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MAJOR PAPER

A Japanese, Multicenter, Open-label, Phase 3 Study to Investigate the Safety and Efficacy of Gadobutrol for Contrast-enhanced MR Imaging of the Central Nervous System

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Purpose: Gadobutrol 1.0 M is macrocyclic gadolinium-based contrast agent for magnetic resonance imaging (MRI). This multicenter, open-label, phase 3 study aimed to investigate the efficacy and safety of gadobutrol-enhanced versus unenhanced MRI in the visualization and diagnosis of central nervous system (CNS) lesions in Japanese patients.

Methods: A total of 223 patients referred for contrast-enhanced MRI of the CNS underwent unenhanced and gadobutrol-enhanced (0.1 mmol/kg body weight) MRI. The unenhanced and combined (unenhanced and enhanced) images were evaluated by three independent readers in a blinded manner for degree of contrast enhancement, border delineation, internal morphology, and number of detected lesions (primary variables), and for primary diagnosis and diagnostic confidence. Final clinical diagnoses were established by an independent truth committee consisting of two neurosurgeons. Sensitivity, specificity, and accuracy were calculated for the detection of malignancy and the preciseness of diagnoses (secondary variables) by comparing the results obtained by the blinded readers and the truth committee.

Results: Gadobutrol enhancement significantly improved three visualization parameters in MR images: contrast enhancement, border delineation, and internal morphology ($P < 0.0001$). Non-inferiority was achieved for mean number of lesions detected. Gadobutrol-enhanced imaging provided significant improvements in sensitivity and accuracy for the detection of malignant disease with no loss in specificity, and also improvements in accuracy of exact match diagnosis and diagnostic confidence. Drug-related adverse events were reported in 6 out of 223 patients (2.7%); all were non-serious.

Conclusion: Gadobutrol is an effective and well-tolerated contrast agent for MR imaging of the CNS.

Keywords: ***phase 3 clinical study, gadobutrol, contrast-enhanced MRI, central nervous system***

Introduction

Gadolinium-based contrast agents (GBCAs) improve contrast in magnetic resonance imaging (MRI). Since gadopentetate dimeglumine was approved as the first GBCA in 1988, combined MR imaging with and without GBCAs constitute the gold standard for imaging of central nervous system (CNS) lesions.[1] CNS lesions with underlying breakdown of the blood-brain-barrier allow GBCAs to leak through, providing contrast enhancement of lesions. Therefore, GBCAs have been

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used to detect and characterize the CNS lesions, such as primary and secondary tumor, inflammation, and demyelination.[1,2]

Gadobutrol (Gadovist: Bayer Healthcare Pharma AG, Berlin, Germany) is a nonionic, paramagnetic, macrocyclic GBCA provided as a 1.0 M solution. Gadobutrol 1.0 M solution has twice the gadolinium content per milliliter compared with standard-concentration GBCAs, which results in half the volume of administration and a more compact contrast bolus to achieve the same enhancement of the T_1 relaxation effect, intensifying signals in T_1-weighted images (T_1 relaxivity = 5.2 L/mmol/s at 1.5 Tesla, 37°C in human plasma).[3–7] The safety and tolerability of gadobutrol have been shown in clinical trials and post-marketing evidence.[8–13] As a macrocyclic agent, gadobutrol is more stable compared with linear GBCAs, which are associated with an increased risk of nephrogenic systemic fibrosis in patients with severely impaired renal function.[11,14–16]

This Japanese study was prospectively planned in reference to another global confirmatory study for the general CNS indication performed in the United States, South America, China, and Korea, in which the efficacy of gadobutrol was demonstrated.[8] The primary objectives of this study were to demonstrate that the efficacy and safety of gadobutrol in CNS MRI is also evident in Japanese patients.

Materials and Methods

Study design

This study was a multicenter (15 study centers in Japan), open-label, controlled study with blinded image evaluation. The protocol was reviewed and approved by the institutional review board of each study site before the start of the study. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization Guideline E6: Good Clinical Practice. Written informed consent was obtained from all participants.

Two sets of MR images were obtained from all patients, before and after gadobutrol administration (unenhanced and gadobutrol-enhanced MR images, respectively). The unenhanced MR image set consisted of T_1-weighted (T_1w), T_2-weighted (T_2w), and fluid attenuated inversion recovery/short inversion time inversion recovery (FLAIR/STIR) images, and the gadobutrol-enhanced image set consisted of T_1w images. The unenhanced and combined (unenhanced and enhanced) MR image sets were evaluated by three independent blinded readers. The final determination regarding presence or absence of disease and final clinical diagnosis were established by an independent truth committee consisting of two neurosurgeons not affiliated with the study, using all available patient-related information collected from patients' referrals for the contrast-enhanced MRI to 3 months after the study MRI procedure, including, but not limited to, medical history, histopathology, clinical laboratory values, symptomatology, received therapies, and imaging interpretation results excluding all study MR image sets.

Patients

Male and female patients, aged ≥ 18 years, and those referred for a contrast-enhanced MRI of the CNS with any indication based on clinical symptoms or previous imaging results were eligible for inclusion. Exclusion criteria included pregnant or nursing women; use of any investigational product or participation in any other clinical trial within 30 days prior to enrollment; participation in any clinical trial using gadobutrol in the past; contraindication for MRI examination or GBCA; history of severe allergic or anaphylactoid reactions to any allergen; administration of any contrast agent within 24 hours prior to the study MRI or plan to receive any contrast agent within 72 (±4) hours after the study MRI; clinically unstable or unpredictable status (e.g., because of previous surgery, acute renal failure); severe cardiovascular diseases (e.g., acute myocardial infarction, unstable angina); severe renal diseases (estimated glomerular filtration rate < 30 mL/min/1.73 m^2); acute renal insufficiency of any severity due to hepato-renal syndrome or in the perioperative liver transplantation period; and requiring dialysis. As baseline data of the enrolled patients, demographic data, weight, and referral diagnosis were recorded.

Administration of gadobutrol and MR imaging

Gadobutrol (0.1 mmol/kg body weight [BW]) was administered by a single intravenous injection at a rate of 2 mL/second, followed by 20 mL 0.9% saline flush at the same rate. The gadobutrol-enhanced MRI scan was started 4 minutes after gadobutrol administration.

MR imaging was performed using a 1.5 Tesla scanner with a dedicated head, neck, or spine coil. After a sagittal localization sequence for the brain and a coronal sequence for the spine, the following pulse sequences were performed: T_1w spin echo images of the whole brain or spine, T_2w fast spin echo (FSE) images of the whole brain or spine, FLAIR for the whole brain or STIR for the spine for the unenhanced image set (axial image presentation for brain, sagittal for spine); and T_1w spin echo images of the whole brain or spine for gadobutrol-enhanced image set (axial and coronal image presentation for brain, sagittal for spine). In each patient, the same parameter settings were used for unenhanced and gadobutrol-enhanced T_1w images (axial for

brain, sagittal for spine). The sequence parameters for brain and spine imaging are shown in Tables 1 and 2.

Image evaluation

The images were evaluated in a blinded manner for patient history, study centers, sequence parameters, contrast agent administration, and details of study protocol by three board-certificated neuroradiologists (all with more than 15 years of experience), who were not affiliated with the clinical study. Each blinded reader evaluated the two sets of images separately in four sessions: (1) unenhanced MR images (T_2w, T_1w, and FLAIR/STIR), (2) combined (unenhanced and enhanced) MR images for brain and spinal cord (part I), (3) unenhanced T_1w axial images, and (4) gadobutrol-enhanced T_1w axial images for brain (part II), with a sufficient interval (at least 2 weeks) between the two sessions in each part to minimize bias due to recall. All images of unenhanced and combined, or unenhanced and enhanced MRI of a specific patient were shown in a randomized order at two sessions of part I and II readings.

Efficacy variables

The primary efficacy variables were visualization parameters, including degree of contrast enhancement, border delineation, internal morphology, and total number of lesions detected. For the evaluation of these variables, except total number of lesions, the investigators/blinded readers scored the CNS lesions and normal brain structures using the image sequence that best depicted each variable.

The degree of contrast enhancement, border delineation, and internal morphology were scored for normal brain structures (pineal gland, pituitary gland, choroid plexus, and sagittal venous sinus) in cases with brain imaging and for lesions in all cases. Any lesion located within the defined normal structures was scored first regardless of size, and a score for the normal brain structure was not given in this case. The largest lesions

Table 1. Sequence parameters for brain imaging

	FSE T_2	SE T_1-axial	SE T_1-coronal	FLAIR
Number of echoes	1	1	1	1
TE (msec)	110–120	Shortest–12	Shortest–12	100–135
TR (msec)	2775–4275	400–519	400–519	6000–8000
Inversion time (msec)	N/A	N/A	N/A	2000
FOV (mm)	220–230	220–230	220–230	220–230
Slice thickness/gap (mm)	**5.0/0.0–1.5**	**5.0/0.0–1.5**	**3.0/0.0–1.5**	**5.0/0.0–1.5**
Matrix	256 × 256	256 × 256	256 × 256	256 × 128

Parameters in bold font were required to be fulfilled, and other parameters (normal font) were recommended to be fulfilled, but were allowed certain variations according to scanner type used and size of the individual patient examined. FLAIR, fluid attenuated inversion recovery; FSE, fast spin echo; FOV, field of view; N/A, not applicable; SE, spin echo; TE, echo time; TR, repetition time.

Table 2. Sequence parameters for spine imaging

	FSE T_2			SE T_1			STIR		
	Cervical	Thoracic	Lumbar	Cervical	Thoracic	Lumbar	Cervical	Thoracic	Lumbar
TE (msec)	120–140	120–140	120–140	10–16	10–16	10–16	20–80	20–80	20–80
TR (msec)	Shortest –3143	Shortest –3143	Shortest –3143	~400	~400	~400	1600	1600	1600
FOV (mm)	230–280	450	270	230–280	450	270	230–280	450	270
RFOV (%)	60–70	50	60	60–70	50	60	60–70	50	60
Slice thickness/ gap (mm)	**2.0–4.0/ 0.0–0.4**	**3.0–4.0/ 0.0–0.4**	**4.0–5.0/ 0.0–0.5**	**2.0–4.0/ 0.0–0.4**	**3.0–4.0/ 0.0–0.4**	**4.0–5.0/ 0.0–0.5**	**2.0–4.0/ 0.0–0.4**	**3.0–4.0/ 0.0–0.4**	**4.0–5.0/ 0.0–0.5**
Matrix	256–512 × 256–512	256 × 256	256 × 256	256–512 × 256–512	256 × 256	256 × 256	256–512 × 256–512	256 × 256	256 × 256

Parameters in bold font were required to be fulfilled, and other parameters (normal font) were recommended to be fulfilled, but were allowed certain variations according to scanner type used and size of the individual patient examined. FSE, fast spin echo; FOV, field of view; RFOV, rectangular field of view; SE, spin echo; STIR, short inversion time inversion recovery; TE, echo time; TR, repetition time.

outside of the normal structures were then scored, with the total number of lesions not to exceed five. A 4-point scale was used to score the degree of contrast enhancement and border delineation as follows: For contrast enhancement, 1 (no), not enhanced; 2 (moderate), weakly enhanced; 3 (good), clearly enhanced; 4 (excellent), clearly and brightly enhanced; For border delineation, 1 (none), no/unclear border delineation; 2 (moderate), some aspects border delineation covered; 3 (good), almost clear but not complete border delineation; 4 (excellent), clear and complete border delineation. A 3-point scale was used to score the internal morphology as follows: 1 (poor), poorly visible; 2 (moderate), partially visible; 3 (good), sufficiently visible structure and the internal morphology of lesion or normal structure. The total number of lesions detected was counted until 30 was reached. If more than 30 lesions were detected, the total number was set as 30 for the statistical analyses that followed.

The secondary efficacy variables were exact match diagnosis, diagnostic confidence, detection of malignant lesions, and detection of abnormal brain tissue.

A specific diagnosis for each image set was given on a per-patient basis by blinded readers for the unenhanced and combined (unenhanced and enhanced) MR image sets (part I) separately and compared with the final clinical diagnosis established by the independent truth committee. The blinded readers were also asked to provide their assessment of whether the brain tissue was abnormal based on unenhanced and enhanced T_1w images of patients, in whom the primary area of interest was the brain (part II). Accuracy of exact match diagnosis was assessed as the matched proportion of blinded readers' diagnoses compared with the final clinical diagnoses established by the truth committee. In addition to the assessment by each blinded reader, diagnoses by "majority reader" were also statistically assessed, if at least two of the three blinded readers provided the same diagnosis, in order to combine the individual reader assessments into one single result. In case three readers gave different diagnoses, the patient was excluded from the analysis of the majority reader's assessment. The determination of malignant lesions was derived from the diagnoses given by the blinded readers and truth committee according to the pre-defined malignant lesions based on the 2007 World Health Organization (WHO) classification of malignant tumors, including those with borderline or uncertain behavior,[17] which contained, e.g., glial tumor (grade I/II, III/IV), metastasis, malignant lymphoma, pineal gland tumor. Since the same diagnosis list was used for the blinded reading and final clinical diagnosis, the possible diagnoses included those based on radiological findings without consideration of histopathological findings. The confidence in diagnosis was scored using a 4-point scale (1 = not confident/ not assessable; 2 = somewhat confident; 3 = confident; 4 = very confident). The sensitivity, specificity, and accuracy for detection of malignant lesions were calculated by comparing diagnoses provided by the blinded readers and the truth committee. The sensitivity was defined as the ratio of correct diagnoses by blinded readers in all patients whose final clinical diagnosis was those classified into "malignant lesions," the specificity as the ratio of correct diagnoses by blinded readers in all patients whose final clinical diagnosis was those classified into "no malignant lesions" (any diagnosis other than the pre-defined malignant lesions) or "no lesions"; and the accuracy as the ratio of correct diagnoses in all patients whose final clinical diagnosis was provided. The sensitivity, specificity, and accuracy for detection of abnormal brain tissues on T_1w images were calculated by comparing the assessment (abnormal or normal) provided by the blinded readers and the truth committee's diagnoses among all patients for whom the brain was imaged. The sensitivity was defined as the ratio of correct assessments by blinded readers in all patients whose final clinical diagnosis was any diagnosis other than "no lesions," the specificity as the ratio of correct assessments by blinded readers in all patients whose final clinical diagnosis was "no lesions"; and the accuracy as the ratio of correct assessments in all patients whose final clinical diagnosis was provided.

Safety assessments

All conditions that started or deteriorated after signing informed consent were considered as adverse events (AEs). Attention was paid to the occurrence of AEs at all stages of the examination until the 72-hour follow-up time-point. In all patients, vital signs, physical examinations, clinical laboratory parameters (blood and urine), and AEs were monitored. Any AE observed, mentioned upon open questioning by investigators or spontaneously reported by the participants, was documented. For outpatients, the 72-hour follow-up was conducted by telephone contact after the 24-hour follow-up by visit. The assessment of the causal relationship between an AE and the administration of gadobutrol was clinically decided based on all available information at the time of the completion of the study.

Statistical analyses

The total number of participants was determined based on the non-inferiority analysis of the total number of lesions detected using the paired *t*-test had sufficient power. The non-inferiority margin was set as 0.35, and the expected mean and standard deviation (0.39 and 3.12, respectively) were assumed taken from two previous global clinical studies.[8,9]

Analyses of the primary and secondary efficacy variables were done in patients for whom at least unenhanced T_1w, either T_2w or FLAIR/STIR, and gadobutrol-enhanced T_1w imaging were performed, and for whom all the images were available. The efficacy analyses of the four primary efficacy variables were done in unenhanced and combined (unenhanced and enhanced) MR image sets using the average (arithmetic mean) of the values from the three blinded readers per patient (average reader assessment). Average of mean score for lesions and normal brain structures was used as "overall average" for each patient. In cases where scores existed only for lesions or only for normal brain structures, the overall averages for these patients were based only on the means of the existing scores. Zero-filled average was used when different numbers of lesions were detected between unenhanced and combined MR image sets, in order for the average to be based on the same number of scores. Enough zeros were included with the scores for the image sets in which fewer lesions were detected. The 95% confidence intervals (CIs) of the mean difference between the combined MR image sets and the unenhanced MR image sets for each variable were constructed using an assumption of a normal distribution based on the large sample size.

The degree of contrast enhancement, border delineation, and internal morphology were tested for the superiority of combined MR image sets over unenhanced MR image sets using a paired *t*-test with two-sided $\alpha = 0.05$. The total number of detected lesions was tested for non-inferiority with a non-inferiority margin of 0.35, which was equivalent to one-sided *t*-test with $\alpha = 0.025$. The inter-reader agreement of the three blinded readers for primary efficacy variables was assessed using intraclass correlation coefficient (ICC).

Results

Patient characteristics

A total of 223 participants received the study drug. The number of males and females was well balanced (males 49.8%). The demographic characteristics are summarized (Table 3). One patient was excluded from the efficacy analysis because of insufficient brain coverage. The referral diagnosis was malignant and non-malignant lesions in 79 patients (35.4%) and 141 patients (63.2%), respectively, and not assessable in 3 patients (1.3%). The main referral lesion types were "other" (36.8%), meningioma (21.5%), metastasis (18.4%), and pituitary adenoma (8.5%). The major specified "other" lesion types recorded were postoperative meningioma (9.4%), postoperative glial tumor of high grade (4.0%), postoperative pituitary adenoma (3.1%), and brain metastasis suspect (2.7%). The imaged region was brain and spinal cord for 219 and 4 patients, respectively.

Table 3. Study population (safety analysis set)

Variable	Statistics/Category	Gadobutrol 0.1 mmol/kg BW N = 223 (100%)
Age group	<45 years	26 (11.7%)
	45–64 years	79 (35.4%)
	≥65 years	118 (52.9%)
Sex	Male	111 (49.8%)
	Female	112 (50.2%)
Age	Mean ± SD	62.7 ± 13.7
	Median (Min–Max)	66.0 (22–86)
Body weight (kg)	Mean ± SD	59.30 ± 11.15
	Median (Min–Max)	59.30 (33.7–113.3)
Region imaged	Brain	219 (98.2%)
	Spinal cord	4 (1.8%)

BW, body weight; SD, standard deviation.

Primary efficacy variables

Among 222 patients for the efficacy analyses, 1 patient was excluded due to a system error in part I image assessment, and the primary efficacy variables were analyzed in 221 patients. Primary efficacy variables were four visualization parameters and assessed for unenhanced and combined (unenhanced and enhanced) sets of images (Table 4). As seen in the representative unenhanced and gadobutrol-enhanced images demonstrated in Figs. 1 and 2, lesion visualization was clearly improved by gadobutrol enhancement.

Contrast enhancement: In the average reader's assessment, the mean contrast enhancement score increased from 0.95 (unenhanced images) to 2.87 (combined [unenhanced and enhanced] images), and the mean change of 1.91 was statistically significant ($P < 0.0001$), proving superiority of the combined unenhanced/enhanced images (Table 4). For all three individual readers' assessments, the increase in score was significant based on the 95% CI analysis, and the mean differences were consistent across the three readers (range: 1.84–2.04), with an approximately 2-point increase on the 4-point scale compared to unenhanced MRI, e.g., increase from no contrast enhancement to good contrast enhancement.

Border delineation: The mean scores of the average reader's assessment for border delineation from unenhanced and combined (unenhanced and enhanced) images were 2.14 and 3.20, respectively, and the change (1.06) was statistically significant ($P < 0.0001$) (Table 4). The mean differences were consistent across the three readers (range: 0.97–1.13), with an approximately 1-point increase on the 4-point scale, e.g., increase from moderate border delineation to good border delineation. In all three individual readers' assessments, the changes in the score were significant based on the 95% CI analysis, indicating significant improvement

Table 4. Visualization parameters—average reader (N = 221)

Variable	Image set	Mean	Median	SD	Min	Max	95% CI		*P*-value*
							Lower limit	Upper limit	
Contrast enhancement[a]	Unenhanced	0.95	1.0	0.09	0.3	1.1			
	Combined	2.87	2.8	0.46	1.0	3.9			
	Difference	1.91	1.8	0.50	0.0	3.4	1.847	1.979	<0.0001
Border delineation[a]	Unenhanced	2.14	2.2	0.26	0.3	2.8			
	Combined	3.20	3.2	0.32	1.7	4.0			
	Difference	1.06	1.0	0.40	–0.3	2.5	1.007	1.115	<0.0001
Internal morphology[b]	Unenhanced	1.15	1.2	0.17	0.3	1.8			
	Combined	2.28	2.2	0.29	1.5	3.0			
	Difference	1.13	1.1	0.30	0.4	2.3	1.088	1.168	<0.0001
Number of detected lesions	Unenhanced	10.79	7	10.18	0	30			
	Combined	11.09	8	10.07	0	30			Non-inferiority** achieved
	Difference	0.30	0	2.75	–8	11	–0.067	0.661	

*Paired *t*-test for contrast enhancement, border delineation, and internal morphology. **Non-inferiority margin = 0.35. a, 4-point scales (1 = none, 2 = moderate, 3 = good, 4 = excellent); b, 3-point scales (1 = poor, 2 = moderate, 3 = good); CI, confidence interval; SD, standard deviation.

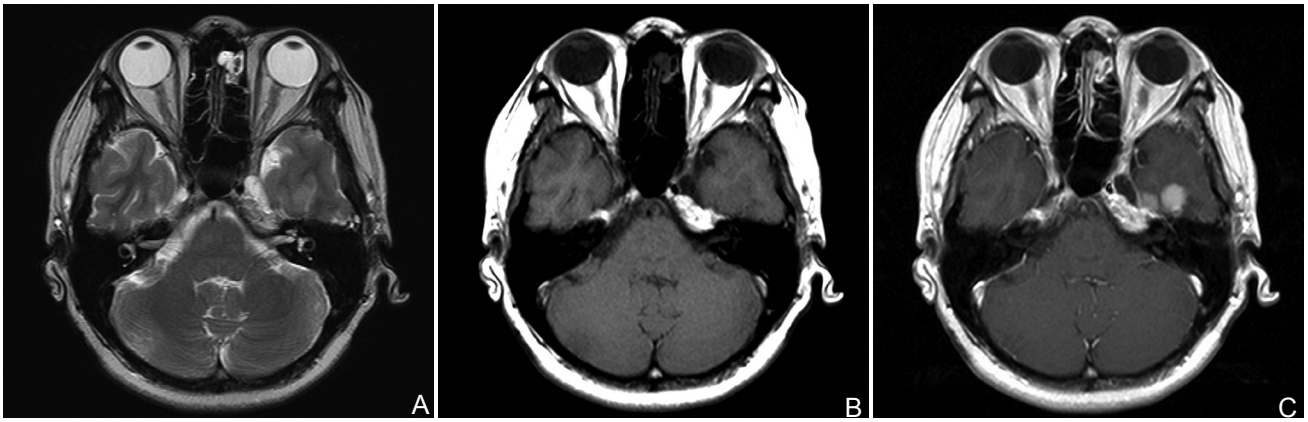

Fig. 1. Magnetic resonance images in a patient with the left middle cranial fossa meningiomas. (**A**) Axial unenhanced T_2w image, (**B**) Axial unenhanced T_1w image; the tumors are difficult to detect in unenhanced images (A and B). (**C**) Gadobutrol-enhanced T_1w image; two tumors are clearly demonstrated.

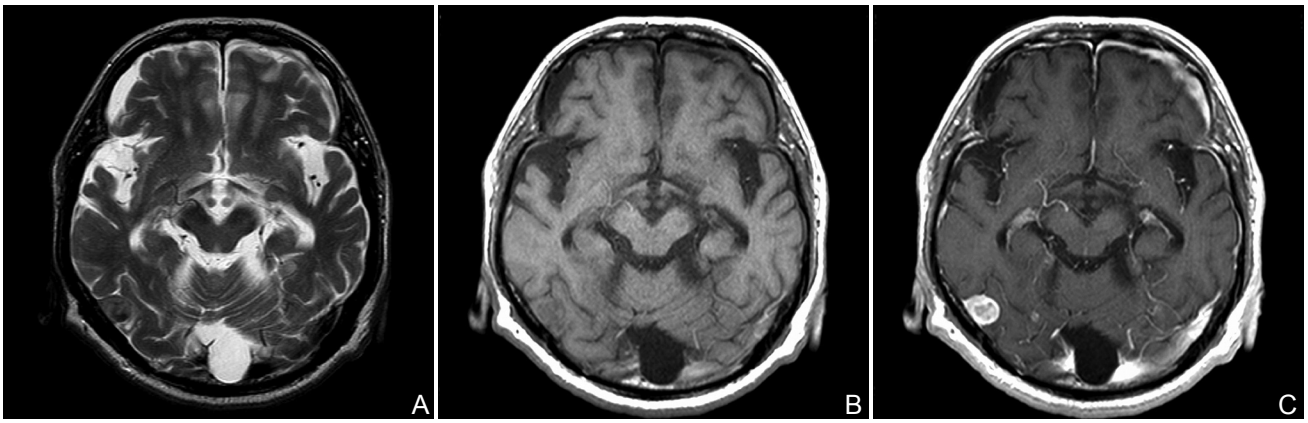

Fig. 2. Magnetic resonance images in a patient with the convexity meningioma. (**A**) Axial unenhanced T_2w image, (**B**) unenhanced T_1w image. (**C**) Gadobutrol-enhanced T_1w image shows strong enhancement of the tumor with clearer border delineation than unenhanced T_1w and T_2w images. Inhomogeneous enhancement reflects internal morphology of the tumor.

for combined (unenhanced and enhanced) images in border delineation.

Internal morphology: The mean scores of the average reader's assessment for internal morphology increased from 1.15 (unenhanced) to 2.28 (combined [unenhanced and enhanced]) (Table 4). The change in scores (1.13) was statistically significant ($P < 0.0001$) showing superiority of the combined images. The mean differences were consistent across the three readers (range: 0.86–1.27), with an approximately 1-point increase on the 3-point scale, e.g., from poor internal morphology to moderate internal morphology. Based on the 95% CI analysis, combined (unenhanced and enhances) images showed significant improvement in internal morphology scores compared with the unenhanced images for all three individual readers' assessments.

Number of lesions: In the average reader's assessment, the mean increase in number of lesions detected was 0.30, with a corresponding 95% CI of –0.067 and 0.661 (Table 4). Since the lower limit of the CI was higher than the pre-specified non-inferiority margin of –0.35, the results demonstrate non-inferiority of the combined image sets over unenhanced image sets. In the individual readers' assessments, there was some variability across readers for this endpoint. The lower limits of 95% CI obtained from two out of three readers were –0.38 and –0.43, which did not achieve non-inferiority.

The ICC among the three blinded readers for contrast enhancement, border delineation, internal morphology, and number of detected lesions of combined image sets were 0.332, 0.523, 0.353, and 0.827, respectively. In general, a value below 0.4, between 0.4 and 0.75, and above 0.75 may be taken to represent poor, fair to good, and excellent agreement, respectively.[18] The observed ICC values were considered excellent for number of detected lesions, and poor to "fair to good" for the other variables.

The results of average reader's primary efficacy variables demonstrated superiority of combined (unenhanced and enhanced) over unenhanced MR image sets in three visualization parameters (contrast enhancement, border delineation, and internal morphology) and non-inferiority in number of lesions detected. All primary efficacy endpoints as pre-specified were achieved.

Secondary efficacy variables

Among final clinical diagnoses of the 222 patients determined by truth committee, the most commonly observed diagnosis was meningioma (N = 49, 22.1%), followed by metastasis (N = 36, 16.2%), no lesion (N = 33, 14.9%), cerebellopontine angle tumor (N = 27, 12.2%), and pituitary adenoma (N = 27, 12.2%). Two patients were diagnosed with "other." No patient was categorized as "not assessable." The final clinical diagnoses were compared with those provided by blinded readers and the sensitivity, specificity, and accuracy in secondary efficacy valuables were evaluated.

Detection of malignant lesions: The accuracy (N = 221) was significantly increased from unenhanced to combined image sets for the majority reader and all three blinded readers based on the 95% CI analysis. The improvements in accuracy were 5.4% (from 86.0% to 91.4%) for the majority reader and 4.1%, 5.4%, and 7.7% for each blinded reader, respectively. The sensitivity (N = 67) increased from unenhanced to combined images for the majority reader (13.4%; from 61.2% to 74.6%) and the three blinded readers (6.0%, 11.9%, and 14.9%). The improvement in the sensitivity by the majority reader and two of the blinded readers were significant based on the 95% CI. There was some variability across readers in specificity (N = 154). No loss in specificity was notable, whereas small improvements were seen in the majority readers' scores (1.9%; from 96.8% to 98.7%) and two blinded readers' scores (5.2% and 5.8%).

Exact match diagnosis: Among 222 patients whose images were assessed, the two patients whose final clinical diagnosis was "other" and the one patient whose image assessment had the system error, both cases mentioned previously, were excluded from this analysis. For a further 51 patients, the three blinded readers provided three different diagnoses and thus the exact match diagnosis of majority reader was assessed for the remaining 168 patients. The accuracy of exact match diagnoses was significantly improved in the majority reader (10.1%; from 55.4% to 65.5%) and all blinded readers (N = 219; 6.8%, 10.0%, and 12.8%) based on the 95% CI.

Confidence in diagnosis: For the average reader assessment, the mean improvement in diagnostic confidence was 0.86 (0.68, 0.90, and 0.99 for each reader) from the unenhanced to the combined image sets. All these improvements were significant based on the 95% CI of the improvement.

Detection of abnormal brain tissues on T_1w images: Among 222 patients, 4 were excluded from the assessments because the primary area of interest was the spinal cord. The accuracy (N = 218) and sensitivity (N = 188) were higher for the gadobutrol-enhanced images compared with those for the unenhanced images. The improvement in accuracy was 11.0% (from 70.6% to 81.7%) for the majority reader (6.9%, 10.6%, and 10.6% for each reader) and sensitivity was 12.8% (from 72.3% to 85.1%) for the majority reader (8.0%, 11.2%, and 13.3% for each reader). All these improvements were significant based on the 95% CI analysis. In the specificity analysis (N = 30), results varied among readers. There was no loss of specificity

for the majority reader (60.0% for the unenhanced and combined images). Specificity increased in the assessment results of one reader (6.7%), there was no change in results of one of the other readers, and the final reader showed a decrease (–6.7%).

Safety: Safety was analyzed in 223 patients who received gadobutrol. No death or severe AE was reported during the study period, and none of the patients discontinued the study due to an AE. A total of 19 patients (8.5%) reported at least one treatment-emergent AE (TEAE) during the study. Of those, 6 patients (2.7%) reported at least one TEAE regarded by the investigators as gadobutrol-related (Table 5). The most common gadobutrol-related TEAE was hot flush in two patients (0.9%).

Table 5. Number (%) of patients with drug-related treatment-emergent AEs by system organ class and preferred term (safety analysis set) (N = 223)

System organ class Preferred term	Gadobutrol 0.1 mmol/kg BW N (%)
With at least one drug-related AE	6 (2.7%)
Gastrointestinal disorders	**3 (1.3%)**
Dry mouth	1 (0.4%)
Nausea	1 (0.4%)
Vomiting	1 (0.4%)
General disorders and administration site conditions	**1 (0.4%)**
Injection site warmth	1 (0.4%)
Skin and subcutaneous tissue disorders	**2 (0.9%)**
Palmar erythema	1 (0.4%)
Rash	1 (0.4%)
Vascular disorders	**2 (0.9%)**
Hot flush	2 (0.9%)

AE, adverse event (MedDRA Version 16.0); BW, body weight.

Discussion

This study, a phase 3 study, aimed to investigate the efficacy of gadobutrol at 0.1 mmol/kg dose in the general and wide population of Japanese patients referred for routine contrast-enhanced MRI of CNS in the clinical practice, without limiting enrollment only to those in whom there was strong suspicion of CNS lesion. Thus, there was a potential and also intention that patients with no pathologic lesions would be enrolled in the study. For this reason, the primary variables were not only assessed for lesions, but also for normally enhanced brain structures (e.g., pituitary gland) which made it possible to assess the variables also in patients without pathologic brain lesions. Those patients referred for ruling out CNS lesions with contrast-enhanced CNS MRI needed to be enrolled in the study for the following reasons: (1) to reflect the actual population in which a contrast-enhanced MRI is indicated and (2) for evaluation of the diagnostic performance in terms of sensitivity, specificity, and accuracy of gadobutrol-enhanced CNS MRI.

Efficacy of gadobutrol was assessed by comparing unenhanced and combined (unenhanced and gadobutrol-enhanced) sets of MR images. The variables chosen as the primary endpoints of the study are relevant in clinical routine when assessing MR images of CNS, as they contribute to the visibility and conspicuity of CNS lesions and provide imaging features that are relevant for the diagnosis of certain lesion types.

Our results demonstrated that combined MRI with gadobutrol enhancement was superior over unenhanced MRI in Japanese patients for visualization parameters of contrast enhancement, border delineation, and internal morphology based on the average and individual reader score, which confirms the results from previously reported studies.[8,9] The fact that unenhanced MR image sets consisting of T_1w, T_2w FSE, and FLAIR/STIR generated using state-of-the-art 1.5 T MR scanners are sensitive in the detection of CNS lesions and already provide substantial information of the lesion, underlines that the shown superiority confirms efficacy of gadobutrol in CNS imaging. Furthermore, non-inferiority for the number of lesions was established for the average reader, which also met the primary efficacy analysis requirements for the success of the study. It was expected that the number of lesions detected on combined MR images of patients referred for contrast-enhanced MRI of the CNS would not relevantly increase compared with unenhanced MR images. The reason is that, in general, most CNS lesions of tumor, inflammation, or ischemia, etc., are well detected with unenhanced FLAIR or T_2w MR images, except for limited cases such as small metastatic lesions not accompanied by peritumoral edema. Therefore, non-inferiority test was selected for comparison of combined versus unenhanced MR images for number of lesions detected in this confirmatory study. The largest clinically acceptable difference in detecting lesions is considered to be 0.5, which can be regarded as difference of one lesion. In the current study, a smaller non-inferiority margin of 0.35 was set. Regardless of this more stringent margin, non-inferiority was achieved, demonstrating the solid non-inferiority of the combined unenhanced and gadobutrol-enhanced images.

Accurate diagnosis is critical for therapy planning and assessment of the patient's prognosis. Our study demonstrated that the diagnostic performance, evaluated in terms of accuracy of exact match diagnosis and sensitivity and accuracy for detection of malignancy,

provided significant and clinically meaningful improvement following gadobutrol administration. Considering that there were nearly 40 potential diagnostic choices, the improvement in exact match diagnosis reveals that gadobutrol enhancement is useful in narrowing the differential diagnostic choices. Since it is crucial for the imaging examination to detect malignancy, considering clinical outcome of the patient, improved sensitivity and accuracy to detect malignancy with no loss of specificity supports the essentiality and also demonstrates the efficacy of gadobutrol. In addition, sensitivity and accuracy in detection of abnormal brain tissue on T_1w images also showed a significant improvement. The varied results of specificity among three readers are likely due to small number of patients (30 patients) with final clinical diagnosis of "no lesion." The blinded readers' confidence for diagnosis also showed significant improvement. These favorable outcomes of the diagnostic performance are consistent with previous clinical studies using gadobutrol as a contrast agent in CNS imaging.[8,9]

Furthermore, the higher T_1 relaxivity of gadobutrol showed better lesion detection and delineation with standard dose of 0.1 mmol/kg compared to other GBCAs in the intra-individual comparative studies performed in the specific patient population of brain metastases.[12,19]

Gadobutrol demonstrated good tolerability. Only 2.7% (6/223) patients showed one or more drug-related AE, and all of them were mild in intensity. Previous studies using gadobutrol 1.0 M reported good tolerability as well, with similar rates of AE occurrence,[8,9,12,19] adding more evidence of the safety of gadobutrol.[8–11]

There may be a difference in number of detected lesions between the publications due to differences in patient population. Compared with the previous CNS studies of gadobutrol[8,9] the present Japanese study population had fewer patients with referral diagnosis of multiple sclerosis, but included more patients of advanced age. The difference in disease and age distribution of the study populations may have impacted the assessment of efficacy in MRI and diagnostic accuracy. The lesions that the blinded readers detected and counted both in unenhanced and combined MRI in this study were all focal lesions seen in any pulse sequence of these image sets, and were not limited to those relevant to the patient's diagnosis. Ischemic lesions of lacunar infarction and unidentified bright objects well seen especially on T_2w and FLAIR images of aged patients were also counted as lesions. This is reflected in the high mean number of lesions detected in unenhanced and combined image sets (10.79 and 11.09 lesions, respectively). However, the same level of slight increase in mean number of detected lesions after gadobutrol enhancement were seen both in the present and previous study (0.30 vs. 0.32),[8] suggesting that there was no relevant impact of the difference in high number of detected lesions.

There are limitations to the study. The study was designed to compare combined and unenhanced image sets and had no active comparator arm. Thus, it is not clear whether there were any differences in the primary efficacy variables and diagnostic performance of gadobutrol compared to other GBCAs in Japanese patients from the study. However, literature available from controlled, confirmatory studies allows to extrapolate non-inferior results of gadobutrol to other GBCAs also in Japanese patients.[9,12] Furthermore, among the four primary efficacy variables, contrast enhancement, border delineation, and internal morphology were subjective assessments, although effort was made to provide uniformity in application of the scoring criteria among the three readers in their training.

Conclusion

The results of this phase 3 study demonstrated that gadobutrol 1.0 M at dose of 0.1 mmol/kg is an effective and well-tolerated contrast agent for MRI of the CNS in Japanese patients. Gadobutrol enhancement provided significant improvements in contrast enhancement, border delineation, and internal morphology versus unenhanced imaging, and showed improvement in sensitivity and accuracy for the detection of malignant disease and accuracy of exact match diagnosis.

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References

1. Runge VM, Muroff LR, Jinkins JR. Central nervous system: review of clinical use of contrast media. Top Magn Reson Imaging 2001; 12:231–263.
2. Runge VM, Muroff LR, Wells JW. Principles of contrast enhancement in the evaluation of brain diseases: an overview. J Magn Reson Imaging 1997; 7:5–13.
3. Rohrer M, Bauer H, Mintorovitch J, Requardt M, Weinmann HJ. Comparison of magnetic properties of MRI contrast media solutions at different magnetic field strengths. Invest Radiol 2005; 40:715–724.
4. Attenberger UI, Runge VM, Jackson CB, et al. Comparative evaluation of lesion enhancement using 1 M gadobutrol vs. 2 conventional gadolinium chelates, all at a dose of 0.1 mmol/kg, in a rat brain tumor model at 3 T. Invest Radiol 2009; 44:251–256.
5. Hammerstingl R, Adam G, Ayuso JR, et al. Comparison of 1.0 M gadobutrol and 0.5 M gadopentetate dimeglumine-enhanced magnetic resonance imaging in five hundred seventy-two patients with known or suspected liver lesions: results of a multicenter, double-blind, interindividual, randomized clinical phase-III trial. Invest Radiol 2009; 44:168–176.
6. Morelli JN, Runge VM, Vu L, Loynachan AT, Attenberger UI. Evaluation of gadodiamide versus gadobutrol for contrast-enhanced MR imaging in a rat brain glioma model at 1.5 and 3 T. Invest Radiol 2010; 45:810–818.
7. Greco A, Parker JR, Ratcliffe CG, Kirchin MA, McNamara MT. Phase III, randomized, double-blind, cross-over comparison of gadoteridol and gadopentetate dimeglumine in magnetic resonance imaging of patients with intracranial lesions. Australas Radiol 2001; 45:457–463.
8. Gutierrez JE, Rosenberg M, Duhaney M, et al. Phase 3 efficacy and safety trial of gadobutrol, a 1.0 molar macrocyclic MR imaging contrast agent, in patients referred for contrast-enhanced MR imaging of the central nervous system. J Magn Reson Imaging 2015; 41:788–796.
9. Gutierrez JE, Rosenberg M, Seeman J, et al. Safety and efficacy of gadobutrol for contrast-enhanced magnetic resonance imaging of the central nervous system: results from a multicenter, double-blind, randomized, comparator study. Magn Reson Insights 2015; 8:1–10.
10. Balzer JO, Loewe C, Davis K, et al. Safety of contrast-enhanced MR angiography employing gadobutrol 1.0 M as contrast material. Eur Radiol 2003; 13:2067–2074.
11. Forsting M, Palkowitsch P. Prevalence of acute adverse reactions to gadobutrol—a highly concentrated macrocyclic gadolinium chelate: review of 14,299 patients from observational trials. Eur J Radiol 2010; 74:e186–e192.
12. Katakami N, Inaba Y, Sugata S, et al. Magnetic resonance evaluation of brain metastases from systemic malignances with two doses of gadobutrol 1.0 m compared with gadoteridol: a multicenter, phase ii/iii study in patients with known or suspected brain metastases. Invest Radiol 2011; 46:411–418.
13. Olukotun AY, Parker JR, Meeks MJ, Lucas MA, Fowler DR, Lucas TR. Safety of gadoteridol injection: U.S. clinical trial experience. J Magn Reson Imaging 1995; 5:17–25.
14. Bellin MF, Van Der Molen AJ. Extracellular gadolinium-based contrast media: an overview. Eur J Radiol 2008; 66:160–167.
15. Khatami SM, Mahmoodian M, Zare E, Pashang M. Safety of older generations of gadolinium in mild-to-moderate renal failure. Ren Fail 2012; 34:176–180.
16. Edwards BJ, Laumann AE, Nardone B, et al. Advancing pharmacovigilance through academic-legal collaboration: the case of gadolinium-based contrast agents and nephrogenic systemic fibrosis-a Research on Adverse Drug Events and Reports (RADAR) report. Br J Radiol 2014; 87:20140307.
17. Louis DN, Ohgaki H, Wiestler OD, et al. The 2007 WHO classification of tumors of the central nervous system. Acta Neuropathol 2007; 114:97–109.
18. Fleiss JL. The Design and Analysis of Clinical Experiments. New York: John Wiley & Sons, 1986.
19. Anzalone N, Scarabino T, Venturi C, et al. Cerebral neoplastic enhancing lesions: multicenter, randomized, crossover intraindividual comparison between gadobutrol (1.0M) and gadoterate meglumine (0.5M) at 0.1 mmol Gd/kg body weight in a clinical setting. Eur J Radiol 2013; 82:139–145.