Clinical trial results:
Intra-individual, comparison of the MRI contrast agents gadoxetic acid (Primovist®) versus gadoterate meglumine (Dotarem®) in liver MRI of patients with HCC and underlying cirrhosis

Summary

EudraCT number	2013-002409-75
Trial protocol	DE
Global end of trial date	13 April 2018

Results information

Result version number	v1 (current)
This version publication date	26 May 2022
First version publication date	26 May 2022

Trial information

Trial identification

Sponsor protocol code	Dota-PrimoLIV

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Charité Universitätsmedizin Campus Mitte
Sponsor organisation address	Charitéplatz 1, Berlin, Germany, 10117
Public contact	PD Dr. med. Timm Denecke, Diagnostische Radiologie Institut für Radiologie, +49 30450527082, timm.denecke@charite.de
Scientific contact	PD Dr. med. Timm Denecke, Diagnostische Radiologie Institut für Radiologie, +49 30450527082, timm.denecke@charite.de

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	13 April 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the peak maximum enhancement between both contrast agents in the lesion with reference to normal tissue (peak enhancement = SI post-contrast (lesion) - SI pre-contrast (lesion)).

Protection of trial subjects:

This prospective intra-individual comparative study was performed in accordance with the Declaration of Helsinki and was approved by the local ethics committee and the Federal Institute for Drugs and Medical Devices. Further all inclusion/exclusion criteria are intended to protect the patients. At each visit, an IV line will be established, a blood sample obtained for determination of the creatinine value (calculation of the GFR), and the patients positioned within the 3.0 T MRI device (Siemens MAGNETOM Skyra). The second visit will include the recording of any changes to the patient’s condition.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 August 2013
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: 23
Worldwide total number of subjects	23
EEA total number of subjects	23

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)	0
From 65 to 84 years	23

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients potentially meeting the in- and exclusion criteria will be informed about the study and invited to participate. Patients will be identified in the HCC out/in-patient departments. Informed and written consent will be obtained directly before the first MRI examination. Patients will have at least 24 hours to consider their participation.

Pre-assignment

Screening details:

Adult patients (> 18 years of age) with liver cirrhosis and diagnosis of HCC based on histology or noninvasive HCC diagnostic criteria were evaluated for study inclusion if they had a clinical indication for liver MRI.

Period 1

Period 1 title	Visitation 1
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

The quantitative and qualitative evaluation of the acquired MRI datasets will be performed by a radiologist experienced in liver MRI who will be blinded to the patient-related information and the type of contrast medium used in each series . The reader will be informed about the suspected lesion and the suspected location of the lesion in order to allow a reliable placement of the ROIs. Both datasets will be evaluated in the same reading session to ensure comparability of ROI placement.

Arms

Arm title	Extracellular contrast agent (ECA)

Arm description:

Dotarem: each 1 mL of Dotarem solution contains 279.32 mg of gadoterate meglumine (representing 0.5 mmol/mL)
The first visit consists of one MRI examination with gadoterate meglumine
Injection of gadoterate meglumine , followed by post-contrast MRI

Arm type	Active comparator
Investigational medicinal product name	Dotarem
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Dotarem:
Single IV bolus injection of an equivalent of 0,5 mmol Gd/kg body weight at an injection speed of 2 mL/sec, followed by a saline flush of 20 mL at an injection speed of 2 mL/sec.

Number of subjects in period 1	Extracellular contrast agent (ECA)
Started	23
Completed	23

Period 2

Period 2 title	Visitation 2
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

The quantitative and qualitative evaluation of the acquired MRI datasets will be performed by a radiologist experienced in liver MRI who will be blinded to the patient-related information and the type of contrast medium used in each series . The reader will be informed about the suspected lesion and the suspected location of the lesion in order to allow a reliable placement of the ROIs. Both datasets will be evaluated in the same reading session to ensure comparability of ROI placement.

Arms

Arm title	Hepatocyte-specific contrast agent (HSCA)

Arm description:

Primovist: each 1 mL of Primovist contains 0.25 mmol gadoxetic acid (Gd-EOP-DTPA disodium)
Injection of gadoxetic acid and followed by post-contrast MRI

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

Dosage and administration details:

Single IV bolus injection of an equivalent of 1 mmol Gd/kg body weight at an injection speed of 1 mL/sec, followed by a saline flush of 20 mL at an injection speed of 1 mL/sec.

Number of subjects in period 2	Hepatocyte-specific contrast agent (HSCA)
Started	23
Completed	23

Baseline characteristics

Reporting groups

Reporting group title	Visitation 1

Reporting group description: -

Reporting group values	Visitation 1	Total	
Number of subjects	23	23	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	69		
full range (min-max)	53 to 87	-	
Gender categorical Units: Subjects			
Female	19	19	
Male	4	4	
causes for liver cirrhosis Units: Subjects			
hepatitis B	3	3	
hepatitis C	4	4	
alcohol abuse	6	6	
cryptogenic	10	10	
HCCs confirmation through histopathology Units: Subjects			
surgical resection	12	12	
image guided biopsy	11	11	

End points

End points reporting groups

Reporting group title	Extracellular contrast agent (ECA)
Reporting group description:	
Dotarem: each 1 mL of Dotarem solution contains 279.32 mg of gadoterate meglumine (representing 0.5 mmol/mL) The first visit consists of one MRI examination with gadoterate meglumine Injection of gadoterate meglumine , followed by post-contrast MRI	
Reporting group title	Hepatocyte-specific contrast agent (HSCA)
Reporting group description:	
Primovist: each 1 mL of Primovist contains 0.25 mmol gadoxetic acid (Gd-EOP-DTPA disodium) Injection of gadoxetic acid and followed by post-contrast MRI	

Primary: Image quality between ECA and HSCA

End point title	Image quality between ECA and HSCA
End point description:	
The results of qualitative analysis for overall image quality, artifacts and lesion conspicuity for both contrast agents and throughout the different perfusion phases are reported LAP: late arterial phase, PVP: portal venous phase and DP: delayed phase	
End point type	Primary
End point timeframe:	
Visitation 1 and Visitation 2	

End point values	Extracellular contrast agent (ECA)	Hepatocyte-specific contrast agent (HSCA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: Score				
median (inter-quartile range (Q1-Q3))				
LAP	5 (4 to 5)	5 (4 to 5)		
PVP	5 (4 to 5)	4 (4 to 5)		
DP	4 (4 to 5)	4 (3 to 5)		

Statistical analyses

Statistical analysis title	qualitative analysis for overall image quality
Statistical analysis description:	
Due to small sample size, a non-parametric distribution of metric data was 167 assumed. In consequence metric data are given as median and interquartile range (25- 168 75th-percentiles) and the paired Wilcoxon signed-rank test was used. Categorical data 169 were analyzed using contingency tables and exact McNemar-test (2x2) as well as 170 McNemar-Bowker-test (>2 categories).	
Comparison groups	Extracellular contrast agent (ECA) v Hepatocyte-specific contrast agent (HSCA)

Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
sides	2-sided

Notes:

[1] - All tests were two-sided and the level of signifi- 171
cance was set to 0.05

Primary: Artefacts between ECA and HSCA

End point title	Artefacts between ECA and HSCA
End point description:	
End point type	Primary
End point timeframe:	
V1-V2	

End point values	Extracellular contrast agent (ECA)	Hepatocyte-specific contrast agent (HSCA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: Score				
median (inter-quartile range (Q1-Q3))				
LAP	4 (4 to 5)	4 (3 to 4)		
PVP	5 (4 to 5)	4 (4 to 5)		
DP	4 (4 to 5)	4 (4 to 5)		

Statistical analyses

Statistical analysis title	qualitative analysis for overall artifacts
Comparison groups	Extracellular contrast agent (ECA) v Hepatocyte-specific contrast agent (HSCA)
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
sides	2-sided

Primary: Lesion conspicuity between ECA and HSCA

End point title	Lesion conspicuity between ECA and HSCA

End point description:

End point type	Primary

End point timeframe:

V1-V2

End point values	Extracellular contrast agent (ECA)	Hepatocyte-specific contrast agent (HSCA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: Score				
median (inter-quartile range (Q1-Q3))				
LAP	5 (4 to 5)	4 (3 to 4.5)		
PVP	5 (4 to 5)	5 (4 to 5)		
DP	5 (4 to 5)	5 (4 to 5)		

Statistical analyses

Statistical analysis title	qualitative analysis: overall lesion conspicuit
Comparison groups	Hepatocyte-specific contrast agent (HSCA) v Extracellular contrast agent (ECA)
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
sides	2-sided

Secondary: Quantitative Analysis comperison SNR and CNR values

End point title	Quantitative Analysis comperison SNR and CNR values

End point description:

SNR= Signal-to-noise ratio; CNR=Contrast-to-noise ratio

End point type	Secondary

End point timeframe:

After Visitation 1 and 2.

