Clinical trial results:
PHASE IV, DOUBLE-BLIND, MULTI-CENTER, RANDOMIZED, TWO-ARM CROSSOVER STUDY TO COMPARE 0.1 mmol/kg OF MULTIHANCE® WITH 0.1 mmol/kg OF DOTAREM® AND 0.05 mmol/kg OF MULTIHANCE® WITH 0.1 mmol/kg OF DOTAREM® IN MAGNETIC RESONANCE IMAGING (MRI) OF THE BRAIN (BENEFIT)

Summary

EudraCT number	2013-003886-33
Trial protocol	CZ
Global end of trial date	17 March 2015

Results information

Result version number	v1 (current)
This version publication date	31 December 2016
First version publication date	31 December 2016

Trial information

Trial identification

Sponsor protocol code	MH-148

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02070380
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bracco Diagnostics, Inc.
Sponsor organisation address	259 Prospect Plains Rd, Cranbury, United States, 08512
Public contact	Gianpaolo Pirovano, Bracco Diagnostics, Inc., 609 514-2200, Gianpaolo.Pirovano@diag.bracco.com
Scientific contact	Gianpaolo Pirovano, Bracco Diagnostics, Inc., 609 514-2200, 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	17 March 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives for this study are:

1) To show superiority of a 0.1 mmol/kg dose of MULTIHANCE as compared to 0.1 mmol/kg dose of DOTAREM, in terms of the by-subject global diagnostic preference between exams (i.e., based on pre-dose plus post-dose image sets).

2) To show superiority of a 0.05 mmol/kg dose of MULTIHANCE as compared to 0.1 mmol/kg dose of DOTAREM, in terms of the by-subject global diagnostic preference between exams (i.e., based on pre-dose plus post-dose image sets).

Protection of trial subjects:

This study was conducted in compliance with Title 21, CFR Part 50, CFR Part 56, and CFR Part 312, with the ethical principles that have their origin in the Declaration of Helsinki (adopted by the 18th World Medical Association [WMA] General Assembly in Helsinki, Finland [June 1964] and amended by the 29th WMA in Tokyo, Japan [October 1975], by the 35th WMA in Venice, Italy [October 1983], by the 41st WMA in Hong Kong [September 1989], by the 48th WMA in Somerset West, Republic of South Africa [October 1996], by the 52nd WMA in Edinburgh, Scotland [October 2000], with note of clarification by the 53rd WMA in Washington DC, United States [2002] and the 55th WMA in Tokyo, Japan [2004], and by the 59th WMA in Seoul, Korea [October 2008]). In addition, this study was conducted in compliance with Good Clinical Practices (GCP) as outlined in ICH E6 (Good Clinical Practice: Consolidated Guideline).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 February 2014
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	Germany: 3
Country: Number of subjects enrolled	Czech Republic: 103
Country: Number of subjects enrolled	United States: 71
Worldwide total number of subjects	177
EEA total number of subjects	106

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)	120
From 65 to 84 years	55
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

A total of 179 patients were recruited from February 2014 through February 2015 at 14 clinical trial sites. Off-site assessment of the images was performed between 19 February - 17 March 2015 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:

179 patients were enrolled and signed informed consent. Each enrolled patient was randomized and 177 were dosed with at least one contrast agent.

Period 1

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

Blinding implementation details:

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.

Arms

Are arms mutually exclusive?	No
Arm title	MultiHance 0.1 mmol/kg Then Dotarem 0.1 mmol/kg

Arm description:

Patients randomized to receive MultiHance 0.1 mmol/kg first

Arm type	Experimental
Investigational medicinal product name	MultiHance 0.1 mmol/kg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

MultiHance 0.5 M solution for injection was manually or automatically (power injector) administered at a dose of 0.1 mmol/kg by venous injection as a rapid bolus using sterile syringes and aseptic techniques; power injections were followed by a 20-30 mL bolus injection of saline.

Arm title	Dotarem 0.1 mmol/kg Then MultiHance 0.1 mmol/kg

Arm description:

Patients randomized to receive Dotarem 0.1 mmol/kg first

Arm type	Active comparator
Investigational medicinal product name	Dotarem 0.1 mmol/kg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Dotarem 0.5 M solution for injection was manually or automatically (power injector) administered at a dose of 0.1 mmol/kg by venous injection as a rapid bolus using sterile syringes and aseptic techniques; power injections were followed by a 20-30 mL bolus injection of saline.

Arm title	MultiHance 0.05 mmol/kg Then Dotarem 0.1 mmol/kg

Arm description:

Patients randomized to receive MultiHance 0.05 mmol/kg first

Arm type	Experimental
Investigational medicinal product name	MultiHance 0.05 mmol/kg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

MultiHance 0.5 M solution for injection was manually or automatically (power injector) administered at a dose of 0.05 mmol/kg by venous injection as a rapid bolus using sterile syringes and aseptic techniques; power injections were followed by a 20-30 mL bolus injection of saline.

Arm title	Dotarem 0.1 mmol/kg Then MultiHance 0.05 mmol/kg

Arm description:

Patients randomized to receive Dotarem 0.1 mmol/kg first

Arm type	Active comparator
Investigational medicinal product name	Dotarem 0.1 mmol/kg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Dotarem 0.5 M solution for injection was manually or automatically (power injector) administered at a dose of 0.1 mmol/kg by venous injection as a rapid bolus using sterile syringes and aseptic techniques; power injections were followed by a 20-30 mL bolus injection of saline.

Number of subjects in period 1	MultiHance 0.1 mmol/kg Then Dotarem 0.1 mmol/kg	Dotarem 0.1 mmol/kg Then MultiHance 0.1 mmol/kg	MultiHance 0.05 mmol/kg Then Dotarem 0.1 mmol/kg
Started	31	39	53
Completed	31	39	53

Number of subjects in period 1	Dotarem 0.1 mmol/kg Then MultiHance 0.05 mmol/kg
Started	54
Completed	54

Period 2

Period 2 title	Washout (no Second Injection/MRI)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	MultiHance 0.1 mmol/kg Then Dotarem 0.1 mmol/kg

Arm description:

Patients randomized to receive MultiHance 0.1 mmol/kg first

Arm type	Experimental
Investigational medicinal product name	MultiHance 0.1 mmol/kg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

MultiHance 0.5 M solution for injection was manually or automatically (power injector) administered at a dose of 0.1 mmol/kg by venous injection as a rapid bolus using sterile syringes and aseptic techniques; power injections were followed by a 20-30 mL bolus injection of saline.

Arm title	Dotarem 0.1 mmol/kg Then MultiHance 0.1 mmol/kg

Arm description:

Patients randomized to receive Dotarem 0.1 mmol/kg first

Arm type	Active comparator
Investigational medicinal product name	Dotarem 0.1 mmol/kg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Dotarem 0.5 M solution for injection was manually or automatically (power injector) administered at a dose of 0.1 mmol/kg by venous injection as a rapid bolus using sterile syringes and aseptic techniques; power injections were followed by a 20-30 mL bolus injection of saline.

Arm title	MultiHance 0.05 mmol/kg Then Dotarem 0.1 mmol/kg

Arm description:

Patients randomized to receive MultiHance 0.05 mmol/kg first

Arm type	Experimental
Investigational medicinal product name	MultiHance 0.05 mmol/kg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

MultiHance 0.5 M solution for injection was manually or automatically (power injector) administered at a dose of 0.05 mmol/kg by venous injection as a rapid bolus using sterile syringes and aseptic techniques; power injections were followed by a 20-30 mL bolus injection of saline.

Arm title	Dotarem 0.1 mmol/kg Then MultiHance 0.05 mmol/kg

Arm description:

Patients randomized to receive Dotarem 0.1 mmol/kg first

Arm type	Active comparator

Investigational medicinal product name	Dotarem 0.1 mmol/kg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Dotarem 0.5 M solution for injection was manually or automatically (power injector) administered at a dose of 0.1 mmol/kg by venous injection as a rapid bolus using sterile syringes and aseptic techniques; power injections were followed by a 20-30 mL bolus injection of saline.

Number of subjects in period 2	MultiHance 0.1 mmol/kg Then Dotarem 0.1 mmol/kg	Dotarem 0.1 mmol/kg Then MultiHance 0.1 mmol/kg	MultiHance 0.05 mmol/kg Then Dotarem 0.1 mmol/kg
Started	31	39	53
Completed	31	34	51
Not completed	0	5	2
Consent withdrawn by subject	-	5	2

Number of subjects in period 2	Dotarem 0.1 mmol/kg Then MultiHance 0.05 mmol/kg
Started	54
Completed	51
Not completed	3
Consent withdrawn by subject	3

Period 3

Period 3 title	Second Injection
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	MultiHance 0.1 mmol/kg Then Dotarem 0.1 mmol/kg

Arm description:

Patients randomized to receive MultiHance 0.1 mmol/kg first

Arm type	Experimental
Investigational medicinal product name	MultiHance 0.1 mmol/kg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

MultiHance 0.5 M solution for injection was manually or automatically (power injector) administered at a

dose of 0.1 mmol/kg by venous injection as a rapid bolus using sterile syringes and aseptic techniques; power injections were followed by a 20-30 mL bolus injection of saline.

Arm title	Dotarem 0.1 mmol/kg Then MultiHance 0.1 mmol/kg

Arm description:

Patients randomized to receive Dotarem 0.1 mmol/kg first

Arm type	Active comparator
Investigational medicinal product name	Dotarem 0.1 mmol/kg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Dotarem 0.5 M solution for injection was manually or automatically (power injector) administered at a dose of 0.1 mmol/kg by venous injection as a rapid bolus using sterile syringes and aseptic techniques; power injections were followed by a 20-30 mL bolus injection of saline.

Arm title	MultiHance 0.05 mmol/kg Then Dotarem 0.1 mmol/kg

Arm description:

Patients randomized to receive MultiHance 0.05 mmol/kg first

Arm type	Experimental
Investigational medicinal product name	MultiHance 0.05 mmol/kg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

MultiHance 0.5 M solution for injection was manually or automatically (power injector) administered at a dose of 0.05 mmol/kg by venous injection as a rapid bolus using sterile syringes and aseptic techniques; power injections were followed by a 20-30 mL bolus injection of saline.

Arm title	Dotarem 0.1 mmol/kg Then MultiHance 0.05 mmol/kg

Arm description:

Patients randomized to receive Dotarem 0.1 mmol/kg first

Arm type	Active comparator
Investigational medicinal product name	Dotarem 0.1 mmol/kg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Dotarem 0.5 M solution for injection was manually or automatically (power injector) administered at a dose of 0.1 mmol/kg by venous injection as a rapid bolus using sterile syringes and aseptic techniques; power injections were followed by a 20-30 mL bolus injection of saline.

Number of subjects in period 3	MultiHance 0.1 mmol/kg Then Dotarem 0.1 mmol/kg	Dotarem 0.1 mmol/kg Then MultiHance 0.1 mmol/kg	MultiHance 0.05 mmol/kg Then Dotarem 0.1 mmol/kg
Started	31	34	51
Completed	31	32	50
Not completed	0	2	1
Image sets missing or technically inadeq	-	1	-
Protocol deviation	-	1	1

Number of subjects in period 3	Dotarem 0.1 mmol/kg Then MultiHance 0.05 mmol/kg
Started	51
Completed	46
Not completed	5
Image sets missing or technically inadeq	-
Protocol deviation	5

Baseline characteristics

Reporting groups	
Reporting group title	MultiHance 0.1 mmol/kg Then Dotarem 0.1 mmol/kg
Reporting group description:	
Patients randomized to receive MultiHance 0.1 mmol/kg first	
Reporting group title	Dotarem 0.1 mmol/kg Then MultiHance 0.1 mmol/kg
Reporting group description:	
Patients randomized to receive Dotarem 0.1 mmol/kg first	
Reporting group title	MultiHance 0.05 mmol/kg Then Dotarem 0.1 mmol/kg
Reporting group description:	
Patients randomized to receive MultiHance 0.05 mmol/kg first	
Reporting group title	Dotarem 0.1 mmol/kg Then MultiHance 0.05 mmol/kg
Reporting group description:	
Patients randomized to receive Dotarem 0.1 mmol/kg first	

Reporting group values	MultiHance 0.1 mmol/kg Then Dotarem 0.1 mmol/kg	Dotarem 0.1 mmol/kg Then MultiHance 0.1 mmol/kg	MultiHance 0.05 mmol/kg Then Dotarem 0.1 mmol/kg
Number of subjects	31	39	53
Age categorical Units: Subjects			
Adults (18-64 years)	24	25	38
Adults (>=65 years)	7	14	15
Gender categorical Units: Subjects			
Female	20	21	26
Male	11	18	27

Reporting group values	Dotarem 0.1 mmol/kg Then MultiHance 0.05 mmol/kg	Total	
Number of subjects	54	177	
Age categorical Units: Subjects			
Adults (18-64 years)	33	108	
Adults (>=65 years)	21	51	
Gender categorical Units: Subjects			
Female	26	93	
Male	28	84	

Subject analysis sets	
Subject analysis set title	MultiHance 0.1 mmol/kg Arm (Reader 1)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
MRI with MultiHance 0.1 mmol/kg versus MRI with Dotarem 0.1 mmol/kg	
Subject analysis set title	MultiHance 0.1 mmol/kg Arm (Reader 2)

Subject analysis set type	Intention-to-treat
Subject analysis set description: MRI with MultiHance 0.1 mmol/kg versus MRI with Dotarem 0.1 mmol/kg	
Subject analysis set title	MultiHance 0.1 mmol/kg Arm (Reader 3)
Subject analysis set type	Intention-to-treat
Subject analysis set description: MRI with MultiHance 0.1 mmol/kg versus MRI with Dotarem 0.1 mmol/kg	
Subject analysis set title	MultiHance 0.05 mmol/kg Arm (Reader 1)
Subject analysis set type	Intention-to-treat
Subject analysis set description: MRI with MultiHance 0.05 mmol/kg versus MRI with Dotarem 0.1 mmol/kg	
Subject analysis set title	MultiHance 0.05 mmol/kg Arm (Reader 2
Subject analysis set type	Intention-to-treat
Subject analysis set description: MRI with MultiHance 0.05 mmol/kg versus MRI with Dotarem 0.1 mmol/kg	
Subject analysis set title	MultiHance 0.05 mmol/kg Arm (Reader 3)
Subject analysis set type	Intention-to-treat
Subject analysis set description: MRI with MultiHance 0.05 mmol/kg versus MRI with Dotarem 0.1 mmol/kg	
Subject analysis set title	Dummy Set
Subject analysis set type	Intention-to-treat

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/group statistical analysis. This is dummy set is a workaround to that limitation.
No subjects in this set.

Reporting group values	MultiHance 0.1 mmol/kg Arm (Reader 1)	MultiHance 0.1 mmol/kg Arm (Reader 2)	MultiHance 0.1 mmol/kg Arm (Reader 3)
Number of subjects	63	62	62
Age categorical Units: Subjects			
Adults (18-64 years)	44	44	44
Adults (>=65 years)	19	19	19
Gender categorical Units: Subjects			
Female	41	41	41
Male	29	29	29

Reporting group values	MultiHance 0.05 mmol/kg Arm (Reader 1)	MultiHance 0.05 mmol/kg Arm (Reader 2	MultiHance 0.05 mmol/kg Arm (Reader 3)
Number of subjects	96	94	95
Age categorical Units: Subjects			
Adults (18-64 years)	64	64	64
Adults (>=65 years)	32	32	32
Gender categorical Units: Subjects			
Female	52	52	52
Male	55	55	55

Reporting group values	Dummy Set		
Number of subjects	1		
Age categorical Units: Subjects			
Adults (18-64 years)	0		
Adults (>=65 years)	0		
Gender categorical Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	MultiHance 0.1 mmol/kg Then Dotarem 0.1 mmol/kg
Reporting group description: Patients randomized to receive MultiHance 0.1 mmol/kg first	
Reporting group title	Dotarem 0.1 mmol/kg Then MultiHance 0.1 mmol/kg
Reporting group description: Patients randomized to receive Dotarem 0.1 mmol/kg first	
Reporting group title	MultiHance 0.05 mmol/kg Then Dotarem 0.1 mmol/kg
Reporting group description: Patients randomized to receive MultiHance 0.05 mmol/kg first	
Reporting group title	Dotarem 0.1 mmol/kg Then MultiHance 0.05 mmol/kg
Reporting group description: Patients randomized to receive Dotarem 0.1 mmol/kg first	
Reporting group title	MultiHance 0.1 mmol/kg Then Dotarem 0.1 mmol/kg
Reporting group description: Patients randomized to receive MultiHance 0.1 mmol/kg first	
Reporting group title	Dotarem 0.1 mmol/kg Then MultiHance 0.1 mmol/kg
Reporting group description: Patients randomized to receive Dotarem 0.1 mmol/kg first	
Reporting group title	MultiHance 0.05 mmol/kg Then Dotarem 0.1 mmol/kg
Reporting group description: Patients randomized to receive MultiHance 0.05 mmol/kg first	
Reporting group title	Dotarem 0.1 mmol/kg Then MultiHance 0.05 mmol/kg
Reporting group description: Patients randomized to receive Dotarem 0.1 mmol/kg first	
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Reporting group description: Patients randomized to receive MultiHance 0.1 mmol/kg first	
Reporting group title	Dotarem 0.1 mmol/kg Then MultiHance 0.1 mmol/kg
Reporting group description: Patients randomized to receive Dotarem 0.1 mmol/kg first	
Reporting group title	MultiHance 0.05 mmol/kg Then Dotarem 0.1 mmol/kg
Reporting group description: Patients randomized to receive MultiHance 0.05 mmol/kg first	
Reporting group title	Dotarem 0.1 mmol/kg Then MultiHance 0.05 mmol/kg
Reporting group description: Patients randomized to receive Dotarem 0.1 mmol/kg first	
Subject analysis set title	MultiHance 0.1 mmol/kg Arm (Reader 1)
Subject analysis set type	Intention-to-treat
Subject analysis set description: MRI with MultiHance 0.1 mmol/kg versus MRI with Dotarem 0.1 mmol/kg	
Subject analysis set title	MultiHance 0.1 mmol/kg Arm (Reader 2)
Subject analysis set type	Intention-to-treat
Subject analysis set description: MRI with MultiHance 0.1 mmol/kg versus MRI with Dotarem 0.1 mmol/kg	
Subject analysis set title	MultiHance 0.1 mmol/kg Arm (Reader 3)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

MRI with MultiHance 0.1 mmol/kg versus MRI with Dotarem 0.1 mmol/kg

Subject analysis set title	MultiHance 0.05 mmol/kg Arm (Reader 1)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

MRI with MultiHance 0.05 mmol/kg versus MRI with Dotarem 0.1 mmol/kg

Subject analysis set title	MultiHance 0.05 mmol/kg Arm (Reader 2
Subject analysis set type	Intention-to-treat

Subject analysis set description:

MRI with MultiHance 0.05 mmol/kg versus MRI with Dotarem 0.1 mmol/kg

Subject analysis set title	MultiHance 0.05 mmol/kg Arm (Reader 3)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

MRI with MultiHance 0.05 mmol/kg versus MRI with Dotarem 0.1 mmol/kg

Subject analysis set title	Dummy Set
Subject analysis set type	Intention-to-treat

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/group statistical analysis. This is dummy set is a workaround to 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 159 patients who had post-dose exams for both MultiHance, 0.1 mmol/kg and 0.05 mmol/kg doses, and Dotarem 0.1 mmol/kg. Readers assessed whether images with MultiHance were preferred or images with Dotarem 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 and endpoints. The 3 blinded readers assessed the available image sets as technically adequate in 84.3-90.7% of cases, depending on reader and study arm.

End point type	Primary

End point timeframe:

Comparison of image sets obtained within 2 to 14 days

End point values	MultiHance 0.1 mmol/kg Arm (Reader 1)	MultiHance 0.1 mmol/kg Arm (Reader 2)	MultiHance 0.1 mmol/kg Arm (Reader 3)	MultiHance 0.05 mmol/kg Arm (Reader 1)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	63	62	62	96
Units: participant exams				
number (not applicable)				
MultiHance Preferred	31	51	43	14
Contrast Agents Equal	31	9	17	75
Dotarem Preferred	1	2	2	7

End point values	MultiHance 0.05 mmol/kg Arm (Reader 2	MultiHance 0.05 mmol/kg Arm (Reader 3)	Dummy Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	94	95	1[1]	
Units: participant exams				
number (not applicable)				
MultiHance Preferred	18	15	0	
Contrast Agents Equal	56	63	0	
Dotarem Preferred	20	17	0	

Notes:

[1] - This is a dummy set.

Statistical analyses

Statistical analysis title	MultiHance 0.1 mmol/kg Arm (Reader 1)

Statistical analysis description:

63 Subjects in this analysis.

Difference in percentage MultiHance better minus percentage Dotarem better (%), 2-sided 95% confidence interval was estimated using Altman's general approximate normal method.

