Clinical trial results:
A PROSPECTIVE MULTICENTER COHORT STUDY EVALUATING THE LONG TERM RETENTION OF GADOLINIUM IN HUMAN BONE AND SKIN AFTER THE RETROSPECTIVE ADMINISTRATION OF MULTIHANCE® OR PROHANCE® IN COMPARISON WITH A CONTROL GROUP RECEIVING NO EXPOSURE TO GADOLINIUM

Summary

EudraCT number	2012-000941-11
Trial protocol	CZ
Global end of trial date	31 December 2019

Results information

Result version number	v1 (current)
This version publication date	25 March 2021
First version publication date	25 March 2021

Trial information

Trial identification

Sponsor protocol code	GMRA-102,Am.No.1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03108378
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bracco Imaging S.p.A
Sponsor organisation address	Via Folli 50, Milan, Italy, 20134
Public contact	Paola Pianezzola, Bracco Imaging S.p.A., 0039 0321772324, paola.pianezzola@bracco.com
Scientific contact	Paola Pianezzola, Bracco Imaging S.p.A., 0039 0321772324, paola.pianezzola@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	19 February 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 April 2018
Global end of trial reached?	Yes
Global end of trial date	31 December 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The objective of this study is to determine the long term Gadolinium (Gd) deposition in human bone and skin tissue (nmol Gd/g bone/skin) in subjects undergoing hip, shoulder or knee replacement surgery, limb amputations or other orthopedic surgical procedures following administration of MULTIHANCE or PROHANCE at least 1 month before their scheduled surgery in comparison with a control group receiving no exposure to Gd contrast agents (GBCA) across different sub groups.

Protection of trial subjects:

Investigators agreed to make no informal changes to the protocol, except when necessary to protect the safety, the rights or the welfare of subjects. In addition, the Sponsor ensures insurance coverage for damages concerning the subject during the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 October 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	Czechia: 1
Country: Number of subjects enrolled	Italy: 18
Country: Number of subjects enrolled	United States: 10
Worldwide total number of subjects	29
EEA total number of subjects	19

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)	8

From 65 to 84 years	20
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Informed consent was collected from 30 October 2014 to 19 April 2018.

Pre-assignment

Screening details:

Subjects >=18 years of age enrolled in the study if they were scheduled to undergo hip, shoulder or knee replacement surgery, limb amputations or other orthopedic surgical AND received at least 1 MultiHance or ProHance dose at least 1 month (3 months in Italy) before the surgery OR had no history of GBCA exposure.

Pre-assignment period milestones

Number of subjects started	29
Number of subjects completed	28

Pre-assignment subject non-completion reasons

Reason: Number of subjects	did not undergo surgery: 1

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Control

Arm description:

Subjects with no history of GBCA exposure.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	MultiHance, Single Dose

Arm description:

Subjects with previous exposure to a single dose of MultiHance

Arm type	No agent administered
Investigational medicinal product name	MultiHance
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

No agent was administered during this study.

Arm title	MultiHance, Multiple Doses

Arm description:

Subjects with previous exposure to multiple doses (2 or 3) of MultiHance

Arm type	No agent administered

Investigational medicinal product name	MultiHance
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

No agent was administered during this study.

Arm title	ProHance, Single Dose

Arm description:

Subjects with previous exposure to a single dose of ProHance

Arm type	No agent administered
Investigational medicinal product name	ProHance
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

No agent was administered during this study.

Number of subjects in period 1[1]	Control	MultiHance, Single Dose	MultiHance, Multiple Doses
Started	10	7	5
Completed	10	7	5

Number of subjects in period 1[1]	ProHance, Single Dose
Started	6
Completed	6

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: One subject, who signed informed consent, did not undergo the bone surgery; therefore, bone and skin tissue samples were not collected, excluding the enrolled subject from study participation.

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	28	28	
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)	8	8	
From 65-84 years	19	19	
85 years and over	1	1	
Gender categorical Units: Subjects			
Female	8	8	
Male	20	20	
Type of Surgery			
Subjects were enrolled in this study if they were scheduled to undergo hip, shoulder or knee replacement surgery, and limb amputations or other orthopedic surgical procedures in countries other than Italy where the subject enrollment was limited to hip and knee replacement.			
Units: Subjects			
Knee	2	2	
Hip	22	22	
Shoulder	0	0	
Limb amputation	2	2	
Other	2	2	

End points

End points reporting groups

Reporting group title	Control
Reporting group description:	
Subjects with no history of GBCA exposure.	
Reporting group title	MultiHance, Single Dose
Reporting group description:	
Subjects with previous exposure to a single dose of MultiHance	
Reporting group title	MultiHance, Multiple Doses
Reporting group description:	
Subjects with previous exposure to multiple doses (2 or 3) of MultiHance	
Reporting group title	ProHance, Single Dose
Reporting group description:	
Subjects with previous exposure to a single dose of ProHance	

Primary: Gadolinium Deposition in Bone Tissue, Trabecular

End point title	Gadolinium Deposition in Bone Tissue, Trabecular[1]
End point description:	

End point type	Primary
End point timeframe:	
At least 1 month (3 months for Italian sites) prior to planned surgery	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The descriptive statistics of mean, standard deviation, median, and range for the Gadolinium depositions were estimated for each study arm.

End point values	Control	MultiHance, Single Dose	MultiHance, Multiple Doses	ProHance, Single Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	7	5	6
Units: microgram(s)/gram				
arithmetic mean (standard deviation)				
Total Gd, trabecular	0.0400 (± 0.00000)	0.8501 (± 0.56026)	1.7180 (± 1.13306)	0.1007 (± 0.08226)

Statistical analyses

No statistical analyses for this end point

Primary: Gadolinium Deposition in Bone Tissue, Cortical

End point title	Gadolinium Deposition in Bone Tissue, Cortical[2]
End point description:	

End point type	Primary

End point timeframe:

At least 1 month (3 months for Italian sites) prior to planned surgery

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The descriptive statistics of mean, standard deviation, median, and range for the Gadolinium depositions were estimated for each study arm.

End point values	Control	MultiHance, Single Dose	MultiHance, Multiple Doses	ProHance, Single Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	6	4	6
Units: microgram(s)/gram				
arithmetic mean (standard deviation)				
Total Gd, cortical	0.0400 (± 0.00000)	0.8930 (± 0.62254)	1.0160 (± 0.69823)	0.0688 (± 0.02774)

Statistical analyses

No statistical analyses for this end point

Primary: Gadolinium Deposition in Skin Tissue

End point title	Gadolinium Deposition in Skin Tissue[3]

End point description:

End point type	Primary

End point timeframe:

At least 1 month (3 months for Italian sites) prior to planned surgery

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The descriptive statistics of mean, standard deviation, median, and range for the Gadolinium depositions were estimated for each study arm.

End point values	Control	MultiHance, Single Dose	MultiHance, Multiple Doses	ProHance, Single Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	7	5	6
Units: microgram(s)/gram				
arithmetic mean (standard deviation)				
Total Gd	0.0400 (± 0.00000)	0.0424 (± 0.00643)	0.0400 (± 0.00000)	0.0400 (± 0.00000)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

This was a prospective study of retrospective data. No investigational product was administered, therefore, adverse events were not collected.

Assessment type	Non-systematic

Dictionary used

Dictionary name	none
Dictionary version	NA

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: This was a prospective study of retrospective data. No investigational product was administered during this study, therefore, adverse events were not collected.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 February 2016	To increase patient recruitment rates, the following changes were made to the original protocol: - Expansion of the patient population for including subjects undergoing additional procedures (i.e., shoulder replacement, limb amputations, or other orthopedic surgical procedures. However, it was agreed that patients with bone resection due to septic, infectious, or ischemic disease that had caused the bone to become diseased should not have been included in the study. This should not have prevented enrolment of patients with a diabetic limb amputation, as long as the complications of diabetes had not resulted in the bone becoming diseased. - Reduction of the minimum time between GBCA exposure and knee or hip surgery from 3 months to 1 month - Removal of the requirement to complete subgroup with multiple doses of the same GBCA and renal impairment - Collection of data for combined renal impairment subgroup with at least moderate renal impairment (eGFR≤60 ml/min) with a target size of at least 5 patients.

Notes:

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.

No robust conclusions could be drawn from the results of this study due to the small sample size.

Notes: