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.

Clinical Trial Results Synopsis

Date of report:	15 Oct 2013
Study title:	An open label, multi-center, phase 3 study with corresponding blinded image reading to determine the efficacy and safety of a single intravenous injection of 0.1 mmol/kg body weight of gadobutrol 1.0 molar (Gadovist®) in patients with newly diagnosed breast cancer referred for contrast-enhanced breast MRI
Sponsor's study number:	91743
NCT number:	NCT01067976
EudraCT number:	2009-009597-27
Sponsor:	Bayer Pharmaceuticals Inc.
Clinical phase:	3
Study objectives:	Objectives described as primary and secondary in this report are those that were defined after database closure in the supplemental statistical analysis plan (SAP). The primary objectives were to demonstrate: 1. Superiority of within-patient sensitivity of combined unenhanced and gadobutrol-enhanced breast MRI (CMRM) over unenhanced breast MRI (UMRM) 2. Breast level specificity of CMRM, based on non-malignant breasts, greater than a performance threshold of 80%. The secondary objectives as defined in the supplemental SAP were to evaluate: 1. Breast level specificity of CMRM, based on malignant breasts, greater than a performance threshold 50% 2. Detection of index cancers using CMRM compared with XRM, UMRM, and CMRM+XRM based on a patient level 3. Detection of additional cancer using CMRM compared with XRM, UMRM, and CMRM+XRM based on a patient level.

Study objectives (continued):	Protocol-defined primary objectives of this study were to demonstrate: 1. Superiority of CMRM versus UMRM 2. Superiority of CMRM plus X-ray mammography (XRM) versus UMRM plus XRM based on categorical accuracy for malignant breast disease on breast region level with 3 categories (unifocal, multifocal malignant disease or no malignant disease present) and verified by the predefined standard of truth (SoT). Protocol-defined secondary objectives were to evaluate categorical accuracy using breast regions with SoT based on histology only, sensitivity and specificity (for malignant breast disease, unifocal malignant disease, and multifocal malignant disease), accuracy of the presence of multicentric malignant disease and bilateral malignant disease and confidence in the diagnosis.
Test drug: **Name of active ingredient:** **Dose:** **Route of administration:** **Duration of treatment:**	Gadovist®1.0 (Gadobutrol 1.0 molar) Gadobutrol (Bay no. 86-4875) 0.1 mmol/kg intravenous (IV) single dose
Reference drug:	None
Indication:	CMRM to assess malignant breast disease
Diagnosis and main criteria for inclusion:	Patients with histologically confirmed breast cancer referred to CMRM prior to surgery after XRM.
Methodology	This study is a Multi-center, open-label, non-randomized, corresponding blinded reading study. Breast MRI performed with 1.5 T MRI scanners and dedicated breast coils enabling bilateral breast imaging. Randomized blinded image evaluation by 3 independent MRI readers experienced in XRM reads as well; onsite image evaluation by investigators; randomized evaluation of XRM image sets by 3 independent blinded XRM readers.
Standard of reference	SoT: Histopathology or alternatively XRM plus ultrasound.
Study centers:	28 recruiting study centers in 7 countries : Germany (9), United States (6), Italy (4), South Korea (4), Colombia (2), Finland (2), and Switzerland (1)

Publication based on the study (references):	None
Study period:	First subject, first visit: 19 FEB 2010 Last subject, last visit: 14 JUL 2011
Early termination	No
Number of subjects:	Planned: 440 patients Analyzed: 446 screened and enrolled, 426 patients in the safety analysis set, 390 patients in the full analysis set (FAS), and 335 patients in the per protocol set (PPS); for more details see section on study patients below.
Criteria for evaluation **Efficacy:**	Co-primary efficacy parameters (supplemental SAP): − Within-patient sensitivity comparison of CMRM to UMRM − Breast level specificity of CMRM, based on non-malignant breasts, greater than a performance threshold of 80%. Secondary efficacy parameters (supplemental SAP): − Breast level specificity for malignant breasts (greater than a performance threshold of 50% for CMRM) − Detection of index cancers on a patient level − Detection of additional cancers on a patient level. Protocol-defined primary efficacy parameters: Categorical accuracy in the determination of malignant breast disease based on regions verified by SoT. Categorical accuracy was defined as the proportion of correct matches of the imaging modality to the SoT for the extent of malignant breast disease. The co-primary comparisons were based on the difference in categorical accuracy for extent of malignant breast disease for CMRM versus UMRM and CMRM+XRM versus UMRM+XRM.
	Protocol-defined secondary efficacy parameters: − Categorical accuracy in the determination of malignant breast disease based on the comparison of CMRM+XRM versus XRM − Categorical accuracy in the determination of malignant breast disease verified by histopathology − Sensitivity and specificity in the determination of malignant breast disease, unifocal breast disease and multifocal breast disease

Criteria for evaluation **Efficacy (continued):**	− Multicentric malignant breast disease by breast − Bilateral malignant disease by patient − Confidence in diagnosis − Inter-reader agreement − Intra-reader variability.
Safety:	AEs, laboratory parameters, and vital signs.
Other:	Not applicable.
Statistical methods:	Efficacy analyses (supplemental SAP): Within-patient sensitivity was defined as the proportion of malignant breast regions within a patient that were recognized by the reader using the respective imaging modality as malignant. Subsequently the mean over all these within-patient sensitivities was calculated. Breast level specificity for non-malignant breasts was defined as number of true negative breasts divided by number of non-malignant breasts in a patient. Subsequently the mean over all patients who contributed with at least one non-malignant breast was calculated. Protocol -defined analyses: The categorical accuracy of assessing the extent of malignant breast disease was analyzed using a method which took into account the non-independence within patients by treating the regions within a patient as a “cluster” when statistical inference and estimates were made. The technique took into account the clustering effect using the Clustered McNemar Test.
Substantial protocol changes:	The supplemental SAP for this study, which re-defined the study objectives and replaced the protocol-defined parameters based on categorical accuracy, was implemented after the conclusion of all protocol defined safety and efficacy assessments. For this reason, no formal amendment to the study protocol was made. The clinical database was not changed. The supplemental SAP is based upon data review of the protocol-defined results and discussions that included advice from the FDA.

Study patients

A total of 446 patients were screened and enrolled at 28 recruiting study centers in 7 countries. Of those, 426 patients received any study treatment and were considered in the safety population. In all, 424 patients completed the study course; 2 patients prematurely discontinued the study after having received the study drug, because they withdrew informed consent without specifying any reasons.

The first patient in each center was defined as test patient and was to be excluded from the efficacy analyses. In total, 28 test patients were excluded from the full analysis set (FAS). Another 8 patients were excluded from the FAS because of missing XRM, CMRM or UMRM, recorded as major protocol deviation. Thus, the FAS encompassed 390 patients.

Another 55 patients with major protocol violations considered to interfere with the primary objectives of the study had to be excluded. The remaining population without major protocol deviations made up the PPS, comprising a total of 335 patients.

Efficacy evaluation

The aim of this study was to show the diagnostic utility of CMRM for the detection of malignant breast disease and the subsequent surgical planning. Patients were included who had been recently diagnosed with a histologically confirmed breast cancer who were referred for breast MRI and had a recent XRM available for comparison prior to breast cancer surgery. Following an unenhanced breast MRI, patients received a single dose of gadobutrol at the standard dose of 0.1 mmol/kg bw for contrast-enhanced MRI.

Efficacy analyses (supplemental SAP)

For sensitivity, patient-level analyses were utilized. Within-patient sensitivities following CMRM ranged from 79.9% to 86.7%, with a median reader value of 83.2%. The sensitivity of UMRM ranged from 36.6% to 63.4%, with a median reader value of 49.1%. CMRM had a median reader sensitivity which was 34.1% greater than UMRM which clearly demonstrates the benefit of CMRM. All 3 readers showed a statistically significant difference between CMRM and UMRM (Table 1). Furthermore, CMRM had a higher sensitivity than XRM (83.2% versus 70.6%), and the addition of XRM to CMRM had little impact on the median sensitivity (83.7% for CMRM+XRM versus 83.2% for CMRM, based on the median blinded reader).

Table 1: Overview of efficacy results for CMRM versus UMRM on a patient level by reader (FAS)

Analyses	Reader	CMRM	UMRM	Lower bound of 95% CI for the difference CMRM-UMRM > 0	Superiority of CMRM
Co-primary analyses (supplemental SAP)					
Within-patient sensitivity for detection of	1	83.2	36.6	41.9	Yes
malignant disease (point estimate, %)	2	79.9	49.1	25.7	Yes
(N = 388 patients)	3	86.7	63.4	19.2	Yes
Secondary analyses (supplemental SAP)					
Proportion of patients whose index cancers	1	84.3	36.4	42.3	Yes
were detected (%)	2	81.2	50.3	24.9	Yes
(N = 382 patients)	3	86.9	65.4	16.6	Yes
Proportion of patients where at least one	1	63.2	20.7	30.1	Yes
additional cancer was detected (%)	2	56.3	31.0	13.0	Yes
(N = 87 patients)	3	65.5	27.6	24.8	Yes

Abbreviation: 95% CI = 95% confidence interval
Note: Superiority was indicated when the lower bound of the 95% CI for the difference CMRM - UMRM was above zero.

For specificity, breast level analyses were utilized. Performance thresholds for specificity of >80% and >50% were defined for breasts without cancer (all regions negative by SoT) and breasts with a known malignancy (at least one region positive by SoT) respectively. The performance thresholds were defined separately because both the incidence of additional malignancy as well as the rationale for assessing the ipsilateral versus contralateral breast differ. For CMRM, breast level specificities were above these pre-defined performance thresholds for each blinded reader and for breasts with and without malignancies (Table 2).

Table 2: Overview of efficacy results for CMRM on breast level specificity by reader (FAS)

Analyses	Reader	Point estimate CMRM (%)	Lower bound of 95% CI	Performance threshold	Performance threshold met
Co-primary analyses (supplemental SAP)					
Breast level specificity for non-malignant	1	85.6	82.0	> 80%	Yes
breasts (point estimate, %)	2	95.0	92.8	> 80%	Yes
(N = 372 patients)	3	88.6	85.3	> 80%	Yes
Secondary analyses (supplemental SAP)					
Breast level specificity for malignant breasts	1	61.1	56.3	> 50%	Yes
(point estimate, %)	2	59.4	54.5	> 50%	Yes
(N = 388 patients)	3	58.5	53.6	> 50%	Yes

Abbreviation: 95% CI = 95% confidence interval
Note: Above, number of patients are provided. As most patients contributed with one normal and one diseased breast, differences to number of breasts are negligible.

For index cancer and additional cancers, two analyses were performed on a patient level. The first analysis examined the correct identification of the index cancer by the blinded readers. The index cancer was defined as the cancer positive regions that made the patients eligible for inclusion in the study. An advantage of CMRM over the other modalities was seen for this parameter as the correct detection of index cancer ranged from 81.2% to 86.9% with a median of 84.3% for the 3 blinded readers, while the performance of the next best imaging modality, XRM, was 71.7% for the median blinded reader. The comparison of CMRM to XRM showed statistically significant results in favor of CMRM as indicated by 95% CI that excluded zero for each reader. The addition of XRM to CMRM had no substantial impact on the diagnostic performance of CMRM. Compared to UMRM, with CMRM proportions of correctly identified index cancers were 21.5% to 47.9% higher, which were statistically significant results in favor of CMRM for each reader (Table 1).

The second analysis looked at the correct identification of patients with additional malignancy. Based on the FAS, 87 patients had at least one additional cancer region, i.e. a malignant breast region that was present according to SoT, not recorded as part of the index cancer for patient inclusion in the trial. With CMRM, 55, 49, and 57 patients (i.e. 63.2%, 56.3%, and 65.5% of the patients) were correctly identified with additional cancer by readers 1 to 3 (Table 1). Adding XRM to CMRM had little impact yielding correct identifications of additional cancer in 57 patients (65.5%) by reader 1 and unchanged patient numbers by readers 2 and 3. With XRM, approximately half the number of patients were correctly identified, 23, 23, and 30 patients (26.4% to 34.5%) depending on the blinded reader. Differences in favor of CMRM were between 29.9% to 36.8% compared to XRM and between 25.3% to 42.5% compared to UMRM. Again, the 95% CI excluded zero in all comparisons which indicated statistically significant differences.

Protocol-defined efficacy analyses

The primary analyses defined in the study protocol were based on differences in categorical accuracy between CMRM versus UMRM and CMRM+XRM versus UMRM + XRM, respectively. Categorical accuracy was defined as the proportion of correct matches of the imaging modality to the SoT for the extent of malignant breast disease. Analyses were performed on a regional basis with 5 regions per breast. The protocol-defined co-primary comparisons demonstrated a statistically significant difference in favor of UMRM and UMRM+XRM compared to CMRM and CMRM+XRM, respectively, based on the majority blinded reader results for both the FAS and PPS (see Table 3 that summarizes majority reader results on accuracy).

Table 3: Overview of majority reader results on (categorical) accuracy by parameter and imaging modalities (FAS)

Parameter	Imaging modalities	Point estimates (%)	
Protocol-defined co-primary analyses			
Categorical accuracy of extent of malignant disease (breast region level, 3883 regions)	CMRM versus UMRM	86.7	87.9
	CMRM+XRM versus UMRM+XRM	86.4	89.5
Protocol-defined secondary analyses			
Categorical accuracy of extent of malignant disease (breast region level, 3883 regions)	CMRM+XRM versus XRM	84.8	89.0
Categorical accuracy of extent of malignant disease based on histopathology as SoT, only (breast region level, 1120 regions)	CMRM versus UMRM	69.6	63.2
	CMRM+XRM versus UMRM+XRM	68.9	71.8
	CMRM+XRM versus XRM	68.9	67.8
Accuracy of presence of multicentric disease (breast level, 777 breasts)	CMRM versus UMRM	88.4	93.6
	CMRM+XRM versus UMRM+XRM	88.2	93.2
	CMRM+XRM versus XRM	88.2	92.0
Accuracy of presence of bilateral disease (patient level, 388 patients)	CMRM versus UMRM	93.0	96.4
	CMRM+XRM versus UMRM+XRM	92.5	95.9
	CMRM+XRM versus XRM	92.5	93.3

The majority blinded reader results of the protocol-defined secondary analyses (on a breast region level, 643 regions) demonstrated a statistically significant and clinically relevant higher sensitivity for CMRM alone (82.4%) or in combination with XRM (82.7%) compared to the other imaging modalities (47.9% for UMRM, 65.3% for XRM, and 70.5% for UMRM+XRM) for detection of SoT-confirmed malignancies. The specificities of CMRM (90.7%) and CMRM+XRM (90.5%) were lower than XRM (94.7%) as well as for UMRM (97.2%) and UMRM+XRM (95.4%) (Table 4).

Specificity (summarized in Table 4) drove the outcome for the (categorical) accuracy parameters due to the very high number of disease-free regions (3240 normal of 3883 regions, i.e. approximately 83%). The composite parameter (categorical) accuracy was not a suitable analysis to show the clinical usefulness of gadobutrol in breast MRI.

Table 4: Overview of majority reader results on sensitivity and specificity by parameter and imaging modalities on a breast region level (FAS)

Parameter	Imaging modalities	Point estimates (%)	
Protocol-defined secondary analyses			
Sensitivity to detect malignant breast disease (643 regions)	CMRM versus UMRM	82.4	47.9
	CMRM+XRM versus UMRM+XRM	82.7	70.5
	CMRM+XRM versus XRM	82.7	65.3
Sensitivity to detect unifocal malignant breast disease (576 regions)	CMRM versus UMRM	70.0	45.3
	CMRM+XRM versus UMRM+XRM	69.3	65.8
	CMRM+XRM versus XRM	69.3	57.5
Sensitivity to detect multifocal malignant breast disease (67 regions)	CMRM versus UMRM	38.8	7.5
	CMRM+XRM versus UMRM+XRM	38.8	10.4
	CMRM+XRM versus XRM	38.8	20.9
Specificity to rule out malignant breast disease (3240 regions)	CMRM versus UMRM	90.7	97.2
	CMRM+XRM versus UMRM+XRM	90.5	95.4
	CMRM+XRM versus XRM	90.5	94.7
Specificity to rule out unifocal malignant breast disease (3307 regions)	CMRM versus UMRM	89.7	95.4
	CMRM+XRM versus UMRM+XRM	89.4	93.7
	CMRM+XRM versus XRM	89.4	93.2
Specificity to rule out multifocal malignant breast disease (3816 regions)	CMRM versus UMRM	87.6	89.4
	CMRM+XRM versus UMRM+XRM	87.3	90.9
	CMRM+XRM versus XRM	87.3	89.1

Multicentric malignant disease was present in 53 of the 777 breasts. For those, compared to UMRM, with CMRM the detection of multicentric malignant disease improved from 4 to 25 correctly identified breasts. For the majority reader, this is an increase in sensitivity of 39.6% (from 7.5% with UMRM to 47.2% with CMRM).

For the 16 of 388 patients with SoT confirmed bilateral disease, from UMRM to CMRM the number of correctly identified patients increased from 2 to 10 patients, corresponding to an increase in sensitivity of 50.0% for the majority reader (from 12.5% with UMRM to 62.5% with CMRM). Increases in diagnostic confidence based on a 4-point scale from 1 (not confident) to 4 (very confident) ranged from 0.32 to 1.42 for the majority reader, resulting in average scores of 3.42 for CMRM and 3.45 for CMRM+XRM.

The inter-reader agreement on categorical accuracy based on the assessment CMRM versus UMRM was judged with a kappa of 0.48, i.e. “moderate agreement”. Intra-reader variability based on CMRM, evaluated on a breast level, resulted in kappa values of 0.19 to 0.26, i.e. in fair to poor agreement for all blinded readers.

Safety evaluation

Gadobutrol administered at a standard dose of 0.1 mmol/kg body weight via a power injector was well tolerated. There were no deaths and no SAEs. Of the 426 patients in the safety population, 35 patients (8.2%) experienced non-serious treatment-emergent AEs. Only 7 patients (1.6%) were recorded to have drug-related treatment-emergent AEs.

The safety data is consistent with the known safety profile of gadobutrol.

Overall conclusions

Results of this clinical study support the clinical usefulness of gadobutrol-enhanced breast MRI at the standard dose of 0.1 mmol/kg body weight for the assessment of malignant breast disease.

The protocol-defined co-primary parameters, based on an analysis of categorical accuracy by breast region, demonstrated significantly lower performance for CMRM and CMRM+XRM compared to UMRM and UMRM+XRM respectively. These analysis results were due to lower specificity values for CMRM coupled with a high percentage of disease-free regions.

Protocol-defined secondary analyses demonstrated that the detection of malignancy on a breast region level was statistically significantly higher for CMRM compared to UMRM, and that the specificity of CMRM was above 90% for the majority reader. These breast-regional results formed the basis for revision of the protocol-defined co-primary parameters in a supplemental analysis plan which considered sensitivity on a patient level and specificity on a breast level.

The primary parameters based on the supplemental analysis plan demonstrated that the detection of malignancy with CMRM was statistically significantly improved over unenhanced imaging. The addition of XRM to CMRM did not substantially improve the detection of malignancy by CMRM. The analysis of breast level specificity of CMRM, based on breasts without cancer, exceeded the defined performance threshold of 80%.

No safety issues were identified in the patients with breast cancer.

Investigational Site List

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Name	Bayer Vital GmbH
Postal Address	D-51368 Leverkusen Germany
Sponsor in Germany (if applicable)	
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Product Identification Information

Product Type	Drug
US Brand/Trade Name(s)	Gadavist
Brand/Trade Name(s) ex-US	Gadovist
Generic Name	Gadobutrol
Main Product Company Code	BAY86-4875
Other Company Code(s)	ZK 135079
Chemical Description	10–[(1SR,2RS)–2,3–dihydroxy–1–hydroxymethylpropyl]–1,4,7,10–tetraazacyclododecane–1,4,7–triacetic acid, gadolinium complex
Other Product Aliases	

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