Clinical trial results:
Open-label, multi-center study to evaluate the safety, efficacy, and plasma gadolinium concentrations after an intravenous injection of 0.1 mL/kg body weight Eovist/Primovist for enhanced magnetic resonance imaging of the liver in children 0 to 2 months of age

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2012-000952-32
Trial protocol	Outside EU/EEA
Global end of trial date	11 August 2015

Results information

Result version number	v1
This version publication date	06 July 2016
First version publication date	06 July 2016

Trial information

Trial identification

Sponsor protocol code	BAY86-4873/16078

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02084628
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer HealthCare AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, D-51368 Leverkusen, Germany,
Public contact	Therapeutic Area Head, Bayer HealthCare AG, clinical-trials-contact@bayerhealthcare.com
Scientific contact	Therapeutic Area Head, Bayer HealthCare AG, clinical-trials-contact@bayerhealthcare.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 August 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 August 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The objectives of this study were to evaluate the safety, efficacy (imaging data), and plasma gadolinium concentrations after administration of Eovist/Primovist in pediatric subjects 0 to 2 months of age with known or suspected hepatobiliary pathology who were undergoing contrast-enhanced magnetic resonance imaging (MRI) of the liver.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to their legally authorized representative. Participating subject's legally authorized representative signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 February 2015
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	United States: 1
Worldwide total number of subjects	1
EEA total number of subjects	0

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)	1
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 9 centres in United States of America (USA) and only one subject was recruited in one centre, between 13 February 2015 (first subject first visit) and 11 August 2015 (Last subject last visit).

Pre-assignment

Screening details:

One subject was enrolled in the study.

Period 1

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

Arms

Arm title	Eovist/Primovist (BAY86-4873)

Arm description:

Subjects to receive single dose of Eovist/Primovist as a manual injection at a dose of 0.1 milliliter per kilogram (mL/kg) body weight (BW) (0.025 millimole [mmol]/kg BW), followed by a flush of at least 5 mL saline (sodium chloride 0.9 percent [%] solution) manually.

Arm type	Experimental
Investigational medicinal product name	Eovist
Investigational medicinal product code	BAY86-4873
Other name	Primovist
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subject recieved Eovist/Primovist injection at a dose of 0.1 mL/kg BW (0.025 mmol/kg BW), followed by a flush of at least 5 mL saline manually.

Number of subjects in period 1	Eovist/Primovist (BAY86-4873)
Started	1
Completed	1

Baseline characteristics

Reporting groups	
Reporting group title	Eovist/Primovist (BAY86-4873)
Reporting group description:	
Subjects to receive single dose of Eovist/Primovist as a manual injection at a dose of 0.1 milliliter per kilogram (mL/kg) body weight (BW) (0.025 millimole [mmol]/kg BW), followed by a flush of at least 5 mL saline (sodium chloride 0.9 percent [%] solution) manually.	

Reporting group values	Eovist/Primovist (BAY86-4873)	Total	
Number of subjects	1	1	
Age categorical			
Age categorical included the age 0 to 2 months (gestational age 37 to 41 weeks inclusive) as well.			
Units: Subjects			
Infants and toddlers (28 days-23 months)	1	1	
Gender categorical Units: Subjects			
Female	1	1	
Male	0	0	

End points

End points reporting groups

Reporting group title	Eovist/Primovist (BAY86-4873)

Reporting group description:

Subjects to receive single dose of Eovist/Primovist as a manual injection at a dose of 0.1 milliliter per kilogram (mL/kg) body weight (BW) (0.025 millimole [mmol]/kg BW), followed by a flush of at least 5 mL saline (sodium chloride 0.9 percent [%] solution) manually.

Primary: Number of Subjects With Additional Diagnostic Information From Combined (Pre-contrast And Post-contrast) Images Compared With Pre-contrast Images

End point title	Number of Subjects With Additional Diagnostic Information From Combined (Pre-contrast And Post-contrast) Images Compared With Pre-contrast Images[1]

End point description:

Additional diagnostic information such as better delineation of the border of the lesion, better definition of the internal morphology of the lesion, better characterization of the lesion, better definition of the location of the lesion, better assessment of the communication of the lesion with respect to the biliary system obtained from the combined magnetic resonance (MR) images compared with pre-contrast MR images. Number of subjects with additional diagnostic information were recorded and analyzed.

End point type	Primary

End point timeframe:

Images were taken pre-injection and post-injection (within about 15 minutes)

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: In this study only one subject was enrolled and hence, inferential statistical analysis was not performed.

End point values	Eovist/Primovist (BAY86-4873)			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Adverse Events

End point title	Number of Subjects With Adverse Events[2]

End point description:

An adverse event (AE) was any untoward medical occurrence that is, any unfavorable and unintended sign (including abnormal laboratory findings), symptom or disease in a subject or clinical investigation subject after providing written informed consent for participation in the study.

End point type	Primary

End point timeframe:

From the signing of the informed consent form until the 6 month post MRI follow-up

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: In this study only one subject was enrolled and hence, inferential statistical analysis was not performed.

End point values	Eovist/Primovist (BAY86-4873)			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Serious Adverse Events

End point title	Number of Subjects With Serious Adverse Events[3]

End point description:

An serious adverse events (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly.

End point type	Primary

End point timeframe:

From the signing of the informed consent form until the 6 month post MRI follow-up

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: In this study only one subject was enrolled and hence, inferential statistical analysis was not performed.

End point values	Eovist/Primovist (BAY86-4873)			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Lesions Detected for the Pre-contrast Images

End point title	Number of Lesions Detected for the Pre-contrast Images

End point description:

End point type	Secondary

End point timeframe:

Images were taken pre-injection

End point values	Eovist/Primovist (BAY86-4873)			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: number of lesions	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Lesions Detected for the Combined Images

End point title	Number of Lesions Detected for the Combined Images

End point description:

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection (within about 15 minutes)

End point values	Eovist/Primovist (BAY86-4873)			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: number of lesions	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Contrast Enhancement of the Liver for the Combined Images Assessed by yes or no Question

End point title	Contrast Enhancement of the Liver for the Combined Images Assessed by yes or no Question

End point description:

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection (within about 15 minutes)

End point values	Eovist/Primovist (BAY86-4873)			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: number of responses				
Yes	1			
No	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Contrast Enhancement of the Biliary System for the Combined Images Assessed by yes or no Question

End point title	Contrast Enhancement of the Biliary System for the Combined Images Assessed by yes or no Question

End point description:

Biliary system included
a. Gall bladder
b. Cystic duct
c. Common bile duct
d. Right main bile duct
e. Left main bile duct

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection (within about 15 minutes)

End point values	Eovist/Primovist (BAY86-4873)			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: number of responses				
Yes	1			
No	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Visualization of the Biliary System for the Pre-contrast and Combined Images Assessed by yes or no Question

End point title	Visualization of the Biliary System for the Pre-contrast and Combined Images Assessed by yes or no Question

End point description:

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection (within about 15 minutes)

End point values	Eovist/Primovist (BAY86-4873)			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: subjects				
Pre-contrast Images: Yes	0			
Pre-contrast Images: No	1			
Combined Images: Yes	0			
Combined Images: No	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Diagnosis for the Combined Images Compared With Pre-contrast Images

End point title	Change in Diagnosis for the Combined Images Compared With Pre-contrast Images

End point description:

Diagnosis based on the pre-contrast images will be indicated. If there is a change in the diagnosis based on the combined images, then the combined images diagnosis will be recorded.

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection (within about 15 minutes)

End point values	Eovist/Primovist (BAY86-4873)			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Diagnostic Confidence for the Pre-contrast and Combined Images Assessed by yes or no Question

End point title	Diagnostic Confidence for the Pre-contrast and Combined Images Assessed by yes or no Question

End point description:

Diagnostic confidence was classified as not confident (No), confident (Yes), very confident (Yes).

End point type	Secondary

End point timeframe:

Images were taken pre-injection and post-injection (within about 15 minutes)

End point values	Eovist/Primovist (BAY86-4873)			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: number of responses				
Pre-contrast Images: Very Confident – Yes	0			
Pre-contrast Images: Confident – Yes	0			
Pre-contrast Images: Not Confident – No	1			
Combined Images: Very Confident – Yes	1			
Combined Images: Confident – Yes	0			
Combined Images: Not Confident - No	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events:	
From the signing of the informed consent form until the 6 month post MRI follow-up	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	Eovist/Primovist (BAY86-4873)

Reporting group description:

Subject recieved Eovist/Primovist injection at a dose of 0.1 mL/kg BW (0.025 mmol/kg BW), followed by a flush of at least 5 mL saline manually.

Serious adverse events	Eovist/Primovist (BAY86-4873)		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (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	Eovist/Primovist (BAY86-4873)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)		

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: In this study only one subject was enrolled, received treatment and completed the study. There were no non-serious adverse event reported for this subject during the study.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Primarily based on study 13729 along with supporting data the FDA revised Eovist labeling to remove any age restriction from indication and decided that there are no further pediatric data requested. Consequently, study was discontinued.

Notes: