Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Bayer HealthCare

Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer HealthCare AG	
Study Number:	91789 (312041)	NCT00764621
Study Phase:	IV Interventional	
Official Study Title:	Multi-center, randomized comparison study to eVALUatE outcomes and resource needs of imaging and treatment following Primovist-enhanced MRI of the liver in comparison to extracellular contrast media (ECCM)-enhanced MRI and contrast-enhanced computed tomography (CT) in patients with a history of colorectal cancer and known or suspected metachronous liver metastases (Primovist VALUE study)	
Therapeutic Area:	Diagnostic Imaging	
Test Product		
Name of Test Product:	Gadoxetic acid disodium (Primovist, BAY86-4873)	
Name of Active Ingredient:	Gadoxetic acid disodium; Gd-EOB-DTPA	
Dose and Mode of Administration:	0.025 mmol/kg body weight administered as intravenous (i.v.) bolus injection	
Reference Therapy/Placebo		
Reference Therapy:	Not applicable	
Dose and Mode of Administration:	Not applicable	
Duration of Treatment:	Single injection of the test drug	
Studied period:	Date of first subjects' first visit:	07 OCT 2008
	Date of last subjects' last visit:	03 NOV 2010
Premature Study Suspension / Termination:	Yes, as the results of the pre-planned interim analysis allowed the reduction in total subjects necessary to be recruited.	
Substantial Study Protocol Amendments:	Amendment no. 1 (dated 11 SEP 2008) specified the following modifications: • The exclusion criterion was changed from originally "subjects with impaired renal function (e.g., acute renal failure) or subjects on dialysis" to "subjects with severe renal impairment (eGFR value <30 ml/min/1.73 m^2)". • A comparison of the 3 different imaging modalities using sensitivity and specificity was included. As specified in the stastical analysis plan (SAP), sensitivity and specificity of each of the three diagnostic procedures and their 95% two-sided confidence intervals were calculated for all subjects in the per-protocol set (PPS) with a final diagnosis. Local Amendment no. 1.1 for Switzerland (dated 07 APR 2009) specified the following modifications: • In all sections of the protocol it was included that the active part of the study ended with the end of the follow-up period up	

	to one hour post injection (p.i.). Amendment no 2 (dated 01 NOV 2009) specified the following modifications: • The number of centers was increased from 35 to 45 centers (from originally 30 to 35 centers). Furthermore the maximum number of subjects per center was increased to 80 (from originally 60 subjects/center).
Study Centre(s):	There were 28 study centers treating subjects in 8 countries: 3 centers in Austria, 8 centers in Germany, 4 centers in Italy, 6 centers in Korea, 2 centers in Spain, 2 centers in Sweden, 1 center in Switzerland, and 2 centers in Thailand.
Methodology:	Subjects were randomized to either undergo Primovist-enhanced magnetic resonance imaging (PV-MRI), ECCM-MRI, or contrast-enhanced CT (CE-CT). Efficacy and safety assessments were carried out onsite by the clinical investigators after the imaging procedure. To determine the proportion of subjects for whom further imaging was required after initial imaging of the liver, a consensus decision by the treating radiologist and surgeon was obtained. If further imaging was required, the subject received a 2nd imaging method with one of the two remaining imaging modalities as decided in the 1st consensus meeting (excluding the method which was used for the 1st imaging). It was recommended that this 2nd imaging be only performed at least 24 hours after the initial imaging, but within 2 weeks after the 1st imaging procedure. The 2nd consensus meeting was planned to take place within one week after the 2nd imaging procedure. Based on the combined evaluation of 1st and 2nd imaging modalities and subject-related clinical information the 2nd consensus decision regarding the assessment of liver lesions, surgical planning as well as the confidence in diagnosis and therapeutic decision were recorded. To determine the proportion of subjects with intra-operatively modified surgical plans following initial surgical planning on the basis of the imaging procedure(s) all available documentation on the surgical procedure and its outcome was collected. In case of subjects with surgery, the final diagnosis was based on intraoperative ultrasound (IOUS)/histopathology; in case of subjects without a surgery, the final diagnosis was based on clinical data obtained within 3 months after initial imaging. The final diagnosis was utilized as the standard of truth for the assessment of diagnostic performance. Safety was assessed based on adverse events (AEs), which were monitored for 1 hour p.i.

