Clinical trial results:
A Phase IV, Double-Blind, Multi-Center Randomized, Crossover Study to Compare 0.1 mmol/kg of ProHance® with 0.1 mmol/kg of Gadovist®/Gadavist™ in Magnetic Resonance Imaging (MRI) of the Brain (TRUTH)

Summary

EudraCT number	2011-006135-29
Trial protocol	CZ IT
Global end of trial date	03 April 2014

Results information

Result version number	v1 (current)
This version publication date	23 October 2020
First version publication date	23 October 2020
Summary attachment (see zip file)	Study PH-107 Publication (TRUTH Final epub ajnr (Study PH-107).pdf)

Trial information

Trial identification

Sponsor protocol code	PH-107

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01613417
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bracco Diagnostics Inc.
Sponsor organisation address	259 Prospect Plains Road, Building H, Monroe Township, United States, 08831
Public contact	Gianpaolo Pirovano, MD Executive Director, MRI, Bracco Diagnostics Inc. Global Medical and Regulatory Affairs (GM&RA), 1 609-514-2226, gianpaolo.pirovano@diag.bracco.com
Scientific contact	Gianpaolo Pirovano, MD Executive Director, MRI, Bracco Diagnostics Inc. Global Medical and Regulatory Affairs (GM&RA), 1 609-514-2226, gianpaolo.pirovano@diag.bracco.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	02 May 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 April 2014
Global end of trial reached?	Yes
Global end of trial date	03 April 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective for this study is to show non-inferiority of a 0.1 mmol/kg dose of ProHance as compared to 0.1 mmol/kg dose of Gadovist/Gadavist, in terms of the by-subject global diagnostic preference between exams (i.e., based on predose + postdose image sets).

Protection of trial subjects:

none

Background therapy:

none

Evidence for comparator: -

Actual start date of recruitment	03 August 2012
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: 23
Country: Number of subjects enrolled	Czech Republic: 71
Country: Number of subjects enrolled	Italy: 17
Country: Number of subjects enrolled	United States: 102
Country: Number of subjects enrolled	Canada: 16
Worldwide total number of subjects	229
EEA total number of subjects	111

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)	162
From 65 to 84 years	66
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

A total of 229 patients were enrolled from August 2012 through December 2013 at 19 clinical trial sites. Offsite assessment of the images was performed between 21 January and 3 April 2014 by 3 board-certified neuroradiologists blinded as to which contrast agent was used, patient clinical information, and the results of other imaging studies.

Pre-assignment

Screening details:

229 patients were enrolled and signed informed consent. Each enrolled patient was randomized and dosed with at least one contrast agent.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	ProHance then Gadovist/Gadavist/Gadobutrol

Arm description:

In this double-blind, two-arm study, the Investigator and the patient were blinded to the investigational product administered for Exam 1 and for Exam 2. A computer generated randomization code list was provided by the Sponsor to each site for the assignment of study arm as well as for the assignment of investigational product. Patients from the 2 arms were mixed in one randomization list.

Arm type	Active comparator
Investigational medicinal product name	Gadobutrol
Investigational medicinal product code	
Other name	Gadovist/Gadavist
Pharmaceutical forms	Injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

0.1 mmol/kg IV

Arm title	Gadovist/Gadavist then ProHance/Gadoteridol

Arm description:

In this double-blind, two-arm study, the Investigator and the patient were blinded to the investigational product administered for Exam 1 and for Exam 2. A computer generated randomization code list was provided by the Sponsor to each site for the assignment of study arm as well as for the assignment of investigational product. Patients from the 2 arms were mixed in one randomization list.

Arm type	Active comparator
Investigational medicinal product name	Gadoteridol
Investigational medicinal product code	
Other name	ProHance
Pharmaceutical forms	Injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

0.1 mmol/kg IV

Number of subjects in period 1	ProHance then Gadovist/Gadavist/Gadobutrol	Gadovist/Gadavist then ProHance/Gadoteridol
Started	113	116
Completed	113	116

Period 2

Period 2 title	Crossover Treatment Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	ProHance then Gadovist/Gadavist

Arm description:

Patients randomized to receive ProHance first then Gadovist/Gadavist

Arm type	Active comparator
Investigational medicinal product name	Gadobutrol
Investigational medicinal product code	
Other name	Gadovist/Gadavist
Pharmaceutical forms	Injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

0.1 mmol/kg IV

Investigational medicinal product name	Gadoteridol
Investigational medicinal product code	
Other name	ProHance
Pharmaceutical forms	Injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

0.1 mmol/kg IV

Arm title	Gadovist/Gadavist then ProHance

Arm description:

Patients randomized to receive Gadovist/Gadavist first then ProHance

Arm type	Active comparator
Investigational medicinal product name	Gadobutrol
Investigational medicinal product code	
Other name	Gadovist/Gadavist
Pharmaceutical forms	Injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

0.1 mmol/kg IV

Investigational medicinal product name	Gadoteridol
Investigational medicinal product code	
Other name	ProHance
Pharmaceutical forms	Injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

0.1 mmol/kg IV

Number of subjects in period 2	ProHance then Gadovist/Gadavist	Gadovist/Gadavist then ProHance
Started	113	116
Completed	93	105
Not completed	20	11
Consent withdrawn by subject	6	5
Adverse event, non-fatal	2	-
Protocol deviation	12	6

Baseline characteristics

Reporting groups	
Reporting group title	Baseline
Reporting group description:	
In this double-blind, two-arm study, the Investigator and the patient were blinded to the investigational product administered for Exam 1 and for Exam 2. A computer generated randomization code list was provided by the Sponsor to each site for the assignment of the sequence of study agents (sequence of investigational products). Patients from the 2sequences were mixed in one randomization list.	

Reporting group values	Baseline	Total	
Number of subjects	229	229	
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)	162	162	
From 65-84 years	67	67	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	55.3		
standard deviation	± 14.39	-	
Gender categorical Units: Subjects			
Female	131	131	
Male	98	98	
Race Units: Subjects			
White	220	220	
Black	3	3	
Asian	4	4	
Other	2	2	

Subject analysis sets	
Subject analysis set title	Blinded Reader 1
Subject analysis set type	Per protocol
Subject analysis set description: Paired Exams Reviewed by Reader 1	
Subject analysis set title	Blinded Reader 2
Subject analysis set type	Per protocol
Subject analysis set description: Paired exams reviewed by Reader 2	

Subject analysis set title	Blinded Reader 3
Subject analysis set type	Per protocol

Subject analysis set description:

Paired exams reviewed by Reader 3

Subject analysis set title	Dummy Set
Subject analysis set type	Per protocol

Subject analysis set description:

Due to the system limitation with the EudraCT system, a Dummy set was created and used to as a comparison group. EudraCT does not allow single arm for paired statistical analysis. This dummy set is a workaround for that limitation. No subjects in this set.

Reporting group values	Blinded Reader 1	Blinded Reader 2	Blinded Reader 3
Number of subjects	198	194	196
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	140	138	139
From 65-84 years	58	56	57
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	55.2	55.2	55.2
standard deviation	± 14.31	± 14.31	± 14.31
Gender categorical Units: Subjects			
Female	108	106	107
Male	90	88	89
Race Units: Subjects			
White	190	186	188
Black	2	2	2
Asian	4	4	4
Other	2	2	2

Reporting group values	Dummy Set		
Number of subjects	1		
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)	1		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	55.2		
standard deviation	± 0		
Gender categorical			
Units: Subjects			
Female	1		
Male	0		
Race			
Units: Subjects			
White	1		
Black	0		
Asian	0		
Other	0		

End points

End points reporting groups

Reporting group title	ProHance then Gadovist/Gadavist/Gadobutrol

Reporting group description:

In this double-blind, two-arm study, the Investigator and the patient were blinded to the investigational product administered for Exam 1 and for Exam 2. A computer generated randomization code list was provided by the Sponsor to each site for the assignment of study arm as well as for the assignment of investigational product. Patients from the 2 arms were mixed in one randomization list.

Reporting group title	Gadovist/Gadavist then ProHance/Gadoteridol

Reporting group description:

In this double-blind, two-arm study, the Investigator and the patient were blinded to the investigational product administered for Exam 1 and for Exam 2. A computer generated randomization code list was provided by the Sponsor to each site for the assignment of study arm as well as for the assignment of investigational product. Patients from the 2 arms were mixed in one randomization list.

Reporting group title	ProHance then Gadovist/Gadavist

Reporting group description:

Patients randomized to receive ProHance first then Gadovist/Gadavist

Reporting group title	Gadovist/Gadavist then ProHance

Reporting group description:

Patients randomized to receive Gadovist/Gadavist first then ProHance

Subject analysis set title	Blinded Reader 1
Subject analysis set type	Per protocol

Subject analysis set description:

Paired Exams Reviewed by Reader 1

Subject analysis set title	Blinded Reader 2
Subject analysis set type	Per protocol

Subject analysis set description:

Paired exams reviewed by Reader 2

Subject analysis set title	Blinded Reader 3
Subject analysis set type	Per protocol

Subject analysis set description:

Paired exams reviewed by Reader 3

Subject analysis set title	Dummy Set
Subject analysis set type	Per protocol

Subject analysis set description:

Due to the system limitation with the EudraCT system, a Dummy set was created and used to as a comparison group. EudraCT does not allow single arm for paired statistical analysis. This dummy set is a workaround for that limitation. No subjects in this set.

Primary: Global Diagnostic Preference Between the Two Exams

End point title	Global Diagnostic Preference Between the Two Exams

End point description:

Assessed by 3 blinded readers for each of the 198 patients who had post-dose exams for both ProHance 0.1 mmol/kg and Gadovist 0.1 mmol/kg. Readers assessed whether images with ProHance were preferred or images with Gadovist were preferred, or whether images after both exams were considered equal. An image set deemed technically inadequate by a blinded reader was excluded from efficacy analysis for that specific reader. Therefore, the number of participant exams evaluated by each reader differed slightly across readers (194-198).

Per Protocol = patients who completed both exams, had global paired image data available, and had no major protocol violations.

End point type	Primary

End point timeframe:

Comparison of image sets obtained within 2 to 14 days

End point values	Blinded Reader 1	Blinded Reader 2	Blinded Reader 3	Dummy Set
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	198	194	196	1[1]
Units: participant exams				
Number of Patient Exams Analyzed	198	194	196	1
ProHance Preferred	14	7	1	0
Contrast Agents Equal	171	180	195	1
Gadovist/Gadavist Preferred	13	7	0	0

Notes:

[1] - Due to the system limitation with the EudraCT system, a Dummy set was created.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Global Diagnostic Preference Between the Two Paired Exams. Difference in percentage of which image is better tested by Wilcoxon signed rank test , 2-sided 95% confidence interval was estimated using Altman's general approximate normal method.

Comparison groups	Blinded Reader 1 v Dummy Set
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
P-value	= 0.8516 [3]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Proportion PH better minus GV better
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.6
upper limit	5.6

Notes:

[2] - Power calculation was based on primary endpoint. 185 patients were deemed necessary for the lower limit of the observed 2-sided 95% confidence interval for the difference to exceed non-inferiority margin of -5% with 85% power.

[3] - Difference in percentage of which image is better tested by Wilcoxon signed rank test.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Global Diagnostic Preference Between the Two Paired Exams. Difference in percentage of which image is better tested by Wilcoxon signed rank test , 2-sided 95% confidence interval was estimated using Altman's general approximate normal method.

Comparison groups	Blinded Reader 2 v Dummy Set

Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
P-value	= 1 [5]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Proportion PH better minus GV better
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.8
upper limit	3.8

Notes:

[4] - Power calculation was based on primary endpoint. 185 patients were deemed necessary for the lower limit of the observed 2-sided 95% confidence interval for the difference to exceed non-inferiority margin of -5% with 85% power.
[5] - Difference in percentage of which image is better tested by Wilcoxon signed rank test.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Global Diagnostic Preference Between the Two Paired Exams. Difference in percentage of which image is better tested by Wilcoxon signed rank test , 2-sided 95% confidence interval was estimated using Altman's general approximate normal method.

Comparison groups	Blinded Reader 3 v Dummy Set
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
P-value	= 1 [7]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Proportion PH better minus GV better
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	1.5

Notes:

[6] - Power calculation was based on primary endpoint. 185 patients were deemed necessary for the lower limit of the observed 2-sided 95% confidence interval for the difference to exceed non-inferiority margin of -5% with 85% power.
[7] - Difference in percentage of which image is better tested by Wilcoxon signed rank test.

Secondary: Lesion Border Delineation

End point title	Lesion Border Delineation

End point description:

Assessed by 3 blinded readers for each of the 198 patients who had post-dose exams for both ProHance 0.1 mmol/kg and Gadovist 0.1 mmol/kg. Readers assessed whether images with ProHance were preferred or images with Gadovist were preferred, or whether images after both exams were considered equal. An image set deemed technically inadequate by a blinded reader was excluded from efficacy analysis for that specific reader. Therefore, the number of participant exams evaluated by each reader differed slightly across readers (194-198).

End point type	Secondary

End point timeframe:

Comparison of image sets obtained within 2 to 14 days

End point values	Blinded Reader 1	Blinded Reader 2	Blinded Reader 3	Dummy Set
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	198	194	196	1[8]
Units: participant exams				
Number of Patient Exams Analyzed	198	194	196	1
ProHance Better	8	2	1	0
No Difference between Prohance and Gadovist/Gadavi	181	189	195	1
Gadovist/Gadavist Better	9	3	0	0

Notes:

[8] - Due to the system limitation with the EudraCT system, a Dummy set was created.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Lesion Border Delineation	
Comparison groups	Blinded Reader 1 v Dummy Set
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 1 [10]
Method	Wilcoxon (Mann-Whitney)

Notes:

[9] - analysis based on paired assessments.

[10] - Difference in percentage of which image is better tested by Wilcoxon signed rank test.

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Lesion Border Delineation	
Comparison groups	Blinded Reader 2 v Dummy Set
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 1 [12]
Method	Wilcoxon (Mann-Whitney)

Notes:

[11] - analysis based on paired assessments.

[12] - Difference in percentage of which image is better tested by Wilcoxon signed rank test.

Statistical analysis title	Statistical Analysis 3
Statistical analysis description: Lesion Border Delineation	
Comparison groups	Blinded Reader 3 v Dummy Set

Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 1 [14]
Method	Wilcoxon (Mann-Whitney)

Notes:

[13] - analysis based on paired assessments.

[14] - Difference in percentage of which image is better tested by Wilcoxon signed rank test.

Secondary: Lesion Internal Morphology

End point title	Lesion Internal Morphology

End point description:

Assessed by 3 blinded readers for each of the 198 patients who had post-dose exams for both ProHance 0.1 mmol/kg and Gadovist 0.1 mmol/kg. Readers assessed whether images with ProHance were preferred or images with Gadovist were preferred, or whether images after both exams were considered equal. An image set deemed technically inadequate by a blinded reader was excluded from efficacy analysis for that specific reader. Therefore, the number of participant exams evaluated by each reader differed slightly across readers (194-198).

End point type	Secondary

End point timeframe:

Comparison of image sets obtained within 2 to 14 days

End point values	Blinded Reader 1	Blinded Reader 2	Blinded Reader 3	Dummy Set
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	198	194	196	1[15]
Units: participant exams				
Number of Patient Exams Analyzed	198	194	196	1
ProHance Better	2	2	1	0
No Difference Between ProHance and Gadovist/Gadavi	195	188	195	1
Gadovist/Gadavist Better	1	4	0	0

Notes:

[15] - Due to the system limitation with the EudraCT system, a Dummy set was created

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Lesion Internal Morphology

Comparison groups	Blinded Reader 1 v Dummy Set
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other[16]
P-value	= 1 [17]
Method	Wilcoxon (Mann-Whitney)

Notes:

[16] - analysis based on paired assessments.

[17] - Difference in percentage of which image is better tested by Wilcoxon signed rank test.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:	
Lesion Internal Morphology	
Comparison groups	Blinded Reader 2 v Dummy Set
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other[18]
P-value	= 0.6875 [19]
Method	Wilcoxon (Mann-Whitney)

Notes:

[18] - analysis is based on paired assessments.

[19] - Difference in percentage of which image is better tested by Wilcoxon signed rank test.

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Lesion Internal Morphology	
Comparison groups	Blinded Reader 3 v Dummy Set
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	other[20]
P-value	= 1 [21]
Method	Wilcoxon (Mann-Whitney)

Notes:

[20] - analysis is based on paired assessments.

[21] - Difference in percentage of which image is better tested by Wilcoxon signed rank test.

Secondary: Extent of Disease

End point title	Extent of Disease

End point description:

Assessed by 3 blinded readers for each of the 198 patients who had post-dose exams for both ProHance 0.1 mmol/kg and Gadovist 0.1 mmol/kg. Readers assessed whether images with ProHance were preferred or images with Gadovist were preferred, or whether images after both exams were considered equal. An image set deemed technically inadequate by a blinded reader was excluded from efficacy analysis for that specific reader. Therefore, the number of participant exams evaluated by each reader differed slightly across readers (194-198).

End point type	Secondary

End point timeframe:

Comparison of image sets obtained within 2 to 14 days.

End point values	Blinded Reader 1	Blinded Reader 2	Blinded Reader 3	Dummy Set
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	198	194	196	1[22]
Units: participant exams				
Number of Patient Exams Analyzed	198	194	196	1
ProHance Better	1	2	1	0
No Difference Between ProHance and Gadovist/Gadavi	196	190	195	1
Gadovist/Gadavist Better	1	2	0	0

Notes:
[22] - Due to the system limitation with the EudraCT system, a Dummy set was created.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:
Extent of Disease

Comparison groups	Blinded Reader 1 v Dummy Set
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other[23]
P-value	= 1 [24]
Method	Wilcoxon (Mann-Whitney)

Notes:
[23] - analysis is based on paired assessments.
[24] - Difference in percentage of which image is better tested by Wilcoxon signed rank test.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:
Extent of Disease

Comparison groups	Blinded Reader 2 v Dummy Set
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other[25]
P-value	= 1 [26]
Method	Wilcoxon (Mann-Whitney)

Notes:
[25] - analysis is based on paired assessments.
[26] - Difference in percentage of which image is better tested by Wilcoxon signed rank test.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:
Extent of Disease

Comparison groups	Blinded Reader 3 v Dummy Set
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	other[27]
P-value	= 1 [28]
Method	Wilcoxon (Mann-Whitney)

Notes:
[27] - analysis is based on paired assessments.
[28] - Difference in percentage of which image is better tested by Wilcoxon signed rank test.

Secondary: Lesion Contrast Enhancement

End point title	Lesion Contrast Enhancement

End point description:

Assessed by 3 blinded readers for each of the 198 patients who had post-dose exams for both ProHance 0.1 mmol/kg and Gadovist 0.1 mmol/kg. Readers assessed whether images with ProHance were

preferred or images with Gadovist were preferred, or whether images after both exams were considered equal. An image set deemed technically inadequate by a blinded reader was excluded from efficacy analysis for that specific reader. Therefore, the number of participant exams evaluated by each reader differed slightly across readers (194-198).

End point type	Secondary
End point timeframe:	
Comparison of image sets obtained within 2 to 14 days	

End point values	Blinded Reader 1	Blinded Reader 2	Blinded Reader 3	Dummy Set
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	198	194	196	1[29]
Units: participant exams				
Number of Patient Exams Analyzed	198	194	196	1
ProHance Better	14	10	2	0
No Difference Between ProHance and Gadovist/Gadavi	170	174	193	1
Gadovist/Gadavist Better	14	10	1	0

Notes:

[29] - Due to the system limitation with the EudraCT system, a Dummy set was created.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Lesion Contrast Enhancement	
Comparison groups	Blinded Reader 1 v Dummy Set
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	other[30]
P-value	= 1 [31]
Method	Wilcoxon (Mann-Whitney)

Notes:

[30] - analysis is based on paired assessments.

[31] - Difference in percentage of which image is better tested by Wilcoxon signed rank test.

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Lesion Contrast Enhancement	
Comparison groups	Blinded Reader 2 v Dummy Set
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other[32]
P-value	= 1 [33]
Method	Wilcoxon (Mann-Whitney)

Notes:

[32] - analysis is based on paired assessments.

[33] - Difference in percentage of which image is better tested by Wilcoxon signed rank test.

Statistical analysis title	Statistical Analysis 3
Statistical analysis description: Lesion Contrast Enhancement	
Comparison groups	Blinded Reader 3 v Dummy Set
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	other[34]
P-value	= 1 [35]
Method	Wilcoxon (Mann-Whitney)

Notes:

[34] - analysis is based on paired assessments.

[35] - Difference in percentage of which image is better tested by Wilcoxon signed rank test.

Secondary: Lesion to Background Ratio on Post T1-weighted Spin Echo Images

End point title	Lesion to Background Ratio on Post T1-weighted Spin Echo Images

End point description:

The Unit of Measure is "Lesion". For each lesion, Lesion-to-background ratio (LBR) = SI of lesion/SI of brain. Firstly, LBR of each lesion was assessed for each contrast agent postdose image separately, then the difference in LBR between ProHance and Gadovist was calculated. The number presented in the result table below is "the mean difference in LBR postdose (ProHance - Gadovist)
Per protocol population

End point type	Secondary

End point timeframe:

Postdose

End point values	Blinded Reader 1	Blinded Reader 2	Blinded Reader 3	Dummy Set
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	194	137	162	1[36]
Units: signal intensity				
arithmetic mean (standard deviation)	-0.02 (± 0.17)	-0.16 (± 1.12)	-0.01 (± 0.18)	0 (± 0)

Notes:

[36] - Due to the system limitation with the EudraCT system, a Dummy set was created.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Lesion to Background Ratio on Post T1-weighted Spin Echo Images	
Comparison groups	Blinded Reader 1 v Dummy Set
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other[37]
P-value	= 0.2758 [38]
Method	Mixed models analysis

Notes:

[37] - 2-sided paired comparison

[38] - Mixed effect model with period, sequence, and IP and fixed effect and subject nested within

sequence as random effect

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Lesion to Background Ratio on Post T1-weighted Spin Echo Images

Comparison groups	Blinded Reader 2 v Dummy Set
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	other[39]
P-value	= 0.0676 [40]
Method	Mixed models analysis

Notes:

[39] - 2-sided paired comparison

[40] - Mixed effect model with period, sequence, and IP and fixed effect and subject nested within sequence as random effect

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Lesion to Background Ratio on Post T1-weighted Spin Echo Images

Comparison groups	Blinded Reader 3 v Dummy Set
Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	other[41]
P-value	= 0.5267 [42]
Method	Mixed models analysis

Notes:

[41] - 2-sided paired comparison

[42] - Mixed effect model with period, sequence, and IP and fixed effect and subject nested within sequence as random effect

Secondary: Percentage Signal Intensity Enhhancement on Postdose Images

End point title	Percentage Signal Intensity Enhhancement on Postdose Images

End point description:

Difference in percentage signal intensity enhancement on postdose T1-weighted SE/FSE images (ProHance - Gadovist/Gadavist).

Per protocol population

End point type	Secondary

End point timeframe:

Postdose

End point values	Blinded Reader 1	Blinded Reader 2	Blinded Reader 3	Dummy Set
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	191	133	159	1[43]
Units: signal intensity				
arithmetic mean (standard deviation)	1.06 (± 28.61)	-2.09 (± 29.06)	-1.59 (± 29.16)	0 (± 0)

Notes:

[43] - Due to the system limitation with the EudraCT system, a Dummy set was created.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Percentage Signal Intensity Enhancement on Postdose Images

Comparison groups	Blinded Reader 1 v Dummy Set
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	other[44]
P-value	= 0.6201 [45]
Method	Mixed models analysis

Notes:

[44] - 2-sided comparison

[45] - Investigation product (IP) effect from mixed model with period, sequence, and IP as fixed effects and subject nested within sequence as random effect.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Percentage Signal Intensity Enhancement on Postdose Images

Comparison groups	Blinded Reader 2 v Dummy Set
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	other[46]
P-value	= 0.4514 [47]
Method	Mixed models analysis

Notes:

[46] - 2-sided comparison

[47] - Investigation product (IP) effect from mixed model with period, sequence, and IP as fixed effects and subject nested within sequence as random effect.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Percentage Signal Intensity Enhancement on Postdose Images

Comparison groups	Blinded Reader 3 v Dummy Set
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	other[48]
P-value	= 0.7722 [49]
Method	Mixed models analysis

Notes:

[48] - 2-sided comparison

[49] - Investigation product (IP) effect from mixed model with period, sequence, and IP as fixed effects and subject nested within sequence as random effect.

Secondary: Lesion Detection Rate

End point title	Lesion Detection Rate

End point description:

Lesion detection rate by contrast agent and reader

Per protocol patients with histologically confirmed lesions

End point type	Secondary

End point timeframe:

Postdose

End point values	Blinded Reader 1	Blinded Reader 2	Blinded Reader 3	Dummy Set
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	139	139	139	1[50]
Units: participant exams				
True Positive (Patients) ProHance	133	137	136	1
True Postive (Patients) Gadovist/Gadavist	135	136	132	1
False Negative (Patients) ProHance	6	2	3	0
False Negative (Patients) Gadovist/Gadavist	4	3	7	0

Notes:

[50] - Due to the system limitation with the EudraCT system, a Dummy set was created

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Lesion Detection Rate
Reader 1 - ProHance, Reader 1 - Gadovist/Gadavist

Comparison groups	Blinded Reader 1 v Dummy Set
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	other[51]
P-value	= 0.3173
Method	Mcnemar

Notes:

[51] - 2-sided paired comparison

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Lesion Detection Rate
Reader 2 - ProHance, Reader 2 - Gadovist/Gadavist

Comparison groups	Blinded Reader 2 v Dummy Set
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	other[52]
P-value	= 0.5637
Method	Mcnemar

Notes:

[52] - 2-sided paired comparison

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Lesion Detection Rate
Reader 3 - ProHance, Reader 3 - Gadovist/Gadavist

Comparison groups	Blinded Reader 3 v Dummy Set
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	other[53]
P-value	= 0.0455
Method	Mcnemar

Notes:

[53] - 2-sided paired comparison

Secondary: Accuracy for Tumor Characterization

End point title	Accuracy for Tumor Characterization

End point description:

Blinded Reader assessment of accuracy of tumor characterization (benign/malignant) - patient level assessment

Subjects with histologically confirmed lesions

End point type	Secondary

End point timeframe:

Postdose

End point values	Blinded Reader 1	Blinded Reader 2	Blinded Reader 3	Dummy Set
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	128	128	128	1[54]
Units: participant exams				
Correctly Categorized (ProHance)	94	106	93	1
Correctly Categorized (Gadovist/Gadavist)	96	101	83	1
Incorrectly Categorized (ProHance)	34	22	35	0
Incorrectly Categorized (Gadovist/Gadavist)	32	27	45	0

Notes:

[54] - Due to the system limitation with the EudraCT system, a Dummy set was created.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Accuracy for Tumor Characterization
Reader 1 - ProHance, Reader 1 - Gadovist/Gadavist

Comparison groups	Blinded Reader 1 v Dummy Set

Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	other[55]
P-value	= 0.6949 [56]
Method	Mcnemar

Notes:

[55] - 2-sided paired comparison

[56] - McNemar test of difference (ProHance minus Gadovist/Gadavist) in accuracy for tumor characterization

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Accuracy for Tumor Characterization
Reader 2 - ProHance, Reader 2 - Gadovist/Gadavist

Comparison groups	Blinded Reader 2 v Dummy Set
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	other[57]
P-value	= 0.1317 [58]
Method	Mcnemar

Notes:

[57] - 2-sided comparison

[58] - McNemar test of difference (ProHance minus Gadovist/Gadavist) in accuracy for tumor characterization

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Accuracy for Tumor Characterization
Reader 3 - ProHance, Reader 3 - Gadovist/Gadavist

Comparison groups	Blinded Reader 3 v Dummy Set
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	other[59]
P-value	= 0.0124 [60]
Method	Mcnemar

Notes:

[59] - 2-sided paired comparison

[60] - McNemar test of difference (ProHance minus Gadovist/Gadavist) in accuracy for tumor characterization

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signed Informed Consent, and within 24 h prior to admin. of 1st drug (Exam 1) to 24 h after admin. of 1st drug. Then 24 h prior to admin. of 2nd drug (Exam 2) to 24 h after admin. of 2nd drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Safety Population (ProHance)

Reporting group description:

All enrolled patients who received a randomized injection of ProHance

Reporting group title	Safety Population (Gadovist/Gadavist)

Reporting group description:

All enrolled patients who received a randomized injection of Gadovist/Gadavist

Serious adverse events	Safety Population (ProHance)	Safety Population (Gadovist/Gadavist)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 222 (0.00%)	0 / 216 (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	Safety Population (ProHance)	Safety Population (Gadovist/Gadavist)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 222 (6.76%)	8 / 216 (3.70%)	
Vascular disorders			
Vascular rupture			
subjects affected / exposed	1 / 222 (0.45%)	0 / 216 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 222 (0.00%)	1 / 216 (0.46%)	
occurrences (all)	0	1	
Dizziness			

subjects affected / exposed	1 / 222 (0.45%)	1 / 216 (0.46%)	
occurrences (all)	1	1	
Dysgeusia			
subjects affected / exposed	4 / 222 (1.80%)	1 / 216 (0.46%)	
occurrences (all)	4	1	
Headache			
subjects affected / exposed	2 / 222 (0.90%)	1 / 216 (0.46%)	
occurrences (all)	2	1	
Lethargy			
subjects affected / exposed	1 / 222 (0.45%)	0 / 216 (0.00%)	
occurrences (all)	1	0	
Migraine			
subjects affected / exposed	1 / 222 (0.45%)	0 / 216 (0.00%)	
occurrences (all)	1	0	
Paraesthesia			
subjects affected / exposed	0 / 222 (0.00%)	1 / 216 (0.46%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 222 (0.00%)	1 / 216 (0.46%)	
occurrences (all)	0	1	
Feeling hot			
subjects affected / exposed	1 / 222 (0.45%)	0 / 216 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 222 (0.45%)	0 / 216 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	4 / 222 (1.80%)	1 / 216 (0.46%)	
occurrences (all)	4	1	
Vomiting			
subjects affected / exposed	1 / 222 (0.45%)	1 / 216 (0.46%)	
occurrences (all)	1	1	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	2 / 222 (0.90%)	0 / 216 (0.00%)	
occurrences (all)	2	0	
Dyspnoea			
subjects affected / exposed	1 / 222 (0.45%)	0 / 216 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	0 / 222 (0.00%)	1 / 216 (0.46%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 222 (0.45%)	0 / 216 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	1 / 222 (0.45%)	0 / 216 (0.00%)	
occurrences (all)	1	0	
Urticaria			
subjects affected / exposed	1 / 222 (0.45%)	0 / 216 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 222 (0.00%)	1 / 216 (0.46%)	
occurrences (all)	0	1	
Mood altered			
subjects affected / exposed	0 / 222 (0.00%)	1 / 216 (0.46%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Histologic confirmation of disease available for only 139/198 patients in PP analysis. Of these, 128 patients had confirmed brain tumors and were available for the analyses of diagnostic performance (tumor detection and tumor characterization).

Notes: