Clinical trial results:
Multicenter, single-blind, adaptive dose finding study of single intravenous injections of BAY 1747846 with corresponding blinded read in adult participants with known or highly suspected CNS lesions referred for contrast-enhanced MRI of the CNS

Summary

EudraCT number	2019-001560-30
Trial protocol	DE BG
Global end of trial date	14 December 2022

Results information

Result version number	v1 (current)
This version publication date	25 December 2023
First version publication date	25 December 2023

Trial information

Trial identification

Sponsor protocol code	BAY1747846/20241

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04307186
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser Wilhelm Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, +49 30 300139003, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, +49 30 300139003, 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	14 December 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 December 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To identify a dose of gadoquatrane for further development that has an overall diagnostic preference rate similar to that of the comparator gadobutrol at 5 min post injection.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the 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	18 November 2020
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	Bulgaria: 9
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Japan: 22
Country: Number of subjects enrolled	United States: 13
Worldwide total number of subjects	57
EEA total number of subjects	22

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)	39
From 65 to 84 years	16
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 17 study centers in 4 countries between 18-Nov-2020 (first subject first visit) and 6-Sep-2022 (last subject last visit).

Pre-assignment

Screening details:

Of the 62 screened subjects 5 were screening failures, resulting in 57 subjects assigned to treatment who started with gadobutrol.

Period 1

Period 1 title	Period 1 - Gadobutrol
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Arm title	Gadobutrol + Gadoquatrane

Arm description:

Subjects received one intravenous (IV) injection of gadobutrol 0.1 millimole(s) gadolinium/kilogram body weight (mmol Gd/kg bw) during treatment Period 1 and one IV injection of gadoquatrane (BAY1747846) 0.04 mmol Gd/kg bw during treatment Period 2.

Arm type	Experimental
Investigational medicinal product name	Gadoquatrane
Investigational medicinal product code	BAY1747846
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Solution for IV injection, 0.04 mmol Gd/kg bw

Investigational medicinal product name	Gadobutrol
Investigational medicinal product code	
Other name	Gadovist/Gadavist
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Solution for IV injection, 0.1 mmol Gd/kg bw

Number of subjects in period 1	Gadobutrol + Gadoquatrane
Started	57
Completed	56
Not completed	1
Consent withdrawn by subject	1

Period 2

Period 2 title	Washout 3-14 days
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Arm title	Gadobutrol + Gadoquatrane

Arm description:

Subjects received one intravenous (IV) injection of gadobutrol 0.1 millimole(s) gadolinium/kilogram body weight (mmol Gd/kg bw) during treatment Period 1 and one IV injection of gadoquatrane (BAY1747846) 0.04 mmol Gd/kg bw during treatment Period 2.

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

Dosage and administration details:

Solution for IV injection, 0.1 mmol Gd/kg bw

Investigational medicinal product name	Gadoquatrane
Investigational medicinal product code	BAY1747846
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Solution for IV injection, 0.04 mmol Gd/kg bw

Number of subjects in period 2	Gadobutrol + Gadoquatrane
Started	56
Completed	53
Not completed	3
Consent withdrawn by subject	1
Pre-specified withdrawal criterion met	1
Progressive disease	1

Period 3

Period 3 title	Period 2 - Gadoquatrane
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Arm title	Gadobutrol + Gadoquatrane

Arm description:

Subjects received one intravenous (IV) injection of gadobutrol 0.1 millimole(s) gadolinium/kilogram body weight (mmol Gd/kg bw) during treatment Period 1 and one IV injection of gadoquatrane (BAY1747846) 0.04 mmol Gd/kg bw during treatment Period 2.

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

Dosage and administration details:

Solution for IV injection, 0.1 mmol Gd/kg bw

Investigational medicinal product name	Gadoquatrane
Investigational medicinal product code	BAY1747846
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Solution for IV injection, 0.04 mmol Gd/kg bw

Number of subjects in period 3	Gadobutrol + Gadoquatrane
Started	53
Completed	52
Not completed	1
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Gadobutrol + Gadoquatrane
Reporting group description:	
Subjects received one intravenous (IV) injection of gadobutrol 0.1 millimole(s) gadolinium/kilogram body weight (mmol Gd/kg bw) during treatment Period 1 and one IV injection of gadoquatrane (BAY1747846) 0.04 mmol Gd/kg bw during treatment Period 2.	

Reporting group values	Gadobutrol + Gadoquatrane	Total	
Number of subjects	57	57	
Age Categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	39	39	
From 65-84 years	16	16	
85 years and over	2	2	
Age Continuous Units: years			
arithmetic mean	55.9		
standard deviation	± 13.6	-	
Gender Categorical Units: Subjects			
Female	34	34	
Male	23	23	
Race Units: Subjects			
Asian	23	23	
Black or African American	1	1	
White	32	32	
More than one race	1	1	

End points

End points reporting groups

Reporting group title	Gadobutrol + Gadoquatrane

Reporting group description:

Subjects received one intravenous (IV) injection of gadobutrol 0.1 millimole(s) gadolinium/kilogram body weight (mmol Gd/kg bw) during treatment Period 1 and one IV injection of gadoquatrane (BAY1747846) 0.04 mmol Gd/kg bw during treatment Period 2.

Reporting group title	Gadobutrol + Gadoquatrane

Reporting group description:

Subjects received one intravenous (IV) injection of gadobutrol 0.1 millimole(s) gadolinium/kilogram body weight (mmol Gd/kg bw) during treatment Period 1 and one IV injection of gadoquatrane (BAY1747846) 0.04 mmol Gd/kg bw during treatment Period 2.

Reporting group title	Gadobutrol + Gadoquatrane

Reporting group description:

Subjects received one intravenous (IV) injection of gadobutrol 0.1 millimole(s) gadolinium/kilogram body weight (mmol Gd/kg bw) during treatment Period 1 and one IV injection of gadoquatrane (BAY1747846) 0.04 mmol Gd/kg bw during treatment Period 2.

Subject analysis set title	Gadobutrol post-contrast
Subject analysis set type	Sub-group analysis

Subject analysis set description:

MR images were taken 5 min after receiving IV injection of gadobutrol.

Subject analysis set title	Gadoquatrane post-contrast
Subject analysis set type	Sub-group analysis

Subject analysis set description:

MR images were taken 5 min after receiving IV injection of gadoquatrane.

Subject analysis set title	Gadobutrol pre-contrast
Subject analysis set type	Sub-group analysis

Subject analysis set description:

MR images were taken before receiving IV injection of gadobutrol.

Subject analysis set title	Gadobutrol combined pre- and post-contrast
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Evaluation of the combined MR image sets taken before and 5 min after receiving IV injection of gadobutrol.

Subject analysis set title	Gadoquatrane pre-contrast
Subject analysis set type	Sub-group analysis

Subject analysis set description:

MR images were taken before receiving IV injection of gadoquatrane.

Subject analysis set title	Gadoquatrane combined pre- and post-contrast
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Evaluation of the combined MR image sets taken before and 5 min after receiving IV injection of gadoquatrane.

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

Subject analysis set description:

All subjects who have completed magnetic resonance (MR) image datasets that qualify for blinded read.

Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects who received any dose of study intervention

Primary: Overall diagnostic preference

End point title	Overall diagnostic preference[1]

End point description:

Overall diagnostic preference using a matched pairs approach was evaluated by 3 blinded readers using an ordinal 5-point scale (greatly prefer gadoquatrane, prefer gadoquatrane, no preference, prefer gadobutrol, greatly prefer gadobutrol). Percentage of participants and the respective Wald confidence intervals (CI) for image preference were reported for each of the 3 readers based on the 3-point preference scale (1=greatly prefer/prefer gadoquatrane, 0=no preference, -1=greatly prefer/prefer gadobutrol). If 2 or 3 readers reach the same conclusion on the recommended action (e.g. no dose adjustment needed), then this will be the recommended action taken.

End point type	Primary

End point timeframe:

At 5 minute post each injection

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analyses were provided as an attachment

End point values	Gadobutrol + Gadoquatrane			
Subject group type	Reporting group			
Number of subjects analysed	50[2]			
Units: Percentage of subjects				
number (confidence interval 95%)				
Reader 1 (1)	10 (1.68 to 18.32)			
Reader 1 (0)	34 (20.87 to 47.13)			
Reader 1 (-1)	56 (42.24 to 69.76)			
Reader 2 (1)	26 (13.84 to 38.16)			
Reader 2 (0)	42 (28.32 to 55.68)			
Reader 2 (-1)	32 (19.07 to 44.93)			
Reader 3 (1)	30 (17.30 to 42.70)			
Reader 3 (0)	28 (15.55 to 40.45)			
Reader 3 (-1)	42 (28.32 to 55.68)			

Notes:

[2] - FAS

Attachments (see zip file)	20241_Statistical Analyses_Primary.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Sum of lesion visualization parameters on post-contrast images

End point title	Sum of lesion visualization parameters on post-contrast images

End point description:

The 3 lesion visualization parameters (border delineation/degree of contrast enhancement/internal morphology) were combined by adding them up for each participant and each blinded reader, leading to

only one variable on an ordinal 11-point scale (the higher values represent a better lesion visualization). Average reader was the mean of the 3 blinded readers averages of the scores per participant. Lesion border delineation: measured on a 4-point scale (1=None [no/unclear delineation of the lesion boundaries] to 4=Excellent [clear and complete delineation]). Degree of lesion contrast enhancement: measured on a 4-point scale (1=No [lesion is not enhanced] to 4=Excellent [lesion is clearly and brightly enhanced]). Lesion internal morphology: measured on a 3-point scale (1=Poor [structure and internal morphology of the lesion is poorly visible] to 3=Good [structure and internal morphology of the lesion is sufficiently visible]).

End point type	Secondary

End point timeframe:

At 5 minute post each injection

End point values	Gadobutrol post-contrast	Gadoquatrane post-contrast		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50[3]	50[4]		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Reader 1 (n=49,49)	9.95 (± 1.447)	9.67 (± 1.541)		
Reader 2 (n=50,50)	7.67 (± 1.292)	7.49 (± 1.406)		
Reader 3 (n=50,49)	9.28 (± 1.877)	9.65 (± 1.598)		
Average reader (n=49,49)	9.00 (± 1.294)	8.94 (± 1.229)		

Notes:

[3] - FAS

[4] - FAS

Statistical analyses

Statistical analysis title	Average reader

Statistical analysis description:

The non-inferiority of gadoquatrane versus gadobutrol was evaluated using CIs based on the t-distribution. A non-inferiority margin of 1 was used, i.e. meaning that a 95% two-sided CI for the mean difference gadoquatrane minus gadobutrol score must exclude the value -1. Number of subjects in this analysis is 49.

Comparison groups	Gadoquatrane post-contrast v Gadobutrol post-contrast
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001 [5]
Method	t-test, 1-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	0.13

Notes:

[5] - P-Value was calculated. Non-inferiority was achieved with a one-sided p-value lower than 0.025.

Secondary: Lesion visualization parameter border delineation on pre-contrast and combined pre- and post-contrast images

End point title	Lesion visualization parameter border delineation on pre-contrast and combined pre- and post-contrast images

End point description:

Lesion border delineation: up to 5 of the largest lesions were selected and scored using a 4-point scale (1=None [no/unclear delineation of the lesion boundaries] to 4=Excellent [clear and complete delineation]; the higher values represent a better lesion border delineation). Average reader was the mean of the 3 blinded readers averages of the scores per participant.

End point type	Secondary

End point timeframe:

At pre-injection and 5 minute post each injection

End point values	Gadobutrol pre-contrast	Gadobutrol combined pre- and post-contrast	Gadoquatrane pre-contrast	Gadoquatrane combined pre- and post-contrast
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	50[6]	50[7]	50[8]	50[9]
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Reader 1 (n=46,46,43,43)	1.83 (± 0.701)	3.39 (± 0.936)	1.88 (± 0.698)	3.28 (± 0.970)
Reader 2 (n=44,44,44,44)	1.70 (± 0.509)	2.45 (± 0.589)	1.67 (± 0.469)	2.39 (± 0.576)
Reader 3 (n=40,40,41,41)	1.98 (± 0.423)	3.28 (± 0.751)	1.87 (± 0.403)	3.21 (± 0.873)
Average reader (n=39,39,39,39)	1.82 (± 0.438)	3.02 (± 0.614)	1.81 (± 0.394)	2.91 (± 0.609)

Notes:

[6] - FAS

[7] - FAS

[8] - FAS

[9] - FAS

Statistical analyses

Statistical analysis title	Average Reader - gadoquatrane

Statistical analysis description:

95% two-sided CIs based on a t-distribution for the difference of combined pre- and post-contrast minus pre-contrast scores. Parameter estimate was the descriptive comparison of the result following gadobutrol with the result following gadoquatrane. Number of subjects in this analysis is 39.

Comparison groups	Gadoquatrane combined pre- and post-contrast v Gadoquatrane pre-contrast
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	1.25

	Average Reader - gadobutrol

Statistical analysis title	

Statistical analysis description:

95% two-sided CIs based on a t-distribution for the difference of combined pre- and post-contrast minus pre-contrast scores. Parameter estimate was the descriptive comparison of the result following gadobutrol with the result following gadoquatrane. Number of subjects in this analysis is 39.

Comparison groups	Gadobutrol combined pre- and post-contrast v Gadobutrol pre-contrast
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.06
upper limit	1.34

Secondary: Lesion visualization parameter contrast enhancement on pre-contrast and combined pre- and post-contrast images

End point title	Lesion visualization parameter contrast enhancement on pre-contrast and combined pre- and post-contrast images

End point description:

Degree of lesion contrast enhancement: up to the 5 largest lesions were selected and scored using a 4-point scale (1=No [lesion is not enhanced] to 4=Excellent [lesion is clearly and brightly enhanced]; the higher values represent a better degree of lesion contrast enhancement). Average reader was the mean of the 3 blinded readers averages of the scores per participant.

End point type	Secondary

End point timeframe:

At pre-injection and 5 minute post each injection

End point values	Gadobutrol pre-contrast	Gadobutrol combined pre- and post-contrast	Gadoquatrane pre-contrast	Gadoquatrane combined pre- and post-contrast
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	50[10]	50[11]	50[12]	50[13]
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Reader 1 (n=46,46,43,43)	1.00 (± 0.000)	3.24 (± 0.917)	1.00 (± 0.000)	3.20 (± 0.825)
Reader 2 (n=44,44,44,44)	1.00 (± 0.000)	2.50 (± 0.629)	1.00 (± 0.000)	2.57 (± 0.587)
Reader 3 (n=40,40,41,41)	1.00 (± 0.000)	3.55 (± 0.904)	0.99 (± 0.078)	3.49 (± 0.925)
Average Reader (n=39,39,39,39)	1.00 (± 0.000)	3.07 (± 0.638)	1.00 (± 0.027)	3.05 (± 0.600)

Notes:

[10] - FAS

[11] - FAS

[12] - FAS

[13] - FAS

Statistical analyses

Statistical analysis title	Average Reader - gadoquatrane

Statistical analysis description:

95% two-sided CIs based on a t-distribution for the difference of combined pre- and post-contrast minus pre-contrast scores. Parameter estimate was the descriptive comparison of the result following gadobutrol with the result following gadoquatrane. Number of subjects in this analysis is 39.

Comparison groups	Gadoquatrane combined pre- and post-contrast v Gadoquatrane pre-contrast
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	2.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.86
upper limit	2.25

Statistical analysis title	Average Reader - gadobutrol

Statistical analysis description:

95% two-sided CIs based on a t-distribution for the difference of combined pre- and post-contrast minus pre-contrast scores. Parameter estimate was the descriptive comparison of the result following gadobutrol with the result following gadoquatrane. Number of subjects in this analysis is 39.

Comparison groups	Gadobutrol combined pre- and post-contrast v Gadobutrol pre-contrast
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	2.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.87
upper limit	2.28

Secondary: Lesion visualization parameter internal morphology on pre-contrast and combined pre- and post-contrast images

End point title	Lesion visualization parameter internal morphology on pre-contrast and combined pre- and post-contrast images

End point description:

Lesion internal morphology: up to 5 of the largest lesions were selected and scored using a 3-point scale (1=Poor [structure and internal morphology of the lesion is poorly visible] to 3=Good [structure and internal morphology of the lesion is sufficiently visible]; the higher values represent a better lesion internal morphology). Average reader was the mean of the 3 blinded readers averages of the scores per participant.

End point type	Secondary

End point timeframe:

At pre-injection and 5 minute post each injection

End point values	Gadobutrol pre-contrast	Gadobutrol combined pre- and post-contrast	Gadoquatrane pre-contrast	Gadoquatrane combined pre- and post-contrast
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	50[14]	50[15]	50[16]	50[17]
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Reader 1 (n=46,46,43,43)	1.27 (± 0.444)	2.62 (± 0.693)	1.40 (± 0.484)	2.58 (± 0.655)
Reader 2 (n=44,44,44,44)	1.05 (± 0.185)	2.13 (± 0.598)	1.05 (± 0.211)	2.11 (± 0.689)
Reader 3 (n=40,40,41,41)	1.05 (± 0.221)	2.45 (± 0.677)	1.04 (± 0.234)	2.44 (± 0.673)
Average Reader (n=39,39,39,39)	1.13 (± 0.194)	2.39 (± 0.493)	1.16 (± 0.218)	2.35 (± 0.500)

Notes:

[14] - FAS

[15] - FAS

[16] - FAS

[17] - FAS

Statistical analyses

Statistical analysis title	Average Reader - gadoquatrane

Statistical analysis description:

95% two-sided CIs based on a t-distribution for the difference of combined pre- and post-contrast minus pre-contrast scores. Parameter estimate was the descriptive comparison of the result following gadobutrol with the result following gadoquatrane. Number of subjects in this analysis is 39.

Comparison groups	Gadoquatrane combined pre- and post-contrast v Gadoquatrane pre-contrast
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.05
upper limit	1.32

Statistical analysis title	Average Reader - gadobutrol

Statistical analysis description:

95% two-sided CIs based on a t-distribution for the difference of combined pre- and post-contrast minus pre-contrast scores. Parameter estimate was the descriptive comparison of the result following gadobutrol with the result following gadoquatrane. Number of subjects in this analysis is 39.

Comparison groups	Gadobutrol combined pre- and post-contrast v Gadobutrol pre-contrast

Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.11
upper limit	1.43

Secondary: Number of lesions on pre-contrast and combined pre- and post-contrast images

End point title	Number of lesions on pre-contrast and combined pre- and post-contrast images

End point description:

The 3 blinded readers recorded the total number of lesions for each pre-contrast and combined pre- and post-contrast magnetic resonance image set separately. The numbers of subjects by number of detected lesions were reported. For Reader 2, the number of subjects analyzed for each reporting groups are: 48, 49, 49, 49.

End point type	Secondary

End point timeframe:

At pre-injection and 5 minute post injection

End point values	Gadobutrol pre-contrast	Gadobutrol combined pre- and post-contrast	Gadoquatrane pre-contrast	Gadoquatrane combined pre- and post-contrast
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	50[18]	50[19]	50[20]	50[21]
Units: Subjects				
Reader 1 (Nr. of lesions=0)	4	1	7	1
Reader 1 (Nr. of lesions=1)	43	40	40	41
Reader 1 (Nr. of lesions=2)	3	7	1	6
Reader 1 (Nr. of lesions=3)	0	2	2	2
Reader 2 (Nr. of lesions=0)	4	0	5	0
Reader 2 (Nr. of lesions=1)	42	43	42	43
Reader 2 (Nr. of lesions=2)	0	3	0	3
Reader 2 (Nr. of lesions=3)	2	3	2	3
Reader 3 (Nr. of lesions=0)	10	1	9	1
Reader 3 (Nr. of lesions=1)	40	41	40	42
Reader 3 (Nr. of lesions=2)	0	7	1	4
Reader 3 (Nr. of lesions=3)	0	1	0	1
Reader 3 (Nr. of lesions=4)	0	0	0	2

Notes:

[18] - FAS

[19] - FAS

[20] - FAS
[21] - FAS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events tables: up to the 24 h ± 4 h follow-up time point following Gadobutrol or Gadoquatrane injection. Adverse event reporting for the deaths (all causes): after signing informed consent up to the last contact per participant, up to 36 days.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Gadoquatrane

Reporting group description:

Subjects received one intravenous (IV) injection of gadoquatrane (BAY1747846) 0.04 millimole(s) gadolinium/kilogram body weight (mmol Gd/kg bw) during treatment Period 2.

Reporting group title	Gadobutrol

Reporting group description:

Subjects received one IV injection of gadobutrol 0.1 mmol Gd/kg bw during treatment Period 1.

Serious adverse events	Gadoquatrane	Gadobutrol	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 52 (0.00%)	0 / 57 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Gadoquatrane	Gadobutrol	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 52 (3.85%)	3 / 57 (5.26%)	
General disorders and administration site conditions			
Injection site bruising			
subjects affected / exposed	0 / 52 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 52 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Gastrointestinal disorders			

Toothache subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 57 (0.00%) 0	
Skin and subcutaneous tissue disorders Dermatitis contact subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	1 / 57 (1.75%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 July 2021	Incorporated an interim analysis to facilitate the planning of future phases of development. Furthermore the inclusion criterion pertaining to eGFR at baseline was clarified and two exclusion criteria were adapted.
06 January 2022	To fulfill the FDA request to add secondary endpoints to the study (lesion visualization parameters and number of lesions).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported