Clinical Study Synopsis

This Clinical Study Synopsis is provided for patients and healthcare professionals to increase the transparency of Bayer's clinical research. This document is not intended to replace the advice of a healthcare professional and should not be considered as a recommendation. Patients should always seek medical advice before making any decisions on their treatment. Healthcare Professionals should always refer to the specific labelling information approved for the patient's country or region. Data in this document or on the related website should not be considered as prescribing advice.
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:	91780	NCT00764387
Study Phase:	IV Interventional	
Official Study Title:	Contrast-enhanced MRI examination of cerebral neoplastic enhancing lesions: comparison of diagnostic efficacy of Gd-DOTA 0.5 M and Gd-D3A-Butrol 1.0 M at 0.1 mmol Gd/kg body weight: Intra-individual comparison clinical study	
Therapeutic Area:	Diagnostic Imaging	
Test Product		
Name of Test Product:	Gadobutrol (Gadovist, BAY86-4875)	
Name of Active Ingredient:	Gadobutrol, SH L 562 BB	
Dose and Mode of Administration:	0.1 mmol/kg body weight (BW) = 0.1 mL/kg BW	
Reference Therapy/Placebo		
Reference Therapy:	Dotarem 0.5 mmol/mL solution for injection (Gd-DOTA)	
Dose and Mode of Administration:	0.1 mmol/kg BW = 0.2 mL/kg BW	
Duration of Treatment:	Single bolus injection	
Studied period:	Date of first subjects' first visit:	04 Mar 2008
	Date of last subjects' last visit:	05 May 2009
Study Center(s):	12 study centers in Italy	

Methodology:	Qualitative and quantitative enhancement in T1 and T2-weighted MR scans were evaluated in the enhancing lesions. Intraindividual comparison between both contrast media were performed by on-site and off-site
Indication/ Main Inclusion Criteria:	Patients (men or women of any ethnic group) with known cerebral intra and extra axial neoplastic lesions (primitive and secondary enhancing lesions) who were scheduled for contrast-enhanced MRI for diagnostic work-up.
Study Objectives:	Overall: Not applicable. Primary: To compare Gadovist (Gd-D3A-Butrol, 0.1 mL/kg BW) to Dotarem (Gd-DOTA, 0.2 mL/kg BW) regarding the overall preference following the qualitative assessment of brain enhancing tumors in post-contrast (T1-weighted) acquisitions. Secondary: Comparison of Gd-D3A-Butrol and Gd-DOTA qualitatively in terms of lesion enhancement, lesion delineation and internal structure, and quantitatively in terms of signal intensity measurements; safety.
Evaluation Criteria:	Efficacy (Primary): Primary efficacy evaluation: Overall preference for Gd-D3AButrol or Gd-DOTA or neither of them following a qualitative assessment of lesion enhancement. Efficacy (Secondary): Secondary efficacy evaluation: qualitative assessment of lesion enhancement, lesion delineation and internal structure, quantitative assessment of signal intensity measurements. Safety: Adverse event (AE) monitoring, physical examination, vital signs. Pharmacokinetics: Not applicable Other: Not applicable

Statistical Methods:	Efficacy (Primary) : The primary efficacy variable for the study was the "Overall preference for one or other session or neither of them" in the PPS. The evaluation was done using a 3-point scale. The assessment was done in a matched-pairs assessment comparing all MR images of a patient after Gd-D3A-Butrol and Gd-DOTA administration. Assessments were provided by 3 independent and blinded readers and combined for the primary efficacy analysis. The primary efficacy variable was tested by a 2-sided Wilcoxon signed rank test with a level of significance of 5%. Efficacy (Secondary) : Secondary efficacy variables for the study and the blinded reading are listed above Results of the individual blinded readers, which formed the basis of the primary analysis, were analysed as part of the secondary efficacy evaluation. The variability among the blinded readers was evaluated by pair wise kappa coefficients. All secondary efficacy variables were analyzed on the PP population. A secondary ITT analysis on the FAS was performed to assess the reliability of the conclusions from the primary PP analysis. The ITT analysis was planned to be performed when the number of patients in the PP and the FAS differed by more than 10%. All p-values for secondary endpoints were of descriptive (hypothesis-generating) character and cannot be used for confirmatory purposes. Following secondary variables were evaluated qualitatively (analogous to the primary efficacy endpoint): ▪ Overall enhancement defined as increased difference in contrast between lesion andsurrounding tissue in post-contrast T1-weighted images ▪ Lesion delineation from surrounding tissue and edema ▪ Information on internal structure The analysis was provided analogous to the primary analysis of the primary efficacy variable. Following secondary variables were evaluated quantitatively: ▪ Total number of enhancing lesions (off-site read) and all lesions (on-site read) ▪ Signal intensity of enhancing lesions (> 10 pixels at least), normal tissue and background Descriptive statistics were provided comparing the 2 contrast agents. Safety: Descriptive statistics were performed. Pharmacokinetics: Not applicable. Other : Not applicable.

Number of Subjects:	166

Study Results

Results Summary — Subject Disposition and Baseline

A total of 166 patients were enrolled in 12 centers in Italy. Depending on the treatment order, patients were either randomized to the Gd-D3A-Butrol first group (treatment sequence Gd-D3A-Butrol in the 1st MRI followed by Gd-DOTA in the 2nd MRI) or to the Gd-DOTA first group (treatment sequence Gd-DOTA in the 1st MRI followed by Gd- D3A-Butrol in the 2nd MRI).
Six (6) patients (3 in each treatment group) had to be regarded as dropouts, as they did not receive any study medication.
The 160 patients who received Gd-D3A-Butrol or Gd-DOTA for their 1st MRI, formed the safety set valid for the safety analyses.
Of those, 151 patients completed the entire study and received also contrast agent for the 2nd MRI, whereas 9 patients terminated the study prematurely before their 2nd MRI was performed:

- Three (3) patients withdrew their informed consent.
- Three (3) patients did not meet all inclusion/exclusion criteria (in 2 patients the 1st MRI showed only ischemic lesions, in 1 patient instead of the 2nd MRI a CT had been performed)
- In case of 2 patients a major surgery had to be performed before the 2nd MRI
- One (1) patient was lost to follow-up

To be eligible for the efficacy analyses, patients had to present with images following both contrast agent administrations. Despite the 9 patients who terminated the study prematurely, another patient had to be excluded from the efficacy analysis, as his 2nd MRI was performed without contrast enhancement T1 sequences. Thus, the FAS encompassed 150 patients.
The PPS encompassed 136 patients; another 14 patients were excluded from the PPS analysis due to major protocol deviations.

Results Summary — Efficacy

Primary efficacy variable:
The primary efficacy variable was the overall preference for Gd-D3A-Butrol or Gd-DOTA by the median blinded reader in the PPS. Superiority of Gd-D3A-Butrol compared to Gd-DOTA was demonstrated by a p-value of 0.0004 (2 sided Wilcoxon signed rank test).
In detail, a preference of Gd-D3A-Butrol compared to Gd-DOTA was given for 42 patients (31.8%) compared to an overall preference for Gd-DOTA for only 16 patients (12.1%). For 74 patients (56.1%) no preference for one or the other contrast agent was given. This result of the median blinded reader was based on those 132 patients of the 136 patients in the PPS who had enhancing cerebral lesions and evaluable images following both MRI examinations.

Secondary efficacy parameters:
Overall preference
The result of the median blinded reader (primary efficacy parameter) was based on the qualitative assessment of 3 blinded readers. In a matched-pairs assessment on all images of both MRI examinations of a patient, each blinded readers had assessed whether he rated one MRI examination as better, equal or worse than the other.
Overall preference for Gd-D3A-Butrol compared to Gd-DOTA also was indicated by the results of the individual blinded readers, who preferred Gd-D3A-Butrol in a higher number of patients

compared to Gd-DOTA; for 2 of the 3 blinded readers the difference in favor of Gd-D3A-Butrol reached statistical significance both in the PPS and in the FAS ($p<0.05$; please note that these p-values are descriptive only and were provided to aid the interpretation; no adjustment for multiple testing has been performed).
Comparable results in the FAS for the median blinded readers and all 3 individual blinded readers supported the outcome for the primary efficacy variable.
Superiority of Gd-D3A-Butrol over Gd-DOTA was also seen on evaluation of the clinical investigators' results.
As the qualitative assessment of 3 individual blinded readers formed the basis for the primary efficacy parameter, their agreement was analyzed. Inter-reader agreement was judged to be "fair" based on Cohen's kappa coefficient calculated for pairwise comparisons [2].

Overall enhancement

For overall enhancement of lesions superiority of Gd-D3A-Butrol over Gd-DOTA was indicated by p-values <0.05. The result was unanimous independent of the observer (median blinded reader, 3 individual blinded readers, clinical investigator) or study population (PPS and FAS).

Lesion delineation from surrounding tissue and edema

For lesion delineation from surrounding tissue and edema, descriptively the contrast agents were assessed to be equal according to the median blinded reader, all 3 individual blinded readers and the clinical investigators both in PPS and FAS.

Internal structure

Superiority of Gd-D3A-Butrol over Gd-DOTA was indicated when assessing information on the internal structure by the median blinded reader in the PPS and the FAS.
According to the individual blinded readers and the clinical investigators, Gd-D3A-Butrol was also preferred in a higher number of patients compared to Gd-DOTA, but descriptively statistical significance was only reached by reader 1 in the PPS.

Presence, number and change in morphology of lesions

The blinded readers had to give their qualitative assessment only in case of enhancing lesions.
For most patients 1 lesion was identified, with a range of 1 to 21 for reader 1 and a range of 1 to 20 for readers 2 and 3; according to the clinical investigators the range was 1 to 23.
Except for one reader in a single patient, the same number of lesions were recorded following Gd-D3A-Butrol and Gd-DOTA.
A change in the morphology between the 2 MRI examinations, to be recorded by the clinical investigators, was noted for 4 patients on pre-contrast images and for 3 patients on post-contrast images.

Signal intensity

For the quantitative efficacy evaluation signal intensity measurements were performed on-site by a clinical investigator blinded to the contrast agent administration and off-site by a blinded signal intensity reader. Signal intensities were determined on pre-contrast and post-contrast T1-weighted images and were evaluated in terms of lesion-to-brain ratio (LBR), contrast-to-noise ratio (CNR), and relative enhancement (% Enh).
LBR was found to be statistically significantly higher for Gd-D3A-Butrol compared to Gd-DOTA both in the PPS and in the FAS. Also, the relative enhancement was higher under Gd-D3A-Butrol compared to Gd-DOTA, with the difference judged to be of statistical significance in case of the blinded reader.

CNR, calculated only for the blinded reader, showed a higher mean value following Gd-D3A-Butrol (122.7, SD 319.59) compared to Gd-DOTA (93.3, SD 140.65). The difference was not judged to be of statistical significance.

Results Summary — Safety
Of the 166 enrolled patients, safety was evaluated for the 160 patients who had received any amount of contrast agent. Of the safety set, 151 patients had received both contrast agents at a dose of 0.1 mmol/kg BW. For each MRI examination, the observation period started with the injection of the contrast agent up to the end of the follow-up period 20 to 28 hours post-contrast. For the 160 patients 10 AEs were reported, 6 AEs after Gd-D3A-Butrol and 4 AEs after Gd-DOTA. All 10 AEs were assessed to be unrelated, i.e. to have no causal relationship to the contrast agent administered. All AEs were of mild intensity. No death was reported and none of the AEs was serious. None of the AEs was assessed to be a tolerance indicator. The most frequently recorded AE were common cold (3 AEs: 1 Gd-D3A-Butrol, 2 Gd-DOTA) and headache (2 AEs Gd-D3A-Butrol). Nausea (Gd-DOTA), diffuse tremor (Gd-D3A-Butrol), lipotimia presyncope (Gd-D3A-Butrol), anemia (Gd-D3A-Butrol), and cutaneous rash (Gd-DOTA) were single events. The time difference between the injection of the contrast agent and the onset of the AEs was 1 hour to 5 days; for 1 AE (headache), which started on the day of contrast agent administration, the exact onset time was not recorded. For 7 AEs patients received a specific drug treatment and for 1 AE a specific non-drug treatment (transfusion) was performed. The duration of the AEs was 2 days at most. At the end of the study, for all AEs the outcome was given as “resolved/recovered”. The vital signs determined immediately before and after the MRI procedure gave no indications for a clinically significant systematic change due to contrast agent administration.
Results Summary — Pharmacokinetics
Not applicable.
Results Summary — Other
Not applicable.
Conclusion(s)
In a clinical setting, Gd-D3A-Butrol proved to be advantageous compared to Gd-DOTA for the visualization of enhancing brain lesions when using equal Gd doses. Both contrast agents were very well tolerated, thus confirming the known good safety profiles.

Publication(s):	none
Date Created or Date Last Updated:	28 March 2011

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	

Date of last Update/Change: 28 May 2013