Clinical trial results:
P03277 Dose Finding Study in Central Nervous System (CNS) Magnetic Resonance Imaging (MRI)

Summary

EudraCT number	2014-003576-23
Trial protocol	BE CZ HU IT
Global end of trial date	23 January 2018

Results information

Result version number	v1 (current)
This version publication date	01 March 2019
First version publication date	01 March 2019

Trial information

Trial identification

Sponsor protocol code	GDX-44-004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02633501
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 123673

Notes:

Sponsors

Sponsor organisation name	Guerbet
Sponsor organisation address	BP 57400, Roissy CDG Cedex, France, 95943
Public contact	Jing HAO, Head of Medical Affairs & Clinical Development, GUERBET, +33 145915000, jing.hao@guerbet.com
Scientific contact	Jing HAO, Head of Medical Affairs & Clinical Development, GUERBET, +33 145915000, jing.hao@guerbet.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	23 January 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 January 2018
Global end of trial reached?	Yes
Global end of trial date	23 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine a safe and effective dose of P03277 based on a comparison of Contrast to Noise Ratio (CNR) between several doses, 0.025, 0.05, 0.1, 0.2 mmol/kg, of P03277 and gadobenate dimeglumine (MultiHance®) at 0.1 mmol/kg.

Protection of trial subjects:

This trial has been conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, that are consistent with Good Clinical Practice (GCP) according to International Conference on Harmonisation (ICH) guidelines and with the applicable regional/local regulations of the country in which the trial was conducted.
The safety of subjects was assessed over 1 day follow-up period after each MRI visit, for vital signs, ECG, injection site tolerance, clinical laboratory parameters and monitoring of adverse events.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2016
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	Poland: 13
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	Hungary: 90
Country: Number of subjects enrolled	Mexico: 93
Country: Number of subjects enrolled	United States: 55
Country: Number of subjects enrolled	Korea, Republic of: 29
Country: Number of subjects enrolled	Italy: 23
Worldwide total number of subjects	312
EEA total number of subjects	135

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)	231
From 65 to 84 years	79
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	312
Intermediate milestone: Number of subjects	Randomization: 280
Number of subjects completed	272

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 11
Reason: Number of subjects	Physician decision: 1
Reason: Number of subjects	Various reasons: 26
Reason: Number of subjects	Adverse event, serious fatal: 1
Reason: Number of subjects	Adverse event, non-fatal: 1

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Data analyst, Assessor, Subject

Arms

Arm title	Overall population

Arm description:

All subjects who had received at least one injection of contrast agent, regardless of the quantity.

Arm type	Experimental
Investigational medicinal product name	P03277
Investigational medicinal product code	
Other name	Gadopiclenol
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

One of the four doses (0.025, 0.05, 0.1 or 0.2 mmol/kg body weight) in a single intravenous injection.

Investigational medicinal product name	Gadobenate dimeglumine
Investigational medicinal product code	
Other name	MultiHance
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

0.1 mmol/kg body weight in a single intravenous injection.

Number of subjects in period 1[1]	Overall population
Started	272
Completed	238
Not completed	34
Consent withdrawn by subject	9
Adverse event, non-fatal	2
Other reasons	20
Lost to follow-up	3

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Among the 312 screened subjects, 32 subjects were screening failure mainly due to not fulfillment of inclusion criteria/ presence of non-inclusion criteria or due to consent withdrawal. Therefore 280 subjects were randomized. Eight randomized subjects were prematurely withdrawn before receiving the first contrast agent administration (2 for withdrawal of subject's consent, 1 for adverse event and 5 for other reason).

Baseline characteristics

Reporting groups	
Reporting group title	Overall population
Reporting group description:	
All subjects who had received at least one injection of contrast agent, regardless of the quantity.	

Reporting group values	Overall population	Total	
Number of subjects	272	272	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
geometric mean	53.8		
standard deviation	± 13.6	-	
Gender categorical Units: Subjects			
Female	159	159	
Male	113	113	

End points

End points reporting groups

Reporting group title	Overall population

Reporting group description:

All subjects who had received at least one injection of contrast agent, regardless of the quantity.

Subject analysis set title	P03277 0.2 mmol/kg - Reader 1
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Set included all subjects who have a Contrast-to-Noise Ratio (CNR) from both enhanced and unenhanced measurements derivable from one MRI by at least one off-site blinded reader and who had no major protocol deviations throughout their whole study period.

Subject analysis set title	P03277 0.1 mmol/kg - Reader 1
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Set included all subjects who have a Contrast-to-Noise Ratio (CNR) from both enhanced and unenhanced measurements derivable from one MRI by at least one off-site blinded reader and who had no major protocol deviations throughout their whole study period.

Subject analysis set title	P03277 0.05 mmol/kg - Reader 1
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Set included all subjects who have a Contrast-to-Noise Ratio (CNR) from both enhanced and unenhanced measurements derivable from one MRI by at least one off-site blinded reader and who had no major protocol deviations throughout their whole study period.

Subject analysis set title	P03277 0.025 mmol/kg - Reader 1
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Set included all subjects who have a Contrast-to-Noise Ratio (CNR) from both enhanced and unenhanced measurements derivable from one MRI by at least one off-site blinded reader and who had no major protocol deviations throughout their whole study period.

Subject analysis set title	P03277 0.2 mmol/kg - Reader 2
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Set included all subjects who have a Contrast-to-Noise Ratio (CNR) from both enhanced and unenhanced measurements derivable from one MRI by at least one off-site blinded reader and who had no major protocol deviations throughout their whole study period.

Subject analysis set title	P03277 0.1 mmol/kg - Reader 2
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Set included all subjects who have a Contrast-to-Noise Ratio (CNR) from both enhanced and unenhanced measurements derivable from one MRI by at least one off-site blinded reader and who had no major protocol deviations throughout their whole study period.

Subject analysis set title	P03277 0.05 mmol/kg - Reader 2
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Set included all subjects who have a Contrast-to-Noise Ratio (CNR) from both enhanced and unenhanced measurements derivable from one MRI by at least one off-site blinded reader and who had no major protocol deviations throughout their whole study period.

Subject analysis set title	P03277 0.025 mmol/kg - Reader 2

Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Set included all subjects who have a Contrast-to-Noise Ratio (CNR) from both enhanced and unenhanced measurements derivable from one MRI by at least one off-site blinded reader and who had no major protocol deviations throughout their whole study period.

Subject analysis set title	P03277 0.2 mmol/kg - Reader 3
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Set included all subjects who have a Contrast-to-Noise Ratio (CNR) from both enhanced and unenhanced measurements derivable from one MRI by at least one off-site blinded reader and who had no major protocol deviations throughout their whole study period.

Subject analysis set title	P03277 0.1 mmol/kg - Reader 3
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Set included all subjects who have a Contrast-to-Noise Ratio (CNR) from both enhanced and unenhanced measurements derivable from one MRI by at least one off-site blinded reader and who had no major protocol deviations throughout their whole study period.

Subject analysis set title	P03277 0.05 mmol/kg - Reader 3
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Set included all subjects who have a Contrast-to-Noise Ratio (CNR) from both enhanced and unenhanced measurements derivable from one MRI by at least one off-site blinded reader and who had no major protocol deviations throughout their whole study period.

Subject analysis set title	P03277 0.025 mmol/kg - Reader 3
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Set included all subjects who have a Contrast-to-Noise Ratio (CNR) from both enhanced and unenhanced measurements derivable from one MRI by at least one off-site blinded reader and who had no major protocol deviations throughout their whole study period.

Subject analysis set title	Gadobenate dimeglumine (P03277 0.2 mmol/kg) - Reader 1
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Set included all subjects who have a Contrast-to-Noise Ratio (CNR) from both enhanced and unenhanced measurements derivable from one MRI by at least one off-site blinded reader and who had no major protocol deviations throughout their whole study period.

Subject analysis set title	Gadobenate dimeglumine (P03277 0.1 mmol/kg) - Reader 1
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Set included all subjects who have a Contrast-to-Noise Ratio (CNR) from both enhanced and unenhanced measurements derivable from one MRI by at least one off-site blinded reader and who had no major protocol deviations throughout their whole study period.

Subject analysis set title	Gadobenate dimeglumine (P03277 0.05 mmol/kg) - Reader 1
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Set included all subjects who have a Contrast-to-Noise Ratio (CNR) from both enhanced and unenhanced measurements derivable from one MRI by at least one off-site blinded reader and who had no major protocol deviations throughout their whole study period.

Subject analysis set title	Gadobenate dimeglumine (P03277 0.025 mmol/kg) - Reader 1
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Set included all subjects who have a Contrast-to-Noise Ratio (CNR) from both enhanced and unenhanced measurements derivable from one MRI by at least one off-site blinded reader and who had no major protocol deviations throughout their whole study period.

Subject analysis set title	Gadobenate dimeglumine (P03277 0.1 mmol/kg) - Reader 2
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Set included all subjects who have a Contrast-to-Noise Ratio (CNR) from both enhanced and unenhanced measurements derivable from one MRI by at least one off-site blinded reader and who had no major protocol deviations throughout their whole study period.

Subject analysis set title	Gadobenate dimeglumine (P03277 0.05 mmol/kg) - Reader 2
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Set included all subjects who have a Contrast-to-Noise Ratio (CNR) from both enhanced and unenhanced measurements derivable from one MRI by at least one off-site blinded reader and who had no major protocol deviations throughout their whole study period.

Subject analysis set title	Gadobenate dimeglumine (P03277 0.025 mmol/kg) - Reader 2
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Set included all subjects who have a Contrast-to-Noise Ratio (CNR) from both enhanced and unenhanced measurements derivable from one MRI by at least one off-site blinded reader and who had no major protocol deviations throughout their whole study period.

Subject analysis set title	Gadobenate dimeglumine (P03277 0.2 mmol/kg) - Reader 3
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Set included all subjects who have a Contrast-to-Noise Ratio (CNR) from both enhanced and unenhanced measurements derivable from one MRI by at least one off-site blinded reader and who had no major protocol deviations throughout their whole study period.

Subject analysis set title	Gadobenate dimeglumine (P03277 0.1 mmol/kg) - Reader 3
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Set included all subjects who have a Contrast-to-Noise Ratio (CNR) from both enhanced and unenhanced measurements derivable from one MRI by at least one off-site blinded reader and who had no major protocol deviations throughout their whole study period.

Subject analysis set title	Gadobenate dimeglumine (P03277 0.05 mmol/kg) - Reader 3
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Set included all subjects who have a Contrast-to-Noise Ratio (CNR) from both enhanced and unenhanced measurements derivable from one MRI by at least one off-site blinded reader and who had no major protocol deviations throughout their whole study period.

Subject analysis set title	Gadobenate dimeglumine (P03277 0.025 mmol/kg) - Reader 3
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Set included all subjects who have a Contrast-to-Noise Ratio (CNR) from both enhanced and unenhanced measurements derivable from one MRI by at least one off-site blinded reader and who had no major protocol deviations throughout their whole study period.

Subject analysis set title	Gadobenate dimeglumine (P03277 0.2 mmol/kg) - Reader 2
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Set included all subjects who have a Contrast-to-Noise Ratio (CNR) from both enhanced and unenhanced measurements derivable from one MRI by at least one off-site blinded reader and who had no major protocol deviations throughout their whole study period.

Primary: Contrast-to-Noise Ratio (CNR)

End point title	Contrast-to-Noise Ratio (CNR)

End point description:

The Contrast-to-Noise Ratio (CNR) was calculated from the signal intensity measurement of maximum 3 enhanced lesions by 3 independent blinded readers.

End point type	Primary

End point timeframe:

1 day procedure

End point values	P03277 0.2 mmol/kg - Reader 1	P03277 0.1 mmol/kg - Reader 1	P03277 0.05 mmol/kg - Reader 1	P03277 0.025 mmol/kg - Reader 1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	44	51	56	54
Units: None				
least squares mean (standard error)	49.99 (± 7.96)	35.94 (± 2.71)	31.78 (± 3.58)	21.13 (± 2.65)

End point values	P03277 0.2 mmol/kg - Reader 2	P03277 0.1 mmol/kg - Reader 2	P03277 0.05 mmol/kg - Reader 2	P03277 0.025 mmol/kg - Reader 2
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	41	43	47	44
Units: None				
least squares mean (standard error)	103.18 (± 10.94)	72.17 (± 6.29)	51.02 (± 5.09)	43.15 (± 7.57)

End point values	P03277 0.2 mmol/kg - Reader 3	P03277 0.1 mmol/kg - Reader 3	P03277 0.05 mmol/kg - Reader 3	P03277 0.025 mmol/kg - Reader 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	42	45	51	49
Units: None				
least squares mean (standard error)	125.08 (± 14.08)	94.17 (± 7.99)	67.05 (± 6.43)	46.74 (± 10.04)

End point values	Gadobenate dimeglumine (P03277 0.2 mmol/kg) - Reader 1	Gadobenate dimeglumine (P03277 0.1 mmol/kg) - Reader 1	Gadobenate dimeglumine (P03277 0.05 mmol/kg) - Reader 1	Gadobenate dimeglumine (P03277 0.025 mmol/kg) - Reader 1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	44	51	56	54
Units: None				
least squares mean (standard error)	35.55 (± 7.96)	27.28 (± 2.71)	29.60 (± 3.58)	31.72 (± 2.65)

End point values	Gadobenate dimeglumine (P03277 0.1 mmol/kg) - Reader 2	Gadobenate dimeglumine (P03277 0.05 mmol/kg) - Reader 2	Gadobenate dimeglumine (P03277 0.025 mmol/kg) - Reader 2	Gadobenate dimeglumine (P03277 0.2 mmol/kg) - Reader 3

Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	43	47	44	42
Units: None				
least squares mean (standard error)	52.79 (± 6.29)	49.11 (± 5.09)	57.29 (± 7.57)	73.12 (± 14.08)

End point values	Gadobenate dimeglumine (P03277 0.1 mmol/kg) - Reader 3	Gadobenate dimeglumine (P03277 0.05 mmol/kg) - Reader 3	Gadobenate dimeglumine (P03277 0.025 mmol/kg) - Reader 3	Gadobenate dimeglumine (P03277 0.2 mmol/kg) - Reader 2
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	45	51	49	41
Units: None				
least squares mean (standard error)	64.94 (± 7.99)	64.58 (± 6.43)	70.70 (± 10.04)	64.81 (± 10.94)

Statistical analyses

Statistical analysis title	Mixed Models - Holm's Step-Down Method
Statistical analysis description:	
The number of subjects analyzed was 44. The difference in CNR was calculated as follow: CNR (P03277) - CNR (gadobenate dimeglumine).	
Comparison groups	P03277 0.2 mmol/kg - Reader 1 v Gadobenate dimeglumine (P03277 0.2 mmol/kg) - Reader 1
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	14.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.64
upper limit	21.25

Notes:

[1] - Superiority confirmed

Statistical analysis title	Mixed Models - Holm's Step-Down Method
Statistical analysis description:	
The number of subjects analyzed was 51. The difference in CNR was calculated as follow: CNR (P03277) - CNR (gadobenate dimeglumine).	
Comparison groups	P03277 0.1 mmol/kg - Reader 1 v Gadobenate dimeglumine (P03277 0.1 mmol/kg) - Reader 1

Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0007 [2]
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	8.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.52
upper limit	13.79

Notes:

[2] - Superiority confirmed

Statistical analysis title	Mixed Models - Holm's Step-Down Method

Statistical analysis description:

The number of subjects analyzed was 56. The difference in CNR was calculated as follow: CNR (P03277) - CNR (gadobenate dimeglumine).

Comparison groups	P03277 0.05 mmol/kg - Reader 1 v Gadobenate dimeglumine (P03277 0.05 mmol/kg) - Reader 1
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1858 [3]
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	2.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.67
upper limit	7.03

Notes:

[3] - Superiority not confirmed

Statistical analysis title	Mixed Models - Holm's Step-Down Method

Statistical analysis description:

The number of subjects analyzed was 54. The difference in CNR was calculated as follow: CNR (P03277) - CNR (gadobenate dimeglumine).

Comparison groups	P03277 0.025 mmol/kg - Reader 1 v Gadobenate dimeglumine (P03277 0.025 mmol/kg) - Reader 1
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-10.59

Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.59
upper limit	-6.58

Statistical analysis title	Mixed Models - Holm's Step-Down Method

Statistical analysis description:

The number of subjects analyzed was 41. The difference in CNR was calculated as follow: CNR (P03277) - CNR (gadobenate dimeglumine).

Comparison groups	P03277 0.2 mmol/kg - Reader 2 v Gadobenate dimeglumine (P03277 0.2 mmol/kg) - Reader 2
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [4]
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	38.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	18.62
upper limit	58.12

Notes:

[4] - Superiority confirmed

Statistical analysis title	Mixed Models - Holm's Step-Down Method

Statistical analysis description:

The number of subjects analyzed was 43. The difference in CNR was calculated as follow: CNR (P03277) - CNR (gadobenate dimeglumine).

Comparison groups	P03277 0.1 mmol/kg - Reader 2 v Gadobenate dimeglumine (P03277 0.1 mmol/kg) - Reader 2
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	19.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.42
upper limit	27.34

Notes:

[5] - Superiority confirmed

Statistical analysis title	Mixed Models - Holm's Step-Down Method

Statistical analysis description:

The number of subjects analyzed was 47. The difference in CNR was calculated as follow: CNR (P03277) - CNR (gadobenate dimeglumine).

Comparison groups	P03277 0.05 mmol/kg - Reader 2 v Gadobenate dimeglumine (P03277 0.05 mmol/kg) - Reader 2
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3384 [6]
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	1.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.28
upper limit	11.1

Notes:

[6] - Superiority not confirmed

Statistical analysis title	Mixed Models - Holm's Step-Down Method

Statistical analysis description:

The number of subjects analyzed was 44. The difference in CNR was calculated as follow: CNR (P03277) - CNR (gadobenate dimeglumine).

Comparison groups	P03277 0.025 mmol/kg - Reader 2 v Gadobenate dimeglumine (P03277 0.025 mmol/kg) - Reader 2
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-14.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.33
upper limit	-4.95

Statistical analysis title	Mixed Models - Holm's Step-Down Method

Statistical analysis description:

The number of subjects analyzed was 42. The difference in CNR was calculated as follow: CNR (P03277) - CNR (gadobenate dimeglumine).

Comparison groups	P03277 0.2 mmol/kg - Reader 3 v Gadobenate dimeglumine (P03277 0.2 mmol/kg) - Reader 3

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	51.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	30.36
upper limit	73.55

Notes:

[7] - Superiority confirmed

Statistical analysis title	Mixed Models - Holm's Step-Down Method

Statistical analysis description:

The number of subjects analyzed was 45. The difference in CNR was calculated as follow: CNR (P03277) - CNR (gadobenate dimeglumine).

Comparison groups	P03277 0.1 mmol/kg - Reader 3 v Gadobenate dimeglumine (P03277 0.1 mmol/kg) - Reader 3
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	29.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.05
upper limit	42.41

Notes:

[8] - Superiority confirmed

Statistical analysis title	Mixed Models - Holm's Step-Down Method

Statistical analysis description:

The number of subjects analyzed was 51. The difference in CNR was calculated as follow: CNR (P03277) - CNR (gadobenate dimeglumine).

Comparison groups	P03277 0.05 mmol/kg - Reader 3 v Gadobenate dimeglumine (P03277 0.05 mmol/kg) - Reader 3
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3249 [9]
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	2.47

Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.39
upper limit	13.32

Notes:

[9] - Superiority not confirmed

Statistical analysis title	Mixed Models - Holm's Step-Down Method

Statistical analysis description:

The number of subjects analyzed was 49. The difference in CNR was calculated as follow: CNR (P03277) - CNR (gadobenate dimeglumine).

Comparison groups	P03277 0.025 mmol/kg - Reader 3 v Gadobenate dimeglumine (P03277 0.025 mmol/kg) - Reader 3
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-23.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.78
upper limit	-14.13

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from informed consent signature up to one day after the second MRI.

Adverse event reporting additional description:

Post-injection adverse events are reported below.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	P03277 all doses

Reporting group description:

Subjects who received one injection of P03277 regardless of the injection order versus gadobenate dimeglumine.

Reporting group title	Gadobenate dimeglumine

Reporting group description:

Subjects who received one injection of gadobenate dimeglumine regardless of the injection order versus P03277.

Serious adverse events	P03277 all doses	Gadobenate dimeglumine	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 256 (0.78%)	2 / 256 (0.78%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Blood creatine increased	Additional description: After injection of P03277 at 0.1 mmol/kg		
subjects affected / exposed	1 / 256 (0.39%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femoral neck fracture	Additional description: After injection of P03277 at 0.2 mmol/kg		
subjects affected / exposed	1 / 256 (0.39%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Meningioma Surgery			

subjects affected / exposed	0 / 256 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Seizure			
subjects affected / exposed	0 / 256 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	P03277 all doses	Gadobenate dimeglumine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	63 / 256 (24.61%)	57 / 256 (22.27%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 256 (0.39%)	1 / 256 (0.39%)	
occurrences (all)	1	1	
Peripheral coldness			
subjects affected / exposed	1 / 256 (0.39%)	0 / 256 (0.00%)	
occurrences (all)	2	0	
Flushing			
subjects affected / exposed	0 / 256 (0.00%)	1 / 256 (0.39%)	
occurrences (all)	0	1	
Hypotension			
subjects affected / exposed	0 / 256 (0.00%)	1 / 256 (0.39%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	14 / 256 (5.47%)	9 / 256 (3.52%)	
occurrences (all)	17	9	
Injection site coldness			
subjects affected / exposed	2 / 256 (0.78%)	4 / 256 (1.56%)	
occurrences (all)	2	4	
Fatigue			

subjects affected / exposed	4 / 256 (1.56%)	1 / 256 (0.39%)	
occurrences (all)	4	1	
Injection site warmth			
subjects affected / exposed	1 / 256 (0.39%)	3 / 256 (1.17%)	
occurrences (all)	1	3	
Feeling hot			
subjects affected / exposed	0 / 256 (0.00%)	2 / 256 (0.78%)	
occurrences (all)	0	3	
Infusion site extravasation			
subjects affected / exposed	0 / 256 (0.00%)	2 / 256 (0.78%)	
occurrences (all)	0	2	
Injection site oedema			
subjects affected / exposed	2 / 256 (0.78%)	0 / 256 (0.00%)	
occurrences (all)	2	0	
Chills			
subjects affected / exposed	1 / 256 (0.39%)	1 / 256 (0.39%)	
occurrences (all)	1	1	
Injection site bruising			
subjects affected / exposed	1 / 256 (0.39%)	0 / 256 (0.00%)	
occurrences (all)	1	0	
Injection site erythema			
subjects affected / exposed	1 / 256 (0.39%)	0 / 256 (0.00%)	
occurrences (all)	1	0	
Injection site haematoma			
subjects affected / exposed	1 / 256 (0.39%)	0 / 256 (0.00%)	
occurrences (all)	1	0	
Injection site inflammation			
subjects affected / exposed	1 / 256 (0.39%)	0 / 256 (0.00%)	
occurrences (all)	1	0	
Injection site paraesthesia			
subjects affected / exposed	0 / 256 (0.00%)	1 / 256 (0.39%)	
occurrences (all)	0	1	
Injection site reaction			
subjects affected / exposed	1 / 256 (0.39%)	0 / 256 (0.00%)	
occurrences (all)	1	0	
Malaise			

subjects affected / exposed	1 / 256 (0.39%)	0 / 256 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	1 / 256 (0.39%)	0 / 256 (0.00%)	
occurrences (all)	1	0	
Pain			
subjects affected / exposed	1 / 256 (0.39%)	0 / 256 (0.00%)	
occurrences (all)	1	0	
Sensation of foreign body			
subjects affected / exposed	0 / 256 (0.00%)	1 / 256 (0.39%)	
occurrences (all)	0	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 256 (0.39%)	1 / 256 (0.39%)	
occurrences (all)	1	1	
Investigations			
Blood pressure increased			
subjects affected / exposed	3 / 256 (1.17%)	2 / 256 (0.78%)	
occurrences (all)	3	2	
Blood creatine increased			
subjects affected / exposed	0 / 256 (0.00%)	2 / 256 (0.78%)	
occurrences (all)	0	2	
Hepatic enzyme increased			
subjects affected / exposed	1 / 256 (0.39%)	2 / 256 (0.78%)	
occurrences (all)	1	2	
Blood urea increased			
subjects affected / exposed	0 / 256 (0.00%)	1 / 256 (0.39%)	
occurrences (all)	0	2	
Electrocardiogram QT interval abnormal			
subjects affected / exposed	1 / 256 (0.39%)	0 / 256 (0.00%)	
occurrences (all)	1	0	
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 256 (0.39%)	0 / 256 (0.00%)	
occurrences (all)	1	0	
Urobilinogen urine			

subjects affected / exposed	1 / 256 (0.39%)	0 / 256 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Ventricular extrasystoles			
subjects affected / exposed	1 / 256 (0.39%)	0 / 256 (0.00%)	
occurrences (all)	2	0	
Palpitations			
subjects affected / exposed	0 / 256 (0.00%)	1 / 256 (0.39%)	
occurrences (all)	0	1	
Sinus arrhythmia			
subjects affected / exposed	1 / 256 (0.39%)	0 / 256 (0.00%)	
occurrences (all)	1	0	
Sinus tachycardia			
subjects affected / exposed	0 / 256 (0.00%)	1 / 256 (0.39%)	
occurrences (all)	0	1	
Tachycardia			
subjects affected / exposed	0 / 256 (0.00%)	1 / 256 (0.39%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 256 (2.73%)	6 / 256 (2.34%)	
occurrences (all)	7	6	
Dizziness			
subjects affected / exposed	2 / 256 (0.78%)	4 / 256 (1.56%)	
occurrences (all)	2	7	
Seizure			
subjects affected / exposed	1 / 256 (0.39%)	1 / 256 (0.39%)	
occurrences (all)	1	1	
Dysgeusia			
subjects affected / exposed	0 / 256 (0.00%)	1 / 256 (0.39%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Lymphocytosis			
subjects affected / exposed	0 / 256 (0.00%)	1 / 256 (0.39%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			

Tinnitus			
subjects affected / exposed	1 / 256 (0.39%)	1 / 256 (0.39%)	
occurrences (all)	1	1	
Ear pain			
subjects affected / exposed	0 / 256 (0.00%)	1 / 256 (0.39%)	
occurrences (all)	0	1	
Eye disorders			
Eye irritation			
subjects affected / exposed	1 / 256 (0.39%)	0 / 256 (0.00%)	
occurrences (all)	1	0	
Periorbital oedema			
subjects affected / exposed	1 / 256 (0.39%)	0 / 256 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 256 (0.39%)	9 / 256 (3.52%)	
occurrences (all)	1	9	
Diarrhoea			
subjects affected / exposed	3 / 256 (1.17%)	0 / 256 (0.00%)	
occurrences (all)	3	0	
Vomiting			
subjects affected / exposed	2 / 256 (0.78%)	1 / 256 (0.39%)	
occurrences (all)	2	2	
Abdominal pain			
subjects affected / exposed	1 / 256 (0.39%)	1 / 256 (0.39%)	
occurrences (all)	1	1	
Abdominal discomfort			
subjects affected / exposed	1 / 256 (0.39%)	0 / 256 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper			
subjects affected / exposed	1 / 256 (0.39%)	0 / 256 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	1 / 256 (0.39%)	0 / 256 (0.00%)	
occurrences (all)	1	0	
Glossitis			

subjects affected / exposed	1 / 256 (0.39%)	0 / 256 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 256 (0.39%)	2 / 256 (0.78%)	
occurrences (all)	1	3	
Cold sweat			
subjects affected / exposed	1 / 256 (0.39%)	0 / 256 (0.00%)	
occurrences (all)	1	0	
Erythema			
subjects affected / exposed	0 / 256 (0.00%)	1 / 256 (0.39%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	1 / 256 (0.39%)	0 / 256 (0.00%)	
occurrences (all)	1	0	
Rash maculo-papular			
subjects affected / exposed	1 / 256 (0.39%)	0 / 256 (0.00%)	
occurrences (all)	1	0	
Urticaria			
subjects affected / exposed	0 / 256 (0.00%)	1 / 256 (0.39%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Leukocyturia			
subjects affected / exposed	5 / 256 (1.95%)	4 / 256 (1.56%)	
occurrences (all)	5	4	
Bilirubinuria			
subjects affected / exposed	2 / 256 (0.78%)	2 / 256 (0.78%)	
occurrences (all)	2	2	
Glycosuria			
subjects affected / exposed	1 / 256 (0.39%)	2 / 256 (0.78%)	
occurrences (all)	1	2	
Haematuria			
subjects affected / exposed	1 / 256 (0.39%)	2 / 256 (0.78%)	
occurrences (all)	1	2	
Haemoglobinuria			

subjects affected / exposed	1 / 256 (0.39%)	2 / 256 (0.78%)	
occurrences (all)	1	2	
Proteinuria			
subjects affected / exposed	3 / 256 (1.17%)	0 / 256 (0.00%)	
occurrences (all)	3	0	
Ketonuria			
subjects affected / exposed	0 / 256 (0.00%)	1 / 256 (0.39%)	
occurrences (all)	0	1	
Nitrituria			
subjects affected / exposed	0 / 256 (0.00%)	1 / 256 (0.39%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 256 (0.39%)	0 / 256 (0.00%)	
occurrences (all)	1	0	
Muscle spasms			
subjects affected / exposed	1 / 256 (0.39%)	0 / 256 (0.00%)	
occurrences (all)	1	0	
Neck pain			
subjects affected / exposed	0 / 256 (0.00%)	1 / 256 (0.39%)	
occurrences (all)	0	1	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	3 / 256 (1.17%)	0 / 256 (0.00%)	
occurrences (all)	3	0	
Influenza			
subjects affected / exposed	0 / 256 (0.00%)	1 / 256 (0.39%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hypertriglyceridaemia			
subjects affected / exposed	2 / 256 (0.78%)	1 / 256 (0.39%)	
occurrences (all)	2	1	
Diabetes mellitus			
subjects affected / exposed	0 / 256 (0.00%)	1 / 256 (0.39%)	
occurrences (all)	0	1	
Hyperglycaemia			

subjects affected / exposed occurrences (all)	1 / 256 (0.39%) 1	0 / 256 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 July 2016	Exclusion of subject presenting with acute relapse of multiple sclerosis Deletion of eGFR evaluation at visit 1 New biochemistry dosage; cystatin C and triglycerides Clarification that radiologist or neuro-radiologist could be involved in the study Update on ECG description Adverse event definition clarification Unusual failure in efficacy deleted from collection of adverse event description Addition of a subject stopping rule related to cystatin C and clarification of the serum creatinine value stopping rule Clarification of technical adequacy of images

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported