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:	17 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:	91782
NCT number:	NCT01104584
EudraCT number:	2009-009598-90
Sponsor:	Bayer Pharmaceuticals Inc.
Clinical phase:	3
Study objectives:	Objectives described as primary and secondary in this report are those that were defined prior to database closure in an amendment of the statistical analysis plan (SAP). All efficacy assessments were performed as described in the study protocol and its amendments. No changes of the clinical database had been performed. 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 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 4. Confidence in 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 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:	39 recruiting study centers in 8 countries: Germany (8), United States (7), Poland (5), Spain (5), Canada (3), Argentina (3), India (3), and Taiwan (5)
Publication based on the study (references):	None
Study period:	First subject, first visit: 16 MAY 2010 Last subject, last visit: 28 SEP 2011
Early termination	No
Number of subjects:	Planned: 440 patients Analyzed: 460 screened and enrolled, 439 patients in the safety analysis set, 397 patients in the full analysis set (FAS), and 351 patients in the per protocol set (PPS); for more details see section on study patients below.

Criteria for evaluation	
Efficacy:	Co-primary efficacy parameters: − 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: − 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 − Confidence in diagnosis Additional efficacy parameters: − Point estimates for the primary and secondary objectives for the imaging modalities UMRM, XRM, CMRM+XRM, and UMRM+XRM − Breast level specificity of CMRM based on all breasts − Sensitivity and specificity in the determination of malignant breast disease, unifocal breast disease and multifocal breast disease − Detection of multicentric malignant breast disease by breast − Detection of bilateral malignant disease by patient − Inter-reader agreement − Intra-reader variability.
Safety:	AEs, laboratory parameters, and vital signs.
Other:	Not applicable.
Statistical methods:	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. The study was considered successful if both null hypotheses of co-primary parameters were rejected by the same 2 blinded readers.

Substantial protocol changes:	The SAP amendment, 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 prior to database closure and breaking the blind. For this reason, no formal amendment to the study protocol was made. The clinical database was not changed. The SAP amendment is based upon data review of results of an identical clinical study within the framework of the "GEMMA" program and discussions that included advice from the Food and Drug Administration (FDA).

Study subjects

A total of 460 patients were screened and enrolled at 39 recruiting study centers in 8 countries. Of those, 439 patients received any study treatment and were considered in the safety population. In all, 437 patients completed the study course; for 2 patients due to a technical failure the exact amount of gadobutrol administered could not be determined.

The first patient in each center was defined as test patient and was to be excluded from the efficacy analyses. In total, 39 test patients were excluded from the full analysis set (FAS). Another 3 patients were excluded from the FAS because of missing XRM, CMRM or UMRM, recorded as major protocol deviation. Thus, the FAS encompassed 397 patients.

Another 46 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 351 patients.

Efficacy

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.

Co-primary efficacy analyses

The overall success criterion of the study was met as the pre-specified null hypotheses of both co-primary parameters were rejected by the same 2 blinded readers.

As one of the co-primary analyses, superiority of within-patient sensitivity was clearly shown for all 3 blinded readers (Table 1). Differences in sensitivity in favor of CMRM compared to UMRM ranged from 15.2% to 31.9%. The null hypothesis could be clearly rejected for all 3 blinded readers as the lower bound of the 95% CI for the difference was larger than zero for each reader.

Table 1: Within-patient sensitivity for detection of malignant disease for CMRM versus UMRM on a patient level by reader (FAS)

Co-primary analysis	Reader	CMRM	UMRM	Lower bound of 95% CI for the difference CMRM-UMRM > 0	Superiority of CMRM
Within-patient sensitivity for detection of	1	88.6	73.3	11.8	Yes
malignant disease (point estimate, %)	2	89.0	57.0	27.3	Yes
(N = 390 patients)	3	85.5	55.1	25.8	Yes

Abbreviation: 95% CI = 95% confidence interval
Note: Superiority was indicated when the lower bound of the 95% confidence intervals was above zero.

In an additional efficacy analysis, CMRM resulted in better within-patient sensitivity values compared to XRM alone (increases ranging from 12.3% to 19.0%). The addition of XRM to CMRM had little impact on sensitivity values observed for each of the blinded readers (88.6% versus 89.6%, 89.0% versus 90.3%, and 85.5% versus 88.0% for CMRM versus CMRM+XRM by readers 1, 2, and 3, respectively).

For specificity, breast level analyses were utilized. For the second co-primary analysis, breast level specificity based on non-malignant breasts (all regions negative by SoT) was evaluated. Breast level specificity of CMRM met the 80% pre-defined performance thresholdfor 2 of the 3 blinded readers. The null hypothesis could be rejected as the lower bound of the 95% CI was >80% for reader 1 (89.1%) and reader 2 (80.2%); this threshold was slightly missed by reader 3 with a lower limit of the 95% CI of 79.0% (Table 2).

Table 2: Breast level specificity of CMRM based on non-malignant breasts by reader (FAS)

Co-primary analysis	Reader	Point estimate CMRM (%)	Lower bound of 95% CI	Performance threshold	Performance threshold met
Breast level specificity for non-malignant	1	91.8	89.1	> 80%	Yes
breasts (point estimate, %)	2	83.9	80.2	> 80%	Yes
(N = 367 patients)	3	82.8	79.0	> 80%	No

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

Secondary efficacy analyses

A performance threshold for specificity of >50% was defined for breasts with a known malignancy (at least one region positive by SoT). 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 specificity based on malignant breasts was greater than the threshold of 50% defined by the lower limit of the 95% CI for reader 3 (50.6%) and just under this performance threshold for reader 1 (49.9%). For reader 2 the null hypothesis could not be rejected as the lower bound of the 2-sided 95% CI was 42.2%, below the 50% threshold (Table 3).

Table 3: Breast level specificity of CMRM based on malignant breasts by reader (FAS)

Secondary analysis	Reader	Point estimate CMRM (%)	Lower bound of 95% CI	Performance threshold	Performance threshold met
Breast level specificity for malignant breasts	1	54.9	49.9	> 50%	No
(point estimate, %)	2	47.2	42.2	> 50%	No
(N = 390 patients)	3	55.5	50.6	> 50%	Yes

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

For index cancer and additional cancers, analyses were performed on a patient level. The index cancer was defined as the cancer positive regions that made the patients eligible for inclusion in the study. An advantage of CMRM was seen with 85.6% to 89.2% of patients where all index cancers were detected (Table 4), while UMRM and XRM resulted in lower proportions of the patients with correctly identified index cancers (UMRM 54.6% to 73.7%; XRM 69.3% to 75.0% depending on the blinded reader). For each reader, these were statistically significant results in favor of CMRM. The addition of XRM to CMRM had no substantial impact on the diagnostic performance of CMRM.

Table 4: Proportions of patients with index cancer and additional cancer for CMRM versus UMRM on a patient level by reader (FAS)

Secondary analyses	Reader	CMRM	UMRM	Lower bound of 95% CI for the difference CMRM-UMRM > 0	Superiority of CMRM
Proportion of patients whose index cancers	1	89.2	73.7	11.1	Yes
were detected (%)	2	88.9	58.8	25.0	Yes
(N = 388 patients)	3	85.6	54.6	25.6	Yes
Proportion of patients where at least one	1	69.0	45.2	12.4	Yes
additional cancer was detected (%)	2	78.6	34.5	31.7	Yes
(N = 84 patients)	3	67.9	33.3	22.6	Yes

Abbreviation: 95% CI = 95% confidence interval
Note: Superiority was indicated when the lower bound of the 95% confidence intervals was above zero.

The analysis of additional cancers was based on 84 patients in the FAS who had at least one additional cancer region, i.e. a malignant breast region that was present according to SoT, but not recorded as part of the index cancer for patient inclusion in the trial. With CMRM, 58, 66, and 57 patients (i.e. 69.0%, 78.6%, and 67.9% of the patients, Table 4) were correctly identified with additional cancer by readers 1 to 3. Adding XRM to CMRM had little impact yielding correct identifications of additional cancer in 2 more patients by reader 3 and unchanged patient numbers by readers 1 and 2. With XRM, approximately half the number of patients were correctly identified, 22, 25, and 35 patients (26.2% to 41.7%) by readers 1 to 3. Differences in favor of CMRM were between 26.2% to 48.8% compared to XRM and between 23.8% to 44.0% compared to UMRM. The 95% CI excluded zero in all comparisons which indicated statistically significant differences.

Diagnostic confidence was assessed based on a 4-point scale from 1 (not confident) to 4 (very confident). Increases in diagnostic confidence with CMRM compared to UMRM ranged from 0.95 to 1.73, resulting in average scores of 2.09 to 2.86 for CMRM. Each of these comparisons was statistically significant with p-values < 0.001 from the paired t-test.

Additional efficacy analyses

For CMRM, the lower bound of the 95% CI for breast level specificity based on all breasts ranged from 61.9% to 70.2%.

Sensitivity of detection of malignant breast disease on a breast region level was based on the 630 regions that were assessed to have malignant disease as verified by the SoT. Sensitivity rates improved considerably based on enhanced compared to unenhanced image sets (Table 5); results were of statistical significance for all 3 blinded readers as the 95% CI excluded zero.

For CMRM and UMRM breast region level specificities to rule out malignant breast disease, unifocal malignant breast disease and multifocal breast disease are presented (Table 5). Values were slightly decreased for CMRM compared to UMRM.

Multicentric malignant disease was present in 44 of the 769 breasts. With CMRM, sensitivity to detect multicentric malignant disease was 72.7% to 88.6%. Compared to UMRM, this was a statistically significant difference in case of all 3 blinded readers ($p < 0.001$) (Table 5).

For the 14 of the 380 patients with SoT confirmed bilateral disease, with CMRM sensitivity ranged from 78.6% to 85.7%. On comparison of CMRM to UMRM, this was a statistically significant difference in favor of CMRM for all 3 blinded readers ($p < 0.001$) (Table 5).

The inter-reader agreement on sensitivity based on the assessment CMRM versus UMRM was judged with a kappa of 0.47, i.e. “moderate agreement”. Intra-reader variability based on CMRM, evaluated on a breast level, resulted in kappa values of 0.21 to 0.25, i.e. in fair to poor agreement for all blinded readers.

Table 5: Overview of results on sensitivity and specificity by parameter for CMRM versus UMRM (FAS)

Parameter	Reader	Point estimates (%)		
		CMRM	UMRM	
Sensitivity				**Superiority of CMRM [a]**
- to detect malignant breast disease (630 regions)	1	85.9	68.4	Yes
	2	87.3	52.4	Yes
	3	82.5	50.5	Yes
- to detect unifocal malignant breast disease (570 regions)	1	50.7	56.5	No
	2	51.6	47.0	No
	3	65.4	46.0	Yes
- to detect multifocal malignant breast disease (60 regions)	1	71.7	25.0	Yes
	2	60.0	8.3	Yes
	3	41.7	10.0	Yes
- to detect multicentric malignant disease (44 breasts)	1	88.6	40.9	Yes [b]
	2	86.4	29.5	Yes [b]
	3	72.7	25.0	Yes [b]
- to detect bilateral malignant breast disease (14 patients)	1	78.6	0.0	Yes [c]
	2	85.7	7.1	Yes [c]
	3	85.7	0.0	Yes [c]
Specificity				
- to rule out malignant breast disease (3197 regions)	1	89.5	93.6	
	2	86.2	94.7	
	3	88.3	94.4	
- to rule out unifocal malignant breast disease (3257 regions)		89.2	92.4	
		85.8	93.1	
		87.4	92.8	
- to rule out multifocal malignant breast disease (3767 regions)		83.6	88.0	
		81.0	87.5	
		84.8	87.1	

a For sensitivity, superiority of CMRM over UMRM was indicated when the lower bound of the 95% confidence interval for the difference CMRM-UMRM was > 0. The confidence interval was adjusted for clustering effect using the Clustered McNemar Test.
b p-values < 0.001, adjusted for clustering effect using the Clustered McNemar Test.
c p-values < 0.001 based on the McNemar test.

Safety

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 439 patients in the safety population, 25 patients (5.7%) experienced non-serious treatment-emergent AEs. Only 8 patients (1.8%) 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 the extent of malignant breast disease. The overall success criterion of the study was met as the null hypotheses of both co-primary parameters were rejected by the same 2 blinded readers.

The detection of malignancy by CMRM was statistically significantly improved over unenhanced imaging as demonstrated by results for sensitivity on a breast region, breast and patient level. The addition of XRM to the 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.

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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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