Indication/ Main Inclusion Criteria:	Indication: Subjects with history of colorectal cancer and known or suspected metachronous liver metastasis (es) who were scheduled to undergo contrast-enhanced tomographic imaging (i.e., CE-MRI or CE-CT) of the liver. Main Inclusion Criteria: Men or women of any ethnic group of at least 18 years of age with known or suspected metachronous liver metastases secondary to colorectal cancer who were scheduled to undergo contrast enhanced tomographic imaging (i.e., CE-MRI or CE-CT).
Study Objectives:	Overall: The main objective of this study was to evaluate outcomes and resource needs of imaging and treatment following PV-MRI as compared to ECCM-MRI and CE-CT in subjects with a history of colorectal cancer and known or suspected metachronous liver metastases based on the evaluation of the following: • Proportion of subjects for whom further imaging was required to come to a therapy decision after initial imaging of the liver with either PV-MRI, ECCM-MRI, or CE-CT (primary efficacy variable) • Proportion of subjects with intra-operatively modified surgical plans based on either PV-MRI, ECCM-MRI, or CE-CT • Diagnostic performance of either PV-MRI, ECCM-MRI, or CECT in comparison to final diagnosis • Confidence in diagnosis and therapeutic decision • Resource needs for imaging and treatment after either PV-MRI, ECCM-MRI, or CE-CT Another objective of this study was to assess safety of PV-MRI as compared to ECCM-MRI and CE-CT in subjects with known or suspected liver metastases based on the evaluation of AEs.
Evaluation Criteria:	Efficacy (Primary): Proportion of subjects for whom further imaging was required to come to a therapy decision after initial imaging of the liver with either PV-MRI, ECCM-MRI, or CE-CT. Efficacy (Secondary): The proportion of subjects with intra-operatively modified plans, diagnostic performance, diagnostic confidence, and resource need were evaluated as secondary efficacy parameters. Safety: Adverse events
Statistical Methods:	Efficacy (Primary): For the primary efficacy variable the null hypothesis of the test with regard to the proportion using PV-MRI (i.e., $P_{PV\text{-}MRI}$) was tested against the alternative hypothesis using the approximate test for equality. There were 3 hierarchical tests using 1. Pooled data from ECCM-MRI and CE-CT as comparator 2. Data from CE-CT as comparator

	3. Data from ECCM-MRI as comparator The following test was only performed if the preceding test was significant. For each test, the corresponding 2-sided 95% confidence interval (CI) was calculated. Efficacy (Secondary): Secondary efficacy variables were evaluated descriptively comparing the 3 imaging techniques. All efficacy analyses were repeated for the subgroup of subjects who underwent liver surgery. All segment based analyses were done for these subjects only. Safety: Safety data were evaluated using descriptive statistics. No statistical tests were performed.
Number of Subjects:	Planned: 660 subjects, 220 in each group. Analyzed: 360 screened, 354 in the safety population (SAF) (122 PV-MRI, 116 ECCM-MRI, 116 CE-CT) 342 in the per-protocol set (PPS) (118 PV-MRI, 112 ECCM-MRI, 112 CE-CT)

Study Results

Results Summary — Subject Disposition and Baseline

A total of 360 subjects were enrolled at 27 study centers treating subjects in 8 countries.

At initial imaging, a premature termination of the study was recorded for 2 subjects (withdrawal of informed consent of 1 subject assigned to PV-MRI, protocol deviation [single-slice CT] causing the premature termination of the study drug for 1 subject assigned to CE-CT).

In case of 67 subjects a 2nd imaging was performed, for which no premature termination of study medication or study was recorded.

The (active) study was completed by 352 subjects.

On average, in the SAF, subjects were 62.8 years (range: 32.0 – 88.0 years) of age with a height of 167.4 cm (range: 140.0 – 194.0 cm) and a weight of 71.8 kg (37.0 – 146.0 Kg). About two-thirds (66.4%) were male subjects and one-third (33.6%) were female subjects. With 54% the largest proportion was Caucasian, followed by Asian (29.7%), and Thai (16.4%). Demographic data of the 3 groups, randomized by initial imaging technique, were comparable.

Results Summary — Efficacy

Primary efficacy variable

By showing superiority of PV-MRI over CE-CT and ECCM-MRI with regard to the requirement for further imaging, the aim of the study was reached. Whereas for none (0%) of the 118 subjects initially randomized to PV-MRI a 2nd imaging was required, further imaging to come

to a therapy decision was required in 19 (17.0%) of the 112 subjects randomized to ECCM-MRI (17%), and in 44 (39.3%) of the 112 subjects randomized to CE-CT.

PV-MRI was tested against the comparator in a hierarchical order to maintain the significance level of 2.5%. First it was tested against the pooled data from ECCM-MRI and CE-CT, then against the data from CE-CT and finally against the data from ECCM-MRI. All 3 tests resulted in statistically significant effects in favor of PV-MRI.

As planned in the study protocol, the primary efficacy parameter had been tested in an interim analysis including 281 subjects (97 subjects PV-MRI, 93 subjects ECCM-MRI, and 91 subjects CE-CT).

Secondary efficacy variables

Chosen imaging modality for 2nd imaging

The clear advantage for Primovist shown by the primary efficacy variable was confirmed by the analysis of the type of imaging chosen in case a 2nd imaging was considered necessary. Of the 63 subjects in the PPS with a 2nd imaging, in all but one subject, PV-MRI was the chosen imaging procedure.

Confidence in diagnosis and therapeutic decision

In agreement that for none of the subjects a 2nd imaging was considered necessary following PV-MRI (primary efficacy parameter), the investigators felt a very high/high confidence in their decision for 98.3% of the subjects. Following ECCM-MRI, very high/high confidence was recorded for 85.7% of the subjects. With CE-CT with very high/high confidence was recorded for 65.2% of the subjects.

Diagnostic performance

To judge the diagnostic performance, the final diagnosis served as the standard of reference (SOR, i.e., histopathology and/or IOUS in case of subjects with liver surgery and all available clinical data in other subjects), which was available for all subjects of the PPS. On interpretation of the following results it was kept in mind that the study was not designed for the evaluation of this secondary efficacy parameter.

On analysis of the total number of lesions by subject, PV-MRI resulted in by far the highest number of equal assessments between the imaging method and the SOR (86.0%), compared to ECCM-MRI (76.5%) and CE-CT (63.6%). Superiority of PV-MRI in detecting the correct number of lesions was also seen, when only the subgroup of subjects with liver surgery was analyzed, which resulted in equal assessments between imaging method and SOR for 88.1% of the subjects following PV-MRI compared to 73.5% (ECCM-MRI) and 62.1% (CE-CT).

As expected due to the inclusion criteria, on a per subject basis, diagnostic performance based on lesion detection, lesion classification, and lesion characterization resulted in high sensitivity values (≥96.6%) for all imaging groups.

The most sensitive method to show the advantage of PV-MRI over ECCM-MRI and CE-CT was the analysis of the detection of metastases over all segments. This analysis was limited to subjects with liver surgery, as only in case of a (planned) surgery the number of metastases

in each segment was recorded. Sensitivity following use of PV-MRI was excellent (93.8%) and higher than sensitivity following ECCM-MRI (89.4%) or CE-CT (84.1%).

Of special interest was the number of cases, in which the 2nd imaging was able to improve or correct the assessment given at the 1st consensus meeting. In subjects with liver surgery following CE-CT, such changes due to PV-MRI occurred in 8 out of 117 segments: in 6 segments, metastases were detected in segments which had been not assessable according to CE-CT, and in 2 segments, the assessment given at the 1st consensus meeting was corrected to the one given by the final diagnosis. Comparable improvements due to PV-MRI following ECCM-MRI in a total of the 90 segments were not recorded.

Modification of surgical plans

Of the 342 subjects in the PPS, 112 subjects had undergone a liver surgery (47 subjects, 35 subjects, and 30 subjects in the PV-MRI, ECCM-MRI, and CE-CT group, respectively). Of the 112 subjects, 23 subjects were referred to surgery only after a 2nd imaging (10 subjects in the ECCM-MRI/PV-MRI sequence and 13 subjects in the CE-CT/PV-MRI sequence).

For subjects with liver surgery, the lesions had been considered primarily resectable at the 1st or, if applicable, at the 2nd consensus meeting. Compared to this assessment, in 3 subjects, no resection was performed during surgery. Of these, for 2 subjects this was due to extra hepatic reasons (in 1 subject [PV-MRI] because another tumor of the sigmoid colon had an unexpected extent; in 1 subject [ECCM-MRI] because of extra hepatic growth and peritoneal metastases). For 1 subject (ECCM-MRI/PV-MRI) this was an unnecessary surgery, because metastases were unresectable due to an unfavorable segment location and disseminated disease.

Modifications of the surgical plan due to liver-associated reasons were present in about half of the subjects (47.1%) who underwent only CE-CT imaging, compared to only 27.7% of the subjects who had PV-MRI, and 32.0% of the subjects who had ECCM-MRI as their single imaging procedure. Subjects with a 2nd imaging showed the lowest proportion of changes (17.4%). Mainly, modifications were due to an unexpected location of the lesion or a higher number of lesions than expected. Such modifications caused an increase in the duration of the surgery in a lower proportion of subjects on use of PV-MRI or ECCM-MRI (12.8% PV-MRI, only; 16.0% ECCM-MRI, only) compared to CE-CT (29.4% CE-CT, only).

Equal assessments with regard to the number of partially/completely resected segments upon assessment following the 1st consensus meeting and the final diagnosis were given for clearly more subjects in the PV-MRI group (76.6%) than in the CE-CT group (66.7%); upon use of ECCM-MRI an intermediate value was reached (74.3%).

Resource needs for imaging and treatment

Detailed cost analyses by country taking into account differences of the health care systems were planned outside of this report. As a means to evaluate the data, duration of the imaging procedure and, in case of surgery subjects, duration of surgery, increase in the duration of the surgery due to the modification of the surgical plan and stay in (intensive) care were analyzed by initial imaging procedure.

Results Summary — Safety

Safety was analyzed based on the SAF.

The entire study encompassed 188 imaging procedures with PV-MRI, 117 with ECCM-MRI, and 116 with CE-CT.

There was 1 SAE, the death of one subject of the CE-CT group. He died in JUN 2009. Initial imaging using CE-CT performed on 10 DEC 2008 had shown a pancreatic neoplasm. Due to the fatal outcome, the event which was considered unrelated to the administration of the contrast agent, had been recorded as SAE. For another subject jaundice was recorded as serious baseline finding before the 2nd imaging procedure; the event was considered unrelated to the 1st imaging with ECCM.

A total of 6 AEs (including the death) were reported in 4 (1.1%) of the 354 SAF subjects. The other 3 subjects had mild AEs: 1 subject with 2 related AEs (chills, myalgia) in the PV-MRI group and 2 subjects with 2 related AEs (pruritus, urticaria) and 1 unrelated AE (cough) in the CE-CT group.

The 2 types of AEs reported following PV-MRI were comparable to those already known after PV or ECCM use and gave no reasons for concern due to any new or unexpected AEs. Therefore, the acceptable safety profile was confirmed.

Conclusion(s)

For the further workup of subjects with known or suspected metachronous liver metastases secondary to colorectal cancer, PV-MRI in this study of 354 subjects, proved to be superior to ECCM-MRI and CE-CT. In these subjects, none of the investigators required another imaging method to come to a therapy decision following PV-MRI.

In addition, upon use of Primovist the investigators were highly confident in their decision. The diagnostic performance in subjects with liver surgery, using a segment based approach, was superior to CE-CT, and, to a lower extent, also to ECCM-MRI. The number of subjects with intraoperatively modified surgical plans as well as the number in which such a modification caused an increase in the duration of the surgery was lowest in the PV-MRI group, showing a clear advantage compared to CE-CT. The results indicate cost savings due to imaging with Primovist; reductions in resource needs will be analyzed separately based on country-specific health care data.

AE records confirmed the known acceptable safety profile of Primovist.

Publication(s):	None		
Date Created or Date Last Updated:	14 MAY 2012	Date of Clinical Study Report:	16 NOV 2011

Investigational Site List

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Name	Bayer Vital GmbH
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Sponsor in Germany	
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2	Krankenanstalt der Stadt Wien - Rudolfstiftung	Zentralröntgeninstitut Diagnostische und interventionelle Radiologie Juchgasse 25	1030	Wien	AUSTRIA
3	Medizinische Universität Graz	Univ. Klinik für Radiologie Klinische Abteilung für Allgemeine Radiologische Diagnostik Auenbruggerplatz 9	8036	Graz	AUSTRIA

4	Klinikum der Ernst-Moritz-Arndt-Universität	Institut für Diagnostische Radiologie und Neuroradiologie Ferdinand-Sauerbruch-Straße	17489	Greifswald	GERMANY
5	Klinikum der Johann Wolfgang Goethe Universität Frankfurt	Institut für Diagnostische und Interventionelle Radiologie Theodor-Stern-Kai 7	60596	Frankfurt	GERMANY
6	Krankenhaus Dresden-Friedrichstadt	Radiologische Klinik Friedrichstraße 41	01067	Dresden	GERMANY
7	LMU Klinikum der Universität München - Großhadern	Institut für Radiologie Marchioninistraße 15	81377	München	GERMANY
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Product Identification Information

Product Type	Drug
US Brand/Trade Name(s)	Eovist
Brand/Trade Name(s) ex-US	Primovist, EOB-Primovist
Generic Name	Gadoxetate disodium
Main Product Company Code	BAY86-4873
Other Company Code(s)	ZK 139834
Chemical Description	Gadoxetic acid disodium: (4S)-4-(4-Ethoxybenzyl)-3,6,9-tris(carboxylatomethyl)-3,6,9-triazaundecanedioic acid, Gadolinium-Complex, Disodium salt
Other Product Aliases	Gd-EOB-DTPA

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