Comparison groups	MultiHance 0.1 mmol/kg Arm (Reader 1) v Dummy Set
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.0001 [3]
Method	Wilcoxon signed-rank test
Parameter estimate	ΔPercentage MH better minus DM better
Point estimate	47.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	34.5
upper limit	60.7

Notes:

[2] - Null hypotheses:
A 0.1 mmol/kg dose of MULTIHANCE is equal to a 0.1 mmol/kg dose of DOTAREM, in terms of the assessment of global diagnostic preference in an off-site pre-dose plus postdose paired global assessment.
[3] - Only 1 primary endpoint, no adjustment for multiple comparisons and the a priori threshold for statistical significance was 0.05.

Statistical analysis title	MultiHance 0.05 mmol/kg Arm (Reader 1)

Statistical analysis description:

96 Subjects in this analysis.

Difference in percentage MultiHance better minus percentage Dotarem better (%) , 2-sided 95% confidence interval was estimated using Altman's general approximate normal method.

Comparison groups	Dummy Set v MultiHance 0.05 mmol/kg Arm (Reader 1)

Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.1295 [5]
Method	Wilcoxon signed-rank test
Parameter estimate	ΔPercentage MH better minus DM better
Point estimate	7.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	16.5

Notes:

[4] - Null hypotheses:
A 0.05 mmol/kg dose of MULTIHANCE is equal to a 0.1 mmol/kg dose of DOTAREM, in terms of the assessment of global diagnostic preference in an off-site pre-dose plus post-dose paired global assessment.
[5] - Only 1 primary endpoint, no adjustment for multiple comparisons and the a priori threshold for statistical significance was 0.05.

Statistical analysis title	MultiHance 0.1 mmol/kg Arm (Reader 2)

Statistical analysis description:

62 Subjects in this analysis.

Difference in percentage MultiHance better minus percentage Dotarem better (%) , 2-sided 95% confidence interval was estimated using Altman's general approximate normal method.

Comparison groups	MultiHance 0.1 mmol/kg Arm (Reader 2) v Dummy Set
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	< 0.0001 [7]
Method	Wilcoxon signed rank test
Parameter estimate	ΔPercentage MH better minus DM better
Point estimate	79
Confidence interval	
level	95 %
sides	2-sided
lower limit	67.1
upper limit	91

Notes:

[6] - Null hypotheses:
A 0.1 mmol/kg dose of MULTIHANCE is equal to a 0.1 mmol/kg dose of DOTAREM, in terms of the assessment of global diagnostic preference in an off-site pre-dose plus postdose paired global assessment
[7] - Only 1 primary endpoint, no adjustment for multiple comparisons and the a priori threshold for statistical significance was 0.05.

Statistical analysis title	MultiHance 0.05 mmol/kg Arm (Reader 2)

Statistical analysis description:

94 Subjects in this analysis.

Difference in percentage MultiHance better minus percentage Dotarem better (%) , 2-sided 95% confidence interval was estimated using Altman's general approximate normal method.

Comparison groups	MultiHance 0.05 mmol/kg Arm (Reader 2 v Dummy Set

Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.7503 [9]
Method	Wilcoxon signed rank test
Parameter estimate	ΔPercentage MH better minus DM better
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15
upper limit	10.7

Notes:

[8] - Null hypotheses:
A 0.05 mmol/kg dose of MULTIHANCE is equal to a 0.1 mmol/kg dose of DOTAREM, in terms of the assessment of global diagnostic preference in an off-site pre-dose plus post-dose paired global assessment.
[9] - Only 1 primary endpoint, no adjustment for multiple comparisons and the a priori threshold for statistical significance was 0.05.

Statistical analysis title	MultiHance 0.1 mmol/kg Arm (Reader 3)

Statistical analysis description:

62 Subjects in this analysis.

Difference in percentage MultiHance better minus percentage Dotarem better (%) , 2-sided 95% confidence interval was estimated using Altman's general approximate normal method

Comparison groups	MultiHance 0.1 mmol/kg Arm (Reader 3) v Dummy Set
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	< 0.0001 [11]
Method	Wilcoxon signed rank test
Parameter estimate	ΔPercentage MH better minus DM better
Point estimate	66.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	52.8
upper limit	79.5

Notes:

[10] - Null hypotheses:

A 0.1 mmol/kg dose of MULTIHANCE is equal to a 0.1 mmol/kg dose of DOTAREM, in terms of the assessment of global diagnostic preference in an off-site pre-dose plus post-dose paired global assessment
[11] - Only 1 primary endpoint, no adjustment for multiple comparisons and the a priori threshold for statistical significance was 0.05.

Statistical analysis title	MultiHance 0.05 mmol/kg Arm (Reader 3)

Statistical analysis description:

95 Subjects in this analysis.

Difference in percentage MultiHance better minus percentage Dotarem better (%) , 2-sided 95% confidence interval was estimated using Altman's general approximate normal method.

Comparison groups	MultiHance 0.05 mmol/kg Arm (Reader 3) v Dummy Set
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.7297 [13]
Method	Wilcoxon signed rank test
Parameter estimate	ΔPercentage MH better minus DM better
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.8
upper limit	9.6

Notes:

[12] - Null hypotheses:

A 0.05 mmol/kg dose of MULTIHANCE is equal to a 0.1 mmol/kg dose of DOTAREM, in terms of the assessment of global diagnostic preference in an off-site pre-dose plus post-dose paired global assessment.

[13] - Only 1 primary endpoint, no adjustment for multiple comparisons and the a priori threshold for statistical significance was 0.05.

Secondary: Lesion Border Delineation

End point title	Lesion Border Delineation

End point description:

Assessed by 3 blinded readers for each of the 159 patients who had post-dose exams for both MultiHance, 0.1 mmol/kg and 0.05 mmol/kg doses, and Dotarem 0.1 mmol/kg. Readers assessed whether images with MultiHance were preferred or images with Dotarem 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 and endpoints. The 3 blinded readers assessed the available image sets as technically adequate in 84.3-90.7% of cases, depending on reader and study arm.

End point type	Secondary

End point timeframe:

Comparison of image sets obtained within 2 to 14 days

End point values	MultiHance 0.1 mmol/kg Arm (Reader 1)	MultiHance 0.1 mmol/kg Arm (Reader 2)	MultiHance 0.1 mmol/kg Arm (Reader 3)	MultiHance 0.05 mmol/kg Arm (Reader 1)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	63	62	62	96
Units: participant exams				
number (not applicable)				
MultiHance Preferred	29	34	25	11
Contrast Agents Equal	33	27	35	76
Dotarem Preferred	1	1	2	9

End point values	MultiHance 0.05 mmol/kg Arm (Reader 2	MultiHance 0.05 mmol/kg Arm (Reader 3)	Dummy Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	94	95	1	
Units: participant exams				
number (not applicable)				
MultiHance Preferred	12	8	0	
Contrast Agents Equal	66	77	0	
Dotarem Preferred	16	10	0	

Statistical analyses

Statistical analysis title	MultiHance 0.1 mmol/kg Arm (Reader 1)
Statistical analysis description:	
63 Subjects in this analysis	
Comparison groups	MultiHance 0.1 mmol/kg Arm (Reader 1) v Dummy Set
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	< 0.0001 [15]
Method	Wilcoxon signed-rank test

Notes:

[14] - This is a secondary analysis.
Null hypotheses:
A 0.05 mmol/kg dose of MULTIHANCE is equal to a 0.1 mmol/kg dose of DOTAREM, in terms of the assessment of Lesion Border Delineation in an off-site pre-dose plus post-dose paired global assessment.ent.
[15] - The priori threshold for statistical significance was 0.05.

Statistical analysis title	MultiHance 0.05 mmol/kg Arm (Reader 1)
Statistical analysis description:	
96 Subjects in this analysis	
Comparison groups	MultiHance 0.05 mmol/kg Arm (Reader 1) v Dummy Set
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	= 0.8238 [17]
Method	Wilcoxon signed-rank test

Notes:

[16] - This is a secondary analysis.
Null hypotheses:
A 0.05 mmol/kg dose of MULTIHANCE is equal to a 0.1 mmol/kg dose of DOTAREM, in terms of the assessment of Lesion Border Delineation in an off-site pre-dose plus post-dose paired global assessment.
[17] - The priori threshold for statistical significance was 0.05.

Statistical analysis title	MultiHance 0.1 mmol/kg Arm (Reader 2)

Statistical analysis description:

62 Subjects in this analysis

Comparison groups	Dummy Set v MultiHance 0.1 mmol/kg Arm (Reader 2)
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Wilcoxon signed-rank test

Statistical analysis title	MultiHance 0.05 mmol/kg Arm (Reader 2)

Statistical analysis description:

94 Subjects in this analysis

Comparison groups	MultiHance 0.05 mmol/kg Arm (Reader 2 v Dummy Set
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	= 0.4597 [19]
Method	Wilcoxon signed-rank test

Notes:

[18] - This is a secondary analysis.
Null hypotheses:
A 0.05 mmol/kg dose of MULTIHANCE is equal to a 0.1 mmol/kg dose of DOTAREM, in terms of the assessment of Lesion Border Delineation in an off-site pre-dose plus postdose paired global assessment.
[19] - The priori threshold for statistical significance was 0.05.

Statistical analysis title	MultiHance 0.1 mmol/kg Arm (Reader 3)

Statistical analysis description:

62 Subjects in this analysis

Comparison groups	MultiHance 0.1 mmol/kg Arm (Reader 3) v Dummy Set
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	< 0.0001 [21]
Method	Wilcoxon signed-rank test

Notes:

[20] - This is a secondary analysis.
Null hypotheses:
A 0.1 mmol/kg dose of MULTIHANCE is equal to a 0.1 mmol/kg dose of DOTAREM, in terms of the assessment of Lesion Border Delineation in an off-site pre-dose plus postdose paired global assessment.
[21] - The priori threshold for statistical significance was 0.05.

Statistical analysis title	MultiHance 0.05 mmol/kg Arm (Reader 3)

Statistical analysis description:

95 Subjects in this analysis

Comparison groups	MultiHance 0.05 mmol/kg Arm (Reader 3) v Dummy Set

Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority[22]
P-value	= 0.8145 [23]
Method	Wilcoxon signed-rank test

Notes:

[22] - This is a secondary analysis.
Null hypotheses:
A 0.05 mmol/kg dose of MULTIHANCE is equal to a 0.1 mmol/kg dose of DOTAREM, in terms of the assessment of Lesion Border Delineation in an off-site pre-dose plus postdose paired global assessment.
[23] - The priori threshold for statistical significance was 0.05.

Secondary: Lesion Internal Morphology

End point title	Lesion Internal Morphology

End point description:

Assessed by 3 blinded readers for each of the 159 patients who had post-dose exams for both MultiHance, 0.1 mmol/kg and 0.05 mmol/kg doses, and Dotarem 0.1 mmol/kg. Readers assessed whether images with MultiHance were preferred or images with Dotarem 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 and endpoints. The 3 blinded readers assessed the available image sets as technically adequate in 84.3-90.7% of cases, depending on reader and study arm.

End point type	Secondary

End point timeframe:

Comparison of image sets obtained within 2 to 14 days

End point values	MultiHance 0.1 mmol/kg Arm (Reader 1)	MultiHance 0.1 mmol/kg Arm (Reader 2)	MultiHance 0.1 mmol/kg Arm (Reader 3)	MultiHance 0.05 mmol/kg Arm (Reader 1)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	63	62	62	96
Units: participant exams				
number (not applicable)				
MultiHance better	10	14	23	4
No Difference Between MultiHance and Dotarem	53	48	38	88
Dotarem better	0	0	1	4

End point values	MultiHance 0.05 mmol/kg Arm (Reader 2	MultiHance 0.05 mmol/kg Arm (Reader 3)	Dummy Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	94	95	1	
Units: participant exams				
number (not applicable)				
MultiHance better	3	5	0	
No Difference Between MultiHance and Dotarem	87	82	0	
Dotarem better	4	8	0	

Statistical analyses

Statistical analysis title	MultiHance 0.1 mmol/kg Arm (Reader 1)

Statistical analysis description:

Subjects in this analysis 63

Comparison groups	MultiHance 0.1 mmol/kg Arm (Reader 1) v Dummy Set
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority[24]
P-value	= 0.002
Method	Wilcoxon signed-rank test

Notes:

[24] - Null hypotheses:
A 0.1 mmol/kg dose of MULTIHANCE is equal to a 0.1 mmol/kg dose of DOTAREM, in terms of the assessment of Lesion Internal Morphology in an off-site pre-dose plus postdose paired global assessment.

Statistical analysis title	MultiHance 0.05 mmol/kg Arm (Reader 1)

Statistical analysis description:

96 Subjects in this analysis

Comparison groups	MultiHance 0.05 mmol/kg Arm (Reader 1) v Dummy Set
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	= 1
Method	Wilcoxon signed-rank test

Notes:

[25] - Null hypotheses:
A 0.05 mmol/kg dose of MULTIHANCE is equal to a 0.1 mmol/kg dose of DOTAREM, in terms of the assessment of Lesion Internal Morphology in an off-site pre-dose plus post-dose paired global assessment.

Statistical analysis title	MultiHance 0.1 mmol/kg Arm (Reader 2)

Statistical analysis description:

62 Subjects in this analysis

Comparison groups	MultiHance 0.1 mmol/kg Arm (Reader 2) v Dummy Set
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority[26]
P-value	= 0.0001
Method	Wilcoxon signed-rank test

Notes:

[26] - Null hypotheses:
A 0.1 mmol/kg dose of MULTIHANCE is equal to a 0.1 mmol/kg dose of DOTAREM, in terms of the assessment of Lesion Internal Morphology in an off-site pre-dose plus postdose paired global assessment.

Statistical analysis title	MultiHance 0.05 mmol/kg Arm (Reader 2)

Statistical analysis description:

94 Subjects in this analysis

Comparison groups	Dummy Set v MultiHance 0.05 mmol/kg Arm (Reader 2
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority[27]
P-value	= 1
Method	Wilcoxon signed-rank test

Notes:

[27] - Null hypotheses:
A 0.05 mmol/kg dose of MULTIHANCE is equal to a 0.1 mmol/kg dose of DOTAREM, in terms of the assessment of Lesion Internal Morphology in an off-site pre-dose plus postdose paired global assessment.

Statistical analysis title	MultiHance 0.1 mmol/kg Arm (Reader 3)

Statistical analysis description:

62 Subjects in this analysis

Comparison groups	MultiHance 0.1 mmol/kg Arm (Reader 3) v Dummy Set
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority[28]
P-value	< 0.0001
Method	Wilcoxon signed-rank test

Notes:

[28] - Null hypotheses:
A 0.1 mmol/kg dose of MULTIHANCE is equal to a 0.1 mmol/kg dose of DOTAREM, in terms of the assessment of Lesion Internal Morphology in an off-site pre-dose plus postdose paired global assessment.

Statistical analysis title	MultiHance 0.05 mmol/kg Arm (Reader 3)

Statistical analysis description:

95 Subjects in this analysis

Comparison groups	MultiHance 0.05 mmol/kg Arm (Reader 3) v Dummy Set
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority[29]
P-value	= 0.5811
Method	Wilcoxon signed-rank test

Notes:

[29] - Null hypotheses:
A 0.05 mmol/kg dose of MULTIHANCE is equal to a 0.1 mmol/kg dose of DOTAREM, in terms of the assessment of Lesion Internal Morphology in an off-site pre-dose plus postdose paired global assessment.

Secondary: Extent of Disease

End point title	Extent of Disease

End point description:

Assessed by 3 blinded readers for each of the 159 patients who had post-dose exams for both MultiHance, 0.1 mmol/kg and 0.05 mmol/kg doses, and Dotarem 0.1 mmol/kg. Readers assessed whether images with MultiHance were preferred or images with Dotarem 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 and endpoints. The 3 blinded readers assessed the available image sets as technically adequate in 84.3-90.7% of cases, depending on reader and study arm.

End point type	Secondary

End point timeframe:

Comparison of image sets obtained within 2 to 14 days

End point values	MultiHance 0.1 mmol/kg Arm (Reader 1)	MultiHance 0.1 mmol/kg Arm (Reader 2)	MultiHance 0.1 mmol/kg Arm (Reader 3)	MultiHance 0.05 mmol/kg Arm (Reader 1)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	63	62	62	96
Units: participant exams				
number (not applicable)				
MultiHance Better	15	18	15	6
No Difference between MultiHance and Dotarem	48	43	45	84
Dotarem Better	0	1	2	6

End point values	MultiHance 0.05 mmol/kg Arm (Reader 2	MultiHance 0.05 mmol/kg Arm (Reader 3)	Dummy Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	94	95	1	
Units: participant exams				
number (not applicable)				
MultiHance Better	5	7	0	
No Difference between MultiHance and Dotarem	83	80	0	
Dotarem Better	6	8	0	

Statistical analyses

Statistical analysis title	MultiHance 0.1 mmol/kg Arm (Reader 1)

Statistical analysis description:

63 Subjects in this analysis

Comparison groups	Dummy Set v MultiHance 0.1 mmol/kg Arm (Reader 1)
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority[30]
P-value	< 0.0001
Method	Wilcoxon signed-rank test

Notes:

[30] - Null hypotheses:
A 0.1 mmol/kg dose of MULTIHANCE is equal to a 0.1 mmol/kg dose of DOTAREM, in terms of the assessment of Extent of Disease in an off-site pre-dose plus postdose paired global assessment.

Statistical analysis title	MultiHance 0.05 mmol/kg Arm (Reader 1)

Statistical analysis description:

96 Subjects in this analysis

Comparison groups	MultiHance 0.05 mmol/kg Arm (Reader 1) v Dummy Set

Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Wilcoxon signed-rank test

Statistical analysis title	MultiHance 0.1 mmol/kg Arm (Reader 2)

Statistical analysis description:

62 Subjects in this analysis

Comparison groups	MultiHance 0.1 mmol/kg Arm (Reader 2) v Dummy Set
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority[31]
P-value	< 0.0001
Method	Wilcoxon signed-rank test

Notes:

[31] - Null hypotheses:

A 0.1 mmol/kg dose of MULTIHANCE is equal to a 0.1 mmol/kg dose of DOTAREM, in terms of the assessment of Extent of Disease in an off-site pre-dose plus postdose paired global assessment.

Statistical analysis title	MultiHance 0.05 mmol/kg Arm (Reader 2)

Statistical analysis description:

94 Subjects in this analysis

Comparison groups	MultiHance 0.05 mmol/kg Arm (Reader 2 v Dummy Set
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority[32]
P-value	= 1
Method	Wilcoxon signed-rank test

Notes:

[32] - Null hypotheses:
A 0.05 mmol/kg dose of MULTIHANCE is equal to a 0.1 mmol/kg dose of DOTAREM, in terms of the assessment of Extent of Disease in an off-site pre-dose plus postdose paired global assessment.

Statistical analysis title	MultiHance 0.1 mmol/kg Arm (Reader 3)

Statistical analysis description:

62 Subjects in this analysis

Comparison groups	MultiHance 0.1 mmol/kg Arm (Reader 3) v Dummy Set
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority[33]
P-value	= 0.0023
Method	Wilcoxon signed-rank test

Notes:

[33] - Null hypotheses:

A 0.1 mmol/kg dose of MULTIHANCE is equal to a 0.1 mmol/kg dose of DOTAREM, in terms of the assessment of Extent of Disease in an off-site pre-dose plus postdose paired global assessment.

Statistical analysis title	MultiHance 0.05 mmol/kg Arm (Reader 3)

Statistical analysis description:	
95 Subjects in this analysis	
Comparison groups	MultiHance 0.05 mmol/kg Arm (Reader 3) v Dummy Set
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority[34]
P-value	= 1
Method	Wilcoxon signed-rank test

Notes:

[34] - Null hypotheses:
A 0.05 mmol/kg dose of MULTIHANCE is equal to a 0.1 mmol/kg dose of DOTAREM, in terms of the assessment of Extent of Disease in an off-site pre-dose plus postdose paired global assessment.

Secondary: Lesion Contrast Enhancement

End point title	Lesion Contrast Enhancement

End point description:

Assessed by 3 blinded readers for each of the 159 patients who had post-dose exams for both MultiHance, 0.1 mmol/kg and 0.05 mmol/kg doses, and Dotarem 0.1 mmol/kg. Readers assessed whether images with MultiHance were preferred or images with Dotarem 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 and endpoints. The 3 blinded readers assessed the available image sets as technically adequate in 84.3-90.7% of cases, depending on reader and study arm.

End point type	Secondary

End point timeframe:

Comparison of image sets obtained within 2 to 14 days

End point values	MultiHance 0.1 mmol/kg Arm (Reader 1)	MultiHance 0.1 mmol/kg Arm (Reader 2)	MultiHance 0.1 mmol/kg Arm (Reader 3)	MultiHance 0.05 mmol/kg Arm (Reader 1)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	63	62	62	96
Units: Participant Exams				
number (not applicable)				
MultiHance Better	31	51	43	10
No Difference between MultiHance and Dotarem	31	9	17	77
Dotarem Better	1	2	2	9

End point values	MultiHance 0.05 mmol/kg Arm (Reader 2	MultiHance 0.05 mmol/kg Arm (Reader 3)	Dummy Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	94	95	1	
Units: Participant Exams				
number (not applicable)				
MultiHance Better	18	14	0	
No Difference between MultiHance and Dotarem	56	64	0	
Dotarem Better	20	17	0	

Statistical analyses

Statistical analysis title	MultiHance 0.1 mmol/kg Arm (Reader 1)

Statistical analysis description:

63 Subjects in this analysis

Comparison groups	MultiHance 0.1 mmol/kg Arm (Reader 1) v Dummy Set
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority[35]
P-value	< 0.0001
Method	Wilcoxon signed-rank test

Notes:

[35] - Null hypotheses:
A 0.1 mmol/kg dose of MULTIHANCE is equal to a 0.1 mmol/kg dose of DOTAREM, in terms of the assessment of Lesion Contrast Enhancement in an off-site pre-dose plus postdose paired global assessment.

Statistical analysis title	MultiHance 0.05 mmol/kg Arm (Reader 1)

Statistical analysis description:

96 Subjects in this analysis

Comparison groups	MultiHance 0.05 mmol/kg Arm (Reader 1) v Dummy Set
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority[36]
P-value	= 1
Method	Wilcoxon signed-rank test

Notes:

[36] - Null hypotheses:
A 0.05 mmol/kg dose of MULTIHANCE is equal to a 0.1 mmol/kg dose of DOTAREM, in terms of the assessment of Lesion Contrast Enhancement in an off-site pre-dose plus post-dose paired global assessment.

Statistical analysis title	MultiHance 0.1 mmol/kg Arm (Reader 2)

Statistical analysis description:

62 Subjects in this analysis

Comparison groups	MultiHance 0.1 mmol/kg Arm (Reader 2) v Dummy Set
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority[37]
P-value	< 0.0001
Method	Wilcoxon signed-rank test

Notes:

[37] - Null hypotheses:
A 0.1 mmol/kg dose of MULTIHANCE is equal to a 0.1 mmol/kg dose of DOTAREM, in terms of the assessment of Lesion Contrast Enhancement in an off-site pre-dose plus postdose paired global assessment.

Statistical analysis title	MultiHance 0.05 mmol/kg Arm (Reader 2)

Statistical analysis description:

94 Subjects in this analysis

Comparison groups	MultiHance 0.05 mmol/kg Arm (Reader 2 v Dummy Set
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority[38]
P-value	= 0.7503
Method	Wilcoxon signed-rank test

Notes:

[38] - Null hypotheses:
A 0.05 mmol/kg dose of MULTIHANCE is equal to a 0.1 mmol/kg dose of DOTAREM, in terms of the assessment of Lesion Contrast Enhancement in an off-site pre-dose plus postdose paired global assessment.

Statistical analysis title	MultiHance 0.1 mmol/kg Arm (Reader 3)

Statistical analysis description:

62 Subjects in this analysis

Comparison groups	MultiHance 0.1 mmol/kg Arm (Reader 3) v Dummy Set
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority[39]
P-value	< 0.0001
Method	Wilcoxon signed-rank test

Notes:

[39] - Null hypotheses:
A 0.1 mmol/kg dose of MULTIHANCE is equal to a 0.1 mmol/kg dose of DOTAREM, in terms of the assessment of Lesion Contrast Enhancement in an off-site pre-dose plus postdose paired global assessment.

Statistical analysis title	MultiHance 0.05 mmol/kg Arm (Reader 3)

Statistical analysis description:

95 Subjects in this analysis

Comparison groups	MultiHance 0.05 mmol/kg Arm (Reader 3) v Dummy Set
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority[40]
P-value	= 0.5983
Method	Wilcoxon signed-rank test

Notes:

[40] - Null hypotheses:
A 0.05 mmol/kg dose of MULTIHANCE is equal to a 0.05 mmol/kg dose of DOTAREM, in terms of the assessment of Lesion Contrast Enhancement in an off-site pre-dose plus postdose paired global assessment.

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

End point title	Lesion to Background Ratio on Post T1-weighed 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 MultiHance and Dotarem was calculated. The number presented in the result table below is "the mean difference in LBR postdose (MultiHance - Dotarem)"

End point type	Secondary

End point timeframe:

5-10 minutes Postdose

End point values	MultiHance 0.1 mmol/kg Arm (Reader 1)	MultiHance 0.1 mmol/kg Arm (Reader 2)	MultiHance 0.1 mmol/kg Arm (Reader 3)	MultiHance 0.05 mmol/kg Arm (Reader 1)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	63	62	62	96
Units: Lesions				
number (not applicable)				
Lesions	64	66	54	85
Mean	0.22	0.24	0.21	-0.01
Standard Deviation	0.24	0.2	0.23	0.21

End point values	MultiHance 0.05 mmol/kg Arm (Reader 2	MultiHance 0.05 mmol/kg Arm (Reader 3)	Dummy Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	94	95	1	
Units: Lesions				
number (not applicable)				
Lesions	89	78	0	
Mean	0.03	0.01	0	
Standard Deviation	0.15	0.15	0	

Statistical analyses

Statistical analysis title	MultiHance 0.1 mmol/kg Arm (Reader 1)
Statistical analysis description: 63 Subjects in this analysis	
Comparison groups	MultiHance 0.1 mmol/kg Arm (Reader 1) v Dummy Set
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis

Statistical analysis title	MultiHance 0.05 mmol/kg Arm (Reader 1)
Statistical analysis description: 96 Subjects in this analysis	
Comparison groups	MultiHance 0.05 mmol/kg Arm (Reader 1) v Dummy Set

Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6898 [41]
Method	Mixed models analysis

Notes:

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

Statistical analysis title	MultiHance 0.1 mmol/kg Arm (Reader 2)

Statistical analysis description:

62 Subjects in this analysis

Comparison groups	MultiHance 0.1 mmol/kg Arm (Reader 3) v Dummy Set
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [42]
Method	Mixed models analysis

Notes:

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

Statistical analysis title	MultiHance 0.05 mmol/kg Arm (Reader 2)

Statistical analysis description:

94 Subjects in this analysis

Comparison groups	MultiHance 0.05 mmol/kg Arm (Reader 2 v Dummy Set
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1156 [43]
Method	Mixed models analysis

Notes:

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

Statistical analysis title	MultiHance 0.1 mmol/kg Arm (Reader 3)

Statistical analysis description:

62 Subjects in this analysis

Comparison groups	MultiHance 0.1 mmol/kg Arm (Reader 3) v Dummy Set
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [44]
Method	Mixed models analysis

Notes:

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

Statistical analysis title	MultiHance 0.05 mmol/kg Arm (Reader 3)

Statistical analysis description:

95 Subjects in this analysis

Comparison groups	MultiHance 0.05 mmol/kg Arm (Reader 3) v Dummy Set

Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7726 [45]
Method	Mixed models analysis

Notes:

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

Secondary: Lesion-brain Contrast-to-noise Ratio

End point title	Lesion-brain Contrast-to-noise Ratio

End point description:

The Unit of Measure is "Lesion". For each lesion, Lesion-brain Contrast-to-noise Ratio (CNR) = [(SI of lesion - SI of brain)/SD for SI of noise] on Postdose Images of each lesion was calculated for each contrast agent image separately, then the difference in CNR between MultiHance and Dotarem was calculated. The number presented in the result table below is "the mean difference in CNR (MultiHance - Dotarem)"

End point type	Secondary

End point timeframe:

5-10 minutes Postdose

End point values	MultiHance 0.1 mmol/kg Arm (Reader 1)	MultiHance 0.1 mmol/kg Arm (Reader 2)	MultiHance 0.1 mmol/kg Arm (Reader 3)	MultiHance 0.05 mmol/kg Arm (Reader 1)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	63	62	62	96
Units: Lesions				
number (not applicable)				
Lesions	64	66	54	85
Mean	17.4	31.82	39.73	15.72
Standard Deviation	36.14	45.28	65.26	36.05

End point values	MultiHance 0.05 mmol/kg Arm (Reader 2	MultiHance 0.05 mmol/kg Arm (Reader 3)	Dummy Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	94	95	1	
Units: Lesions				
number (not applicable)				
Lesions	89	78	0	
Mean	19.06	23.03	0	
Standard Deviation	29.37	49.53	0	

Statistical analyses

Statistical analysis title	MultiHance 0.1 mmol/kg Arm (Reader 1)

Statistical analysis description:

63 Subjects in this analysis

Comparison groups	MultiHance 0.1 mmol/kg Arm (Reader 1) v Dummy Set
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [46]
Method	Mixed models analysis

Notes:

[46] - 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	MultiHance 0.05 mmol/kg Arm (Reader 1)

Statistical analysis description:

96 Subjects in this analysis

Comparison groups	MultiHance 0.05 mmol/kg Arm (Reader 1) v Dummy Set
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [47]
Method	Mixed models analysis

Notes:

[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	MultiHance 0.1 mmol/kg Arm (Reader 2)

Statistical analysis description:

62 Subjects in this analysis

Comparison groups	MultiHance 0.1 mmol/kg Arm (Reader 2) v Dummy Set
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [48]
Method	Mixed models analysis

Notes:

[48] - 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	MultiHance 0.05 mmol/kg Arm (Reader 2)

Statistical analysis description:

94 Subjects in this analysis

Comparison groups	MultiHance 0.05 mmol/kg Arm (Reader 2 v Dummy Set
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [49]
Method	Mixed models analysis

Notes:

[49] - 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	MultiHance 0.1 mmol/kg Arm (Reader 3)

Statistical analysis description:

62 Subjects in this analysis

Comparison groups	MultiHance 0.1 mmol/kg Arm (Reader 3) v Dummy Set
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [50]
Method	Mixed models analysis

Notes:

[50] - 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	MultiHance 0.05 mmol/kg Arm (Reader 3)

Statistical analysis description:

95 Subjects in this analysis

Comparison groups	MultiHance 0.05 mmol/kg Arm (Reader 3) v Dummy Set
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003 [51]
Method	Mixed models analysis

Notes:

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

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 24 hours after contrast media injection	
Adverse event reporting additional description:	
All adverse events collected were categorized using MedDRA 17.1 and tabulated	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	Arm 1: MultiHance 0.1 mmol/kg
Reporting group description: -	
Reporting group title	Arm 1: Dotarem 0.1 mmol/kg
Reporting group description: -	
Reporting group title	Arm 2: MultiHance 0.05 mmol/kg
Reporting group description: -	
Reporting group title	Arm 2: Dotarem 0.1 mmol/kg
Reporting group description: -	

Serious adverse events	Arm 1: MultiHance 0.1 mmol/kg	Arm 1: Dotarem 0.1 mmol/kg	Arm 2: MultiHance 0.05 mmol/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 65 (0.00%)	0 / 70 (0.00%)	0 / 104 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Arm 2: Dotarem 0.1 mmol/kg		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 105 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Arm 1: MultiHance 0.1 mmol/kg	Arm 1: Dotarem 0.1 mmol/kg	Arm 2: MultiHance 0.05 mmol/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 65 (1.54%)	2 / 70 (2.86%)	3 / 104 (2.88%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumor pain			
subjects affected / exposed	0 / 65 (0.00%)	0 / 70 (0.00%)	0 / 104 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	0 / 65 (0.00%)	0 / 70 (0.00%)	1 / 104 (0.96%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 65 (0.00%)	0 / 70 (0.00%)	1 / 104 (0.96%)
occurrences (all)	0	0	1
Dysgeusia			
subjects affected / exposed	0 / 65 (0.00%)	0 / 70 (0.00%)	0 / 104 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	0 / 65 (0.00%)	2 / 70 (2.86%)	0 / 104 (0.00%)
occurrences (all)	0	2	0
General disorders and administration site conditions			
Injection site pruritus			
subjects affected / exposed	0 / 65 (0.00%)	0 / 70 (0.00%)	0 / 104 (0.00%)
occurrences (all)	0	0	0
Injection site swelling			
subjects affected / exposed	0 / 65 (0.00%)	0 / 70 (0.00%)	0 / 104 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 65 (0.00%)	0 / 70 (0.00%)	1 / 104 (0.96%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 65 (0.00%)	0 / 70 (0.00%)	0 / 104 (0.00%)
occurrences (all)	0	0	0

Infections and infestations Skin infection subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1	0 / 70 (0.00%) 0	0 / 104 (0.00%) 0

Non-serious adverse events	Arm 2: Dotarem 0.1 mmol/kg		
Total subjects affected by non-serious adverse events subjects affected / exposed	5 / 105 (4.76%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Tumor pain subjects affected / exposed occurrences (all)	1 / 105 (0.95%) 1		
Injury, poisoning and procedural complications Procedural pain subjects affected / exposed occurrences (all)	0 / 105 (0.00%) 0		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Dysgeusia subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	0 / 105 (0.00%) 0 1 / 105 (0.95%) 1 2 / 105 (1.90%) 2		
General disorders and administration site conditions Injection site pruritus subjects affected / exposed occurrences (all) Injection site swelling subjects affected / exposed occurrences (all)	1 / 105 (0.95%) 1 1 / 105 (0.95%) 1		
Gastrointestinal disorders Nausea			

subjects affected / exposed occurrences (all)	0 / 105 (0.00%) 0		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	 1 / 105 (0.95%) 1		
Infections and infestations Skin infection subjects affected / exposed occurrences (all)	 0 / 105 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 June 2014	The final protocol (dated 10 September 2013) was amended on 25 June 2014 (Protocol Amendment 1). There were seven changes to the protocol as described in Amendment 1: RATIONALE 1. The Sponsor physical address had changed. Cover pages in Protocol and Synopsis and Appendix G in the protocol were updated to reflect this change. 2. In addition to centers in North America and Europe, the Protocol was revised to allow centers also in Latin America. 3. The reference documents for the storage of the contrast agents for Latin America were added to the Storage Section (Sect. 6.2) of the Protocol 4. Table D was corrected to state that Parallel Image acquisitions are not permitted for T1 pre and post IP injection sequences, but for the T2 pre and post IP injections sequences, Parallel Imaging acquisitions could be used. 5. The Bracco personnel in Serious Adverse Event Sponsor Contact Personnel were changed. The 'Serious Adverse Event Contact Personnel Table' was changed in the Protocol to reflect these changes. 6. The following was added to Appendix B for Latin America: MultiHance 'Sample Vial Label,' 'Dotarem Sample Vial Label,' and 'Sample Medication Box Label.' 7. CRO Contact information was added to the Administrative Structure for Europe (Appendix H in the Protocol) for Ecron Acunova, the designated monitoring CRO for European sites in this study. Contact information for Clinical Research Personnel in Latin America was also added to the Administrative Structure.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported