  | 55 <sup>[46]</sup>          |  |  |
| Units: Subjects             |                      |                             |  |  |
| Non-contrast MRA            | 0                    | 0                           |  |  |
| Contrast-enhanced MRA       | 114                  | 2                           |  |  |
| CTA                         | 12                   | 50                          |  |  |
| Ultrasound                  | 0                    | 0                           |  |  |
| Nuclear medicine study      | 1                    | 3                           |  |  |

Notes:

[45] - FAS with subjects who were recommended for additional imaging studies.

[46] - FAS with subjects who were recommended for additional imaging studies.

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were assessed from the time the consent was signed until 72 (+/-6) hours follow-up after the study MRA and continued until the end of the study (either the 72 hour follow-up or the CTA, if performed after the MRA as part of the study)

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 15.1 |
|--------------------|------|

### Reporting groups

|                       |                                    |
|-----------------------|------------------------------------|
| Reporting group title | Gadobutrol (Gadavist, BAY 86-4875) |
|-----------------------|------------------------------------|

Reporting group description:

Gadobutrol was administered to all subjects receiving study drug at the standard dose of 0.1 mmol/kg BW by single IV bolus injection. During the course of the study, non-contrast MRA images were obtained before the administration of gadobutrol, and Gadobutrol-enhanced MRA images were obtained after injection.

| Serious adverse events                            | Gadobutrol<br>(Gadavist, BAY 86-4875) |  |  |
|---------------------------------------------------|---------------------------------------|--|--|
| Total subjects affected by serious adverse events |                                       |  |  |
| subjects affected / exposed                       | 0 / 315 (0.00%)                       |  |  |
| number of deaths (all causes)                     | 0                                     |  |  |
| number of deaths resulting from adverse events    | 0                                     |  |  |

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

| Non-serious adverse events                            | Gadobutrol<br>(Gadavist, BAY 86-4875) |  |  |
|-------------------------------------------------------|---------------------------------------|--|--|
| Total subjects affected by non-serious adverse events |                                       |  |  |
| subjects affected / exposed                           | 14 / 315 (4.44%)                      |  |  |
| Nervous system disorders                              |                                       |  |  |
| Headache                                              |                                       |  |  |
| subjects affected / exposed                           | 7 / 315 (2.22%)                       |  |  |
| occurrences (all)                                     | 7                                     |  |  |
| Gastrointestinal disorders                            |                                       |  |  |
| Nausea                                                |                                       |  |  |
| subjects affected / exposed                           | 8 / 315 (2.54%)                       |  |  |
| occurrences (all)                                     | 8                                     |  |  |





## **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**

None reported