End point values	Extracellular contrast agent (ECA)	Hepatocyte-specific contrast agent (HSCA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: SI				
median (inter-quartile range (Q1-Q3))				
Signal-to-noise ratio	298.7 (183.3 to 482.9)	264.1 (220.3 to 380.4)		
Contrast-to-noise ratio	72.7 (50.8 to 165)	49.4 (18.1 to 154.4)		

Statistical analyses

Statistical analysis title	Comperison between V1 and V2

Statistical analysis description:

Due to small sample size, a non-parametric distribution of metric data was 167
assumed. In consequence metric data are given as median and interquartile range (25- 168
75th-percentiles) and the paired Wilcoxon signed-rank test was used.Categorical data 169
were analyzed using contingency tables and exact McNemar-test (2x2) as well as 170
McNemar-Bowker-test (>2 categories).

Comparison groups	Extracellular contrast agent (ECA) v Hepatocyte-specific contrast agent (HSCA)
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.05 [3]
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
sides	2-sided

Notes:

[2] - This study assesses the diagnostic value of Primovist® in patients with liver cirrhosis. If successful, the study will show superiority of Primovist® in lesion identification in these "difficult-to-diagnose" patients which would warrant additional clinical studies (aiming at an overall improvement of diagnostic accuracy).
[3] - All tests were two-sided and the level of significance was set to 0.05.

Secondary: Quantitative Analysis comperison Wash-in/-out

End point title	Quantitative Analysis comperison Wash-in/-out

End point description:

End point type	Secondary

End point timeframe:

After V1 and V2

End point values	Extracellular contrast agent (ECA)	Hepatocyte-specific contrast agent (HSCA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: [1/s]				
median (inter-quartile range (Q1-Q3))				
Wash-in	0.9 (0.6 to 1.5)	0.4 (0.1 to 0.7)		
Wash-out	19.8 (7.3 to 35.6)	9.3 (-6.5 to 21)		

Statistical analyses

Statistical analysis title	Comperison the Wash-in and -out values
Comparison groups	Extracellular contrast agent (ECA) v Hepatocyte-specific contrast agent (HSCA)
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
sides	2-sided

Other pre-specified: The frequencies Arterial phase hyperenhancement

End point title	The frequencies Arterial phase hyperenhancement
End point description:	
End point type	Other pre-specified
End point timeframe: V1-V2	

End point values	Extracellular contrast agent (ECA)	Hepatocyte-specific contrast agent (HSCA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: Subjects				
LAP	21	17		
PVP	0	0		
DP	0	0		

Statistical analyses

Statistical analysis title	analyzed fields of major imaging features
Comparison groups	Hepatocyte-specific contrast agent (HSCA) v Extracellular contrast agent (ECA)
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
sides	2-sided

Other pre-specified: The frequencies Non-peripheral washout

End point title	The frequencies Non-peripheral washout
End point description:	

End point type	Other pre-specified
End point timeframe:	
V1-V2	

End point values	Extracellular contrast agent (ECA)	Hepatocyte-specific contrast agent (HSCA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: Subjects				
LAP	0	0		
PVP	19	17		
DP	21	20		

Statistical analyses

Statistical analysis title	analyzed fields: Non-peripheral washout
Comparison groups	Extracellular contrast agent (ECA) v Hepatocyte-specific contrast agent (HSCA)
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Confidence interval	
sides	2-sided

Other pre-specified: The frequencies of Enhancing capsule

End point title	The frequencies of Enhancing capsule
End point description:	
End point type	Other pre-specified
End point timeframe:	
V1-V2	

End point values	Extracellular contrast agent (ECA)	Hepatocyte-specific contrast agent (HSCA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: Subjects				
LAP	0	0		
PVP	15	10		
DP	17	12		

Statistical analyses

Statistical analysis title	analyzed fields of Enhancing capsule
Comparison groups	Extracellular contrast agent (ECA) v Hepatocyte-specific contrast agent (HSCA)
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
sides	2-sided

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: From Visitation 1 to Visitation 2	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Frequency threshold for reporting non-serious adverse events: 0.5 %

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: No SAEs and no non-serious adverse events were reported

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 December 2015	update study protocol Version 3.0 (22/12/2015): change PI (LKP)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported