Document Type:	Protocol
Official Title:	LowEr Administered Dose with highEr Relaxivity: Gadovist vs Dotarem (LEADER 75)
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Cover page of the integrated protocol

LowEr **A**dministered **D**ose with high**E**r **R**elaxivity: Gadovist vs Dotarem (LEADER 75)

This protocol version is an integration of the following documents / sections:

- **Original protocol,** Version 1.0, dated 23 JAN 2018
- **Amendment no. 1** (described in Section 15) forming integrated protocol Version 2.0, dated 26 MAR 2019

Amendments not included in the consecutive numbering of amendments are local amendments not forming part of this integrated global protocol

1. Title page (AMENDED)

LowEr **A**dministered **D**ose with high**E**r **R**elaxivity: Gadovist vs Dotarem (LEADER 75)

Test drug:	BAY No. 86-4875/ Gadobutrol / (GADOVIST)		
Study purpose:	Comparison of Gadovist 75% standard dose to Dotarem at full standard dose		
Clinical study phase:	4	Date:	26 MAR 2019
Registration:	EudraCT: 2018-000690-78	Version no.:	2.0
Sponsor's study no.:	IMPACT no. 19773		
Sponsor:	a) Sponsor (Non-US): Bayer AG, D-51368 Leverkusen, Germany b) Sponsor (US territory): Bayer HealthCare Pharmaceuticals Inc., 100 Bayer Boulevard, P.O. Box 915, Whippany NJ 07981-0915, USA		
Sponsor's medical expert:	PPD MRI Special Indications & Support Bayer HealthCare Pharmaceuticals Inc., 100 Bayer Boulevard, P.O. Box 915, Whippany NJ 07981-0915, USA PPD		

The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

Signature of the sponsor's medically responsible person

The signatory agrees to the content of the final clinical study protocol as presented.

Name: PPD Role: Medical Affairs Responsible

Date: 26-MAR-2019 Signature: PPD

Signature of principal investigator

The signatory agrees to the content of the final clinical study protocol as presented.

Name: _____

Affiliation: _____

Date: ..... Signature: .....

Signed copies of this signature page are stored in the sponsor's study file and in the respective center's investigator site file.

In the protocol document, this page may remain unsigned.

2. Synopsis

Title	**L**owEr **A**dministered **D**ose with high**E**r **R**elaxivity: Gadovist vs Dotarem
Acronym	LEADER 75
Clinical study phase	Phase 4
Study objective(s)	**The primary objectives of this study are to demonstrate:** Noninferiority of gadobutrol (0.075 mmol/kg BW) compared to gadoterate (0.1 mmol/kg BW) based on a blinded read for: • Degree of contrast enhancement • Assessment of border delineation • Internal morphology of lesions **The secondary objectives of this study are to:** • Demonstrate non-inferiority for number of lesions • Confidence in diagnosis • Compare the 0.075 mmol/kg BW dose of gadobutrol to standard dose gadoterate (Dotarem) for: o T1w MRI image quality in a paired comparison o Sensitivity/Specificity for presence of malignant disease versus the final clinical diagnosis. • Compare the overall contrast enhancement of gadobutrol (0.075 mmol/kg BW) to the standard dose of gadoterate 0.1 mmol/kg) for steady-state CNS imaging. Quantitative contrast enhancement will be performed using an exploratory Overall Contrast Enhancement Estimation Algorithm. • Assess the safety profile of the reduced dose of 0.075 mmol/kg BW of gadobutrol and standard dose gadoterate after IV administration
Test drug(s)	gadobutrol (Gadovist®/Gadavist®) 1.0 molar
Name of active ingredient	gadobutrol
Dose(s)	0.075 mmol/kg
Route of administration	IV
Duration of treatment	single dose
Reference drug(s)	gadoterate (Dotarem®/Clariscan™) 0.5 molar
Name of active ingredient	gadoterate
Dose(s)	0.1 mmol/kg
Route of administration	IV
Duration of treatment	single dose

Indication	Contrast-enhancement in MRI of the central nervous system (CNS) for the detection/visualization of areas with normal and disrupted blood brain barrier (BBB) and/or abnormal vascularity
Diagnosis and main criteria for inclusion /exclusion	Adult patients with known or highly suspected CNS pathology referred for contrast-enhanced MRI of the CNS based on current clinical symptoms or on a previous imaging procedure.
Study design	Open label multi-center comparative, cross-over trial open to adult patients with known or highly suspected of having CNS pathology referred for imaging of the CNS.
Methodology	Two CNS MRIs will be obtained for each enrolled patient: • Unenhanced MRI consisting of steady-state sequences (T1-weighted, T2-weighted, and FLAIR) and gadoterate-enhanced MRI consisting of steady-state sequence (T1-weighted) • Unenhanced MRI consisting of steady-state sequences (T1-weighted, T2-weighted, and FLAIR) and gadobutrol-enhanced MRI consisting of steady-state sequence (T1-weighted) The unenhanced MRI, combined unenhanced and gadoterate-enhanced MRI, and the unenhanced, and the combined unenhanced and gadobutrol-enhanced MRI will be evaluated by 3 independent blinded readers for the primary efficacy endpoints. The investigator will note the referring diagnosis, and identify the size and location of the enhancing lesion which makes the subject eligible for study inclusion. The investigator will also provide the final clinical diagnosis and whether this represents malignant disease. The final clinical diagnosis will be based on all available clinical information up to 30 days after the first MRI. All AEs from the signing of informed consent will be recorded. Safety will be assessed using data from treatment emergent adverse events (TEAEs).
Type of control	Gadoterate-enhanced MRI
Number of patients	Total: 180 enrolled patients Minimum per center: N/A Maximum per center:~ 20
Primary variable(s)	The 3 primary efficacy variables (visualization parameters) are: • the degree of lesion contrast enhancement, • assessment of lesion border delineation, and • internal morphology of lesions
Time point/frame of measurement for primary variable(s)	The primary variable requires completion of a blinded read, done in three sessions

Plan for statistical analysis	**Co-primary target variable(s):** • Lesion contrast enhancement • Lesion border delineation • Lesion internal morphology Up to 5 of the largest lesions will be selected and scored using a pre-specified scale by the blinded readers. The related statistical hypotheses read as follows: • H_0: (gadobutrol - gadoterate) ≤ -0.2*(gadoterate – unenhanced) vs. ~~K_0~~ H_1: (gadobutrol – gadoterate) > -0.2*(gadoterate – unenhanced) The study is considered successful if all 3 hypotheses related to these co-primary target variables can be rejected at a one-sided alpha of 0.025, which will be equivalent to a two-sided alpha of 0.05. Rejection of such a hypothesis means that it is demonstrated that gadobutrol (Gadovist) at reduced dose preserves at least 80% of the effect gadoterate (Dotarem) as compared to unenhanced images. Enrolling 180 subjects allows for approximately 25% of non-evaluable patients, and guarantees 90% power for border delineation. For the remaining two variables the power will be close to 100% with this sample size. Hence, the overall power of this study will be at least 90%.

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List of abbreviations and Definitions of terms

AE	adverse event
ADR	adverse drug reaction
BBB	blood brain barrier
BR	blinded reader
BW	body weight
CNR	contrast to noise ratio
CNS	central nervous system
CRA	clinical research assistant/associate
CRO	clinical research organization
CSF	cerebrospinal fluid
DICOM	digital images and communications in medicine
GBCA	gadolinium-based contrast agent
GCIS	General Clinical Imaging Service
ECCM	extracellular contrast medium/media
ECG	electrocardiogram
eCRF	electronic case report form
EudraCT	EU data repository for clinical trials
FAS	full analysis set
FDA	Food and Drug Administration
FLAIR	Fluid Attenuated Inversion Recovery
FSE	fast spin echo
GCP	Good clinical practice
Gd/Gd^{3+}	gadolinium
GFR	glomerular filtration rate
GMP	Good manufacturing practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	independent ethics committee
IND	Investigational New Drug
Inv	investigator
IRB	institutional review board
ITF	investigator's trial file
IV	intravenous
IVRS	Interactive Voice Response System
MedDRA	Medical Dictionary for Regulatory Activities
MR	magnetic resonance
MRI	magnetic resonance imaging
NFD	Nephrogenic Fibrosing Dermopathy
nos.	numbers

NSF	Nephrogenic Systemic Fibrosis
PID	patient identification number
PPS	per protocol analysis set
SAE	serious adverse event
SDMB	study data management book
SH	sponsor's formulation code numbering system
SI	signal intensity
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
T1	longitudinal relaxation time
T1w	T1-weighted
T2	transversal relaxation time
T2w	T2-weighted
TMF	trial master file
WHODD	World Health Organization Drug Dictionary

3. Introduction

The constant evolution of magnetic resonance (MR) systems with faster sequences, functional imaging, and multichannel technology necessitates a contrast agent with the potential to benefit from these technical advances.

Gadobutrol (Gadovist) was first developed for the indication "contrast enhancement in cranial and spinal MRI" in doses of up to 0.3 mmol/kg BW.

First approved in Switzerland in 1998, gadobutrol has since been approved in more than 100 countries worldwide (including the European Union countries, USA, Japan, Canada, Australia, South Africa, Mexico, New Zealand, Turkey, and several Eastern European and Asian countries). In addition, gadobutrol has proven to be an effective contrast medium for all of its approved indications (CNS, MR angiography, liver and kidney, other body regions) and has exhibited an excellent safety profile, comparable to that of other marketed extracellular gadolinium based contrast agents.

The ideal extracellular gadolinium-based contrast agent (GBCA) for MRI would have a favorable safety profile and a low risk of potential long-term deposition within normal tissue. In this regard, macrocyclic agents GBCA (e.g. gadobutrol, gadoteridol, or gadoterate meglumine) that have higher in-vitro and in-vivo stability and longer dissociation half-lives are reasonable alternatives. The standard dose for all marketed GBCAs, including gadobutrol and gadoterate, is 0.1 mmol/kg BW regardless of each agent's relaxivity.

This study is designed to examine if a 75 percent dose of gadobutrol (0.075 mmol/kg), which has a high relaxivity, is noninferior to a 100% dose of gadoterate (Dotarem) (0.1 mmol/kg) for steady state CNS imaging.

4. Study objectives

4.1 Primary objectives

The primary objective of this study is to demonstrate noninferiority of gadobutrol-enhanced CNS imaging (at a dose of 0.075 mmol/kg) compared to gadoterate (0.1 mmol/kg BW) - enhanced CNS imaging (at a dose of 0.1 mmol/kg) for 3 lesion visualization parameters (degree of contrast enhancement, assessment of border delineation, and internal morphology of lesions) based on a blinded read.

4.2 Secondary objectives

The secondary objectives of this study are to:

- Demonstrate noninferiority for number of lesions based on a blinded read
- Confidence in diagnosis
- Compare the 0.075 mmol/kg BW dose of gadobutrol to standard dose gadoterate for:
    - T1w MRI image quality in a paired blinded comparison

- Sensitivity/Specificity for presence of malignant disease based on a blinded read

- Compare the overall contrast enhancement of gadobutrol (0.075 mmol/kg BW) to the standard dose of gadoterate (0.1 mmol/kg) for steady-state CNS imaging. Quantitative contrast enhancement will be performed using an exploratory Overall Contrast Enhancement Estimation Algorithm.
- Assess the safety profile of the reduced dose of 0.075 mmol/kg BW of gadobutrol and standard dose gadoterate after intravenous (IV) administration.

5. Study design

5.1 Design overview

This study is a Phase 4, multicenter, controlled, cross-over study with corresponding blinded image evaluations in male and female patients at least 18 years of age, who are referred for a contrast-enhanced MRI of the CNS based on a known or highly suspected lesion of the CNS.

Patients will undergo an unenhanced and contrast-enhanced MRI of the CNS using gadoterate at the standard dose of 0.1 mmol/kg BW. If the investigator does not identify an enhancing lesion of the CNS, then this patient will be considered a screening failure. If an enhancing lesion is identified, then the patient will undergo a second unenhanced and contrast-enhanced MRI of the CNS using gadobutrol at a dose of 0.075 mmol/kg BW.

Safety will be assessed from the first administration of gadoterate through 24 hours after the second administration of gadobutrol. Adverse events will be collected from the signing of informed consent through the end of the follow-up period. Serious adverse events (SAEs) will be followed through resolution. Patients who receive only the first MRI scan (considered screening failures) will be followed for SAEs only.

Gadobutrol will be administered at the dose of 0.075 mmol/kg body weight by single IV injection at a rate of 2 mL/sec, followed by 20-mL 0.9% saline flush at the same rate. Gadoterate will be administered at the approved standard dose of 0.1 mmol/kg body weight by single IV injection at 2 mL/sec, followed by 20-mL 0.9% saline flush at the same rate. The 2 injections will be separated by at least 24 hours, but not more than 15 days.

During the course of the study, 2 MRIs will be obtained from each patient as follows: before the administration of each of the contrast agent (unenhanced MRI) consisting of steady-state sequences (T1w, T2w, and FLAIR), following the gadoterate injection (gadoterate-enhanced MRI) consisting of steady-state sequences T1; and following the gadobutrol injection (gadobutrol-enhanced MRI) consisting of steady-state sequences (T1w).

The unenhanced MR image set, combined unenhanced and gadobutrol-enhanced MR image sets, and the unenhanced and combined unenhanced and gadoterate-enhanced MR image sets will be evaluated by 3 independent blinded readers. The blinded readers will also evaluate the

gadobutrol-enhanced T1w images compared to the gadoterate-enhanced T1w images in a paired read for image quality.

The final clinical diagnosis will be determined by the site investigator using all available clinical information up to 30 days post the first MRI. This final clinical diagnosis will be utilized as the standard of truth for the blinded assessment of diagnostic performance (sensitivity/specificity for malignant disease).

The safety of the patients will be assessed by monitoring of adverse events and treatment emergent adverse events (TEAEs).

5.2 Primary variable(s)

The 3 primary efficacy variables will be lesion visualization parameters based on a blinded read (see Section 10.2.1.5 for details):

- Degree of lesion contrast enhancement
- Lesion border delineation
- Lesion internal morphology

5.3 Secondary efficacy variables

The secondary efficacy variables are the:

- Number of lesions identified (up to 10) based on a blinded read
- Identification of benign or malignant disease based on blinded read
- Confidence in diagnosis based on a blinded read
- Image quality based on a blinded read
- Contrast enhancement utilizing an exploratory Overall Contrast Enhancement Estimation Algorithm.

5.4 Justification of the design

Gadoterate is an approved macrocyclic contrast agent for steady-state CNS imaging. It has the lowest relaxivity among all approved gadolinium contrast agents and was therefore chosen as the comparator. Gadoterate belongs to the same chemical class as gadobutrol, which is also a macrocyclic contrast agent. Macrocyclic contrast agents may be considered preferable to linear agents in certain situations, for example, in light of Nephrogenic Systemic Fibrosis (NSF), which has been rarely observed in renally impaired patients who received multiple and/or high doses of primarily linear GBCAs, and in the accumulation of gadolinium in tissues, also thought to occur to a lesser extent with macrocyclic agents. In addition, as both of these conditions appear to be dose-related, the lowest dose of gadolinium is recommended.

The purpose of this study is to demonstrate that the higher relaxivity of gadobutrol compared to gadoterate will permit a dose reduction by 25% for gadobutrol and still provide noninferior efficacy to a full dose of gadoterate.

The patient population for this study will be those with known or highly suspected lesions of the CNS referred for a contrast-enhanced MRI of the CNS.

The multicenter design is used to gain a wide range of experience and to reduce bias.

A prospective planned blinded image evaluation by independent readers will be performed in order to facilitate an independent evaluation and permit randomization of the image evaluation. The blinded readers will be experienced radiologists who will not have been involved in the clinical portion of the study and are considered independent from the study. Selecting experienced readers and performing adequate and extensive reader training prior to the evaluation of the images is expected to sufficiently address standardization issues and to minimize inter-reader variability. All quantitative measurements and qualitative evaluations of the MRI data will be performed in a core laboratory in a standardized fashion using validated software.

5.5 End of study

The end of the patients' participation in the study will be reached at the last patient last visit, defined as when the final clinical diagnosis is obtained for the last patient enrolled. The end of the study will be considered the end of the blinded read, approximately 30 days after the LPLV.

5.6 Primary objectives

The primary objective of this study is to demonstrate noninferiority of gadobutrol-enhanced CNS imaging (at a three-quarter dose of 0.075 mmol/kg) compared to gadoterate -enhanced CNS imaging (at a full dose of 0.1 mmol/kg) for 3 lesion visualization parameters (degree of enhancement, border delineation, internal morphology) based on a blinded read.

5.7 Primary completion

The primary completion event for this study is completion of the blinded read for all patients.

The primary completion date for this study according to the FDA Amendment Act is specified in a separate document (not part of this study protocol).

6. Study population

6.1 Eligibility

Male and female patients (≥ 18 years of age) of any ethnic group, who meet the inclusion criteria and none of the exclusion criteria, and who give written informed consent will be eligible for enrollment into the study.

6.2 Inclusion criteria

To be included in the study a patient must:

1. Have known or highly suspected CNS pathology referred for contrast-enhanced MRI of the CNS based on current clinical symptoms or on a previous procedure.
2. If female and of child bearing potential, have a negative urine pregnancy test within 1 hour prior to the administration of gadoterate (the first MRI).
3. Have an estimated glomerular filtration rate (eGFR) value ≥ 60 mL/min/1.73m^2 derived from a serum creatinine result within four (4) weeks prior to the first study MRI.
4. Be fully informed about the study, including provisions of the Health Insurance Portability and Accountability Act (HIPAA) as applicable, and consent to participate

6.3 Exclusion criteria

A patient will be excluded from the study if he/she:

1. Has no enhancing lesion visible on the gadoterate-enhanced MRI scan.
2. Is pregnant or breast feeding
3. Has received any investigational product or has participated in any other clinical trial within 30 days prior to enrolling in this study
4. Has any contraindication to the MRI examinations or the use of gadolinium-containing contrast agents
5. Has a history of severe allergic or anaphylactic/anaphylactoid reaction to any allergen including drugs and contrast agents
6. Has received any gadolinium-based contrast agent < 24 hours prior to the study MRIs, or is scheduled to receive any contrast agent within 24 hours after the second study MRI
7. Is considered clinically unstable
8. Has severe cardiovascular disease (eg, known long QT syndrome, acute myocardial infarction [< 14 days], unstable angina, congestive heart failure New York Heart Association class IV or acute stroke (< 48 hours)
9. Is expected or is scheduled to have a change in any treatment or procedure between the gadoterate and gadobutrol MRIs that may alter image comparability
10. Is scheduled or is likely to require a biopsy or any interventional therapeutic procedure from the first study MRI up to 24 hours after the second study MRI

6.4 Justification of selection criteria

The following is the FDA class warning for gadolinium-based contrast agents:

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS
Gadolinium-based contrast agents increase the risk for Nephrogenic Systemic Fibrosis (NSF) in patients with: acute or chronic severe renal insufficiency (glomerular filtration rate < 30 mL/min/1.73m^2), or acute renal insufficiency of any severity due to hepato-renal syndrome or in the perioperative liver transplantation period.
In these patients, avoid use of gadolinium-based contrast agents unless the diagnostic information is essential and not available with non-contrast-enhanced MRI. NSF may result in fatal or debilitating systemic fibrosis affecting the skin, muscle and internal organs. Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests.
When administering a gadolinium-based contrast agent, do not exceed the recommended dose and allow a sufficient period of time for elimination of the agent from the body prior to any readministration.

It must be ensured that each patient is suitable for the technical requirements of a MRI examination, and especially that each patient has no metallic implants that would be affected by magnetic fields (Exclusion criterion 4).

In order to prevent interference with the investigational product and to ensure that the cause of TEAEs can be easily traced, no other contrast agents are to be administered (Exclusion criteria 6 and 7).

The physical condition of each patient must be stable and must not be significantly influenced by other therapies so that the patient does not have the potential for demonstrating unrelated TEAEs after contrast agent administration (Exclusion criterion 6).

To ensure that the patient's clinical picture is the same during gadobutrol-enhanced MRI and the gadoterate-enhanced MRI and there is no change due to external influences, no local or systemic therapy or biopsy/interventional therapeutic procedure should occur between the 2 MRI examinations (Exclusion criteria 10 and 11).

6.5 Recruitment

Patient recruitment will be from the patient populations at the investigative study centers who are referred for a contrast-enhanced CNS MRI.

6.6 Withdrawal of patients from study

6.6.1 Withdrawal

Withdrawal criteria

Patients *must* be withdrawn from the study if any of the following occurs:

- At their own request or at the request of their legally acceptable representative. At any time during the study and without giving reasons, a patient may decline to participate further. The patient will not suffer any disadvantage as a result.

Patients *may* be withdrawn from the study if any of the following occurs:

- If, in the investigator's opinion, continuation of the study would be harmful to the patient's well-being
- At the specific request of the sponsor and in liaison with the investigator (e.g. obvious non-compliance, safety concerns).

Depending on the time point of withdrawal, a withdrawn patient is referred to as either "screening failure" or "dropout" as specified in the following:

Screening failure

A patient who for any reason (e.g. failure to satisfy the inclusion/exclusion criteria), terminates the study before the time point used for the definition of "dropout" (see below) is regarded a "screening failure".

Dropout

A patient who satisfies all eligibility criteria, and discontinues study participation prior to the second MRI not due to an adverse event is defined as a "dropout" if the patient has already been submitted to the first study MRI.

General procedures

In all cases, the reason for withdrawal must be recorded in the CRF and in the patient's medical records.

The patient may object to the generation and processing of post-withdrawal data as specified in Section 13.4.

Any patient removed from the trial will remain under medical supervision until discharge or transfer is medically acceptable.

Details for the premature termination of the study as a whole (or components thereof) are provided in Section 13.

6.6.2 Replacement

Patients who have undergone a gadoterate-enhanced MRI but have no enhancing lesions identified will not be enrolled. Recruitment will, therefore, continue until at least 180 patients have completed both the gadoterate and gadobutrol studies.

6.7 Patient identification

The patient number is a 9-digit number consisting of:

Digits 1 to 5 = Unique center number

Digits 6 to 9 = Current patient number within the center

After patients have signed an informed consent form, they will be identified by a unique 9 digit patient identification number (PID). The PID will identify the patient throughout the study. The first 2 digits represent the country number, the second 3 digits represent the center number, and the third 4 digits represent a sequential number in the order in which the patient signed the informed consent at the study center. For example, the third patient PPD enrolled at center number PPD in the PPD (14) would be PID PPD

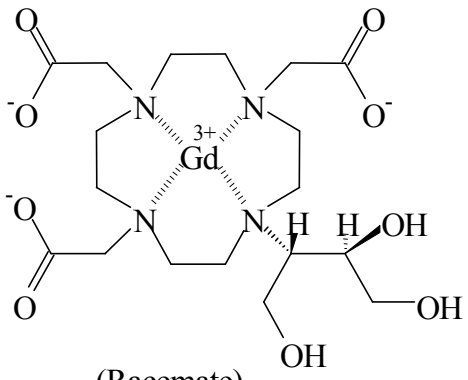
7. Treatments

7.1 Treatments to be administered

7.1.1 Gadobutrol

Gadobutrol injection (Gadovist/Gadavist) is the gadolinium complex of 10-[2,3-dihydroxy-1-(hydroxymethyl) propyl]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetate (see Figure 7-1). This is a neutral chelated, racemic complex of the rare earth element gadolinium (Gd3+). Gadobutrol injection is a white to off-white, highly water soluble substance that is an injectable contrast medium for MRI. Gadobutrol is to be administered by IV injection.

Figure 7-1: Structural Formula of Gadobutrol



(Racemate)

Molecular weight: 604.72 g/mol

Each milliliter of 1.0 molar gadobutrol injection (SH L 562 BB) contains 604.72 mg of pure gadobutrol, 0.513 mg calcium sodium butrol, 1.211 mg tromethamine, 0.1N hydrochloric acid and water for injection. Gadobutrol injection contains no antimicrobial preservative. For a description of the product characteristics, including pertinent physicochemical data, see the Investigator's Brochure.

7.1.2 Gadoterate treatment

The comparator contrast agent is gadoterate (Dotarem®/ Clariscan™), which is approved for steady-state CNS imaging. (See www.guerbet.com for Dotarem package insert, GE Healthcare for Clariscan.)

7.2 Dosage and administration

Patients will receive a single dose of gadoterate at the approved dose, 0.1 mmol/kg BW (± 10 percent), via IV bolus administration using a power injector via a peripheral vein (the antecubital vein is preferred). Gadoterate will be injected at a rate of 2 mL/second followed by a 20-mL 0.9% saline flush at the same rate. If the patient is eligible for inclusion in the study, the patient will undergo a second contrast-enhanced MRI using a single dose of gadobutrol 0.075 mmol/kg BW via IV bolus administration using a power injector via a peripheral vein (the antecubital vein is preferred). Gadobutrol will be injected at a rate of 2 mL/second followed by a 20-mL 0.9% saline flush at the same rate.

The administration of gadoterate and gadobutrol is not randomized. During the 24-hour follow-up period after the gadoterate injection and during the 24-hour follow-up period after the gadobutrol injection, no other contrast agent should be given.

7.3 Identity of study treatment

Marketed drugs will be used for this study. If required at country level, the study drugs will be labeled according to the requirements of local law and legislation. Label text will be approved according to the sponsor's agreed procedures, and a copy of the labels will be made available to the study site upon request.

A complete record of batch numbers and expiry dates of all study treatment as well as the labels will be maintained in the sponsor's study file.

7.4 Blinding

The study is formally unblinded, however, all primary and most secondary efficacy endpoints (except for the open-label site investigator assessments) are blinded.

For the off-site blinded read, study images for each subject will be reviewed both unpaired and paired. The gadoterate and gadobutrol image sets from the same patient will be randomized. For the paired reading, the gadoterate and gadobutrol images will be shown randomly on either the right or left monitor.

Three experienced radiologists who are not involved with the conduct of the study, the evaluation of local study images at the site, and/or the recruitment of patients will be selected to perform the independent blinded image evaluations. Each blinded reading session will have sufficient separation (at least 2 weeks) between the unenhanced and combined unenhanced and enhanced MRI for each contrast agent to minimize recall bias (see Section 11.4). The images used for blinded evaluation sessions will not contain any information regarding the patient's privacy or clinical data. Information on study center, scanner manufacturer, or imaging times will not be provided to the blinded reviewers.

7.5 Drug logistics and accountability

The investigator will use the study drug only within the framework of this clinical study and in accordance with this study protocol. A record of the volume received will be recorded in the patients' eCRFs. Receipt and return of the study drugs must be properly documented on the forms provided by the sponsor.

7.6 Treatment compliance

The study drugs are administered by study center personnel who will record:

- Location of injection
- Study drug start date and time
- Study drug volume and rate of injection

The injection volume and rate of injection of the saline flush will be recorded in the eCRF.

8. Non-study therapy

8.1 Prior and concomitant therapy

Patients are not to receive any contrast agent within 24 hours prior to the first study MRI or 24 hours after the second study MRI. Patients may receive other concomitant medications, including sedation for the MRI examination, during the study. A patient's current medication regimen and/or any additional medication taken from baseline up to 24 hours after the second study MRI will be recorded in the eCRF.

8.2 Post-study therapy

Not applicable as this is a diagnostic-imaging study.

9. Procedures and variables

9.1 Tabular schedule of evaluations

Table 9-1 displays the schedule of evaluations and procedures for the study.

Table 9-1: Schedule of Study Events

		Study Period 1[a]				Study Period 2[a]			Final Diagnosis up to 30 days Phone call
Evaluation/Procedure	Baseline[b]	MRI		Post Injection Phone Contact[c]	Baseline[c]	MRI		Post Injection Phone Contact[c]	
Time Point	Up to 72 hours prior to the 1st MRI	Unenhanced	Enhanced	24h±4h	Within 24 h of the 2nd MRI	Unenhanced	Enhanced	24h (±4 h)	
Sign informed consent	X								
Demographic data	X								
Medical/surgical history	X								
Baseline findings	X								
Referral diagnosis	X								
Previous/concomitant medications[d]	X			X	X			X	
Weight [e]	X[i]				X[i]				
Urine pregnancy test [f]	X[i]								
Creatinine value[g]	X								
Gadoterate administration			X						
Gadobutrol administration							X		
Adverse event monitoring	X	X	X	X	X	X	X	X	
Final clinical diagnosis up to 30 day post first MRI[h]									X

Abbreviations: h = hour(s); immed = immediately; inj = injection; min = minutes

Notes;

[a] A period of 24 h up to 15 days is required between the contrast agent injections;

[b] Baseline for study period 1 is from after signing informed consent up to 72 hours for gadoterate administration;

[c] Baseline for study period 2 is within the 24 h prior to administration of gadobutrol. At least 2 h is required between the 24-h follow-up evaluations from study period 1 and the baseline evaluations for study period 2. The patient will be contacted by phone after 24-hour (± 4 hours) after each contrast agent injection. The two MRI contrast agents will be separated by at least 24 hours, but not more than 15 days. Any TEAEs or TESAEs and/or concomitant medications reported during this period will be recorded in the eCRF.

[d] All concomitant medication will be collected

[e] Weight will be obtained at baseline and reconfirmed prior to the second MRI

[f] Urine pregnancy test (if applicable) to be done at the site, according to the standard of the institution, and the results must be available prior to the gadoterate MRI.

[g] Serum creatinine (eGFR value calculated using either MDRD or the CKD-EPI Creatinine Equation, 2009) derived up to 4 weeks prior to the first study MRI value and date obtained and method used needs to be recorded at Screening.

[h] The final clinical diagnosis will be recorded by the investigator within 30 days of the first study MRI.

i Within 1h of injection

9.2 Study periods

9.2.1 Baseline study period 1

Baseline is the up to 72 hour period from signing informed consent to administration of gadoterate (including saline flush).

Prior to administration of gadoterate the following will be performed: placement of IV injection line, urine pregnancy test (in women of child bearing potential the date and time of the pregnancy test sample and the result of the pregnancy test will be recorded in the eCRF). Results of the pregnancy test must be negative prior to the administration of any contrast agent.

The IV injection line will consist of a large bore indwelling catheter (at least 18 gauge) preferably placed in an antecubital vein. The location of the IV injection line must be documented in the eCRF.

9.2.2 Study period 1

The administration of gadoterate is study period 1 and the administration of the gadobutrol is study period 2.

The following procedures will be performed during study period 1:

1. An unenhanced MRI of the brain will be performed according to the standards of the institution.

2. The appropriate volume corresponding to 0.1 mmol/kg of gadoterate will be administered IV as a bolus injection at the rate of 2 mL/sec using a power injector via a peripheral vein (the antecubital vein is preferred) followed by a 20-mL 0.9% saline flush using a power injector at the same flow rate. The dose and volume of the contrast agent will be recorded.

3. AE monitoring will begin at baseline. All TEAEs will be monitored for 24 hours after the administration of each contrast agent. However, if no enhancing lesion is identified in the first imaging study, the patient will not be included in the safety database and only SAEs for that patient would be reported.

4. Conventional steady-state contrast-enhanced imaging with a T1w sequence according to the parameters listed in Section 10.2.1.2 will start 4 to 10 minutes following the injection of the contrast agent.

5. The patient will be asked about his/her physical condition. Any clinically significant changes in the patient's physical condition from the baseline values are to be recorded in the eCRF, and the TEAE section is to be completed accordingly.

According to the internal clock of the MR device, the date and start time of the first MR sequence, date and start time of the contrast injection and the end time of the complete MR examination will be recorded in the eCRF. Any deviation from the specified MRI procedures and the reason for it (scanner-related problem or patient-related problem) will be recorded in the eCRF.

9.2.3 Baseline study period 2

Any changes in concomitant diseases and concomitant medication will be recorded in the eCRF. The IV injection line will consist of a large bore indwelling catheter (at least 18 gauge) preferably placed in an antecubital vein. The location of the IV injection line must be documented in the eCRF.

9.2.4 Study period 2

The following procedures will be performed:

1. An unenhanced MRI will be performed exactly as done in Study Period 1.

2. The appropriate volume of 75% of the standard gadobutrol dose (0.075 mmol/kg BW) will be administered IV as a bolus injection at the rate of 2 mL/sec using a power injector via a peripheral vein (the antecubital vein is preferred) followed by a 20-mL 0.9% saline flush using a power injector at the same flow rate. The dose and volume of the contrast agent will be recorded.

3. Conventional steady-state contrast-enhanced imaging with a T1w sequence according to the parameters listed in Section 10.2.1.2 will start 4 to 10 minutes following the injection of the contrast agent.
4. The patient will be asked about his/her physical condition. Any clinically significant changes in the patient's physical condition from the baseline values are to be recorded in the eCRF, and the TEAE section is to be completed accordingly.

The date and start time of the first MR sequence, date and start time of the contrast injection and the end time of the complete MR examination will be recorded in the eCRF. Any deviation from the specified MRI procedures and the reason for it (scanner-related problem or patient-related problem) will be recorded in the eCRF.

9.2.5 Post-Injection phone contact

The patient must be contacted by phone after 24-hour (± 4 hours) after each contrast injection. The two MRI contrast agents will be separated by at least 24 hours, but not more than 15 days.

Any TEAEs or TESAEs and/or concomitant medications reported during this period will be recorded in the eCRF.

The end of Study Period 2 is after the 24 hour post injection AE follow-up phone call.

9.2.6 Final clinical diagnosis

The final clinical diagnosis and whether this represents malignant disease will be determined by the investigator using all available clinical information available up to 30 days post-first MRI.

10. Procedures and variables

10.1 Population characteristics

Male and female patients of any ethnic group, who meet the inclusion criteria and none of the exclusion criteria, will be eligible for enrollment into the study.

10.1.1 Demographic

Demographic data (year of birth, age, sex, ethnic group), height, weight, baseline findings, and the suspected or known referral diagnosis according to Table 10-1 will be obtained at baseline.

Table 10-1: Referral Diagnosis of CNS Lesions

- Meningioma
- Anaplastic/malignant meningioma
- Glial tumor, low grade (I/II)
- Glial *tumor*, high grade (III/IV)
- Glial tumor, tumor grade cannot be determined
- Metastases
- Multiple sclerosis (acute and chronic)
- Optic neuritis
- Meningeal disease (focal enhancement)
- Pituitary adenomas (macro and micro)
- Craniopharyngiomas
- Tumors of the choroidal plexus
- Tumors of the pineal gland
- Meningeal carcinomatosis
- Oligodendrogliomas grade II
- Oligodendrogliomas grade III (anaplastic/malignant)
- Chordomas
- Primary lymphoma
- Dermoid/Epidermoid tumors
- Infectious disease (eg, brain abscess, cisticercosis, etc)
- Venous angiomas
- Meningeal spread of meningiomas (dural involvement)
- Cerebelopontine angle tumors
- Von Hippel Lindau syndrome
- Hypertensive leukoencephalopathy
- Subacute/chronic ischemia
- Encephalitis
- Others, specify
- Not assessable

10.1.2 Medical history

Medical history findings (i.e. previous diagnoses, diseases or surgeries) meeting all criteria listed below will be collected as available to the investigator:

- Start before signing of the informed consent
- Considered relevant for the patient's study eligibility.

Detailed instructions on the differentiation between (i) medical history and (ii) adverse events can be found in Section 10.4.1.1.

10.1.3 Prior and concomitant medications

Any medication received within 72 hours prior to the first contrast agent through 24 hours after the second contrast agent will be recorded in the eCRF, including the drug name (brand name is preferred), indication, total daily dose, route of administration, and start and stop dates. Any changes in concomitant medication will also be recorded.

No contrast agent is allowed to be administered within 24 hours prior to the study MRIs or during the study period.

10.2 Efficacy

10.2.1 MRI procedures

10.2.1.1 MRI equipment — AMENDED

The procedure will be performed using either a 1.5 or a 3.0 Tesla MRI scanner that can perform the required pulse sequences (see Section 10.2.1.2) with a dedicated head coil. The manufacturer, model, software version, and field strength of the MRI device will be recorded in the eCRF. The same scanner and required pulse sequences must be used for both the gadoterate and gadobutrol enhanced MRI's.

The same field strength (either 1.5 or 3.0) must be used for both scans. Mixed field strength scans are not permitted.

In addition, T1w enhanced sequences must be performed at or near the same post-dose timepoint (4-10 mins) for each study drug (gadoterate and gadobutrol).

10.2.1.2 Pulse sequences — AMENDED

The same parameter setting must be used for unenhanced T1w images and for contrast-enhanced T1w images in each patient.T1w spin echo/FSE acquisition should be performed in 2D mode. The required pulse sequences for gadobutrol and gadoterate are:

- Unenhanced (axial and sagittal image presentation for brain)
  - T1w spin-echo/FSE images of the whole brain - axial
  - Fluid Attenuated Inversion Recovery (FLAIR) of the whole brain – axial

- Optional: T2w spin-echo images of the whole brain – sagittal or axial

- Contrast-enhanced (axial and coronal image presentation for brain)
  - T1w spin echo/ FSE images of the whole brain

- General considerations
  - The MR scanner should NOT be actively retuned after the unenhanced sequences

Deviations from the specified MRI procedure will be recorded in the eCRF.

10.2.1.2.1 Sequence parameters for brain imaging — AMENDED

The recommended sequence parameters for brain imaging is displayed below in Table 10-2.

Table 10-2: Orientation parallel to the planum sphenoidale (only for axial) — AMENDED

	T2	SE/FSE T1	FLAIR
Plane	Sagittal or Axial	Axial or Coronal	Axial
Pulse Sequence	Spin echo/FSE	Spin echo/FSE	IR
Patient position	Supine	Supine	Supine
Coil	Head	Head	Head
Slice thick/spacing	3-5 skip 0-1.5	3-5 skip 0-1.5	3-5 skip 0-1.5
Frequency	≥256	≥256	≥256
Phase	≥256	≥256	≥128
Nex	≥2	≥2	≥1

10.2.1.3 Quality assurance of images

The investigator must assure that the unenhanced MRI image set (T1w, FLAIR and T2w) is of acceptable diagnostic quality. It is known that in CNS imaging, motion artifacts, aliasing artifacts, and/or other disturbing artifacts (e.g. metal implants or dental brace) can, in rare instances impact the ability to interpret images of the brain. In such cases, the enhanced images will also be similarly impacted. The investigator must insure that the unenhanced images are interpretable, or document why the technical quality impacts the evaluation.

All image sets will be sent to the imaging core lab (the Bayer internal General Clinical Imaging Service, GCIS).

Quality control and quality assurance of the MR images and conduct of the blinded readings will be done at the image core laboratory, GCIS in Berlin, Germany.

10.2.1.4 Image archiving and copying

Once all the study-related images are acquired, both sets of unenhanced images and all contrast-enhanced MRI images must be stored on appropriate archival media at the site. Study images should be uploaded to GCIS without time delay (max. 5 business days).

The images must not include the patient's privacy data such as name or initials or other personal identifier, sex and birth date, but his/her patient number and the study number must be included. No further information needs to be given. Further details and guidance for the sites will be provided in the Imaging Manual by GCIS. An overview of the imaging efficacy variables is provided in Table 10-3.

Table 10-3: Overview of the imaging efficacy variables

	Unenhanced MRI 1	Combined unenhanced and gadoterate-enhanced MR	Unenhanced MRI 2	Combined unenhanced and gadobutrol-enhanced MRI	Paired Gadobutrol-enhanced T1w and Gadoterate-enhanced T1w MRI
Variables	BR	BR	BR	BR	BR
Degree of contrast enhancement (lesions)	✓	✓	✓	✓	
Assessment of border delineation (lesions)	✓	✓	✓	✓	
Internal morphology (lesions)	✓	✓	✓	✓	
Overall contrast enhancement (Core Lab)	✓	✓	✓	✓	
Total number of lesions detected	✓	✓	✓	✓	
Malignant Disease		✓		✓	
Confidence in diagnosis		✓		✓	
Image quality					✓

10.2.1.5 Primary efficacy variables

The following 3 lesion visualization parameters scored by the blinded readers constitute the primary efficacy variables:

- Degree of lesion contrast enhancement
- Lesion Border delineation

- Lesion Internal morphology

The independent blinded readers will evaluate the 3 primary variables (visualization parameters) for up to the 5 largest lesions in each of the following images/image sets separately:

- Unenhanced and Combined unenhanced (T1w, T2w, FLAIR) and gadoterate-enhanced (T1w) MR image sets
- Unenhanced and Combined unenhanced (T1w, T2w, FLAIR) and gadobutrol-enhanced (T1w) MR image sets

For the evaluation of the degree of contrast enhancement, border delineation, and internal morphology the blinded readers will score the lesion using the image sequence which best depicts each variable.

10.2.1.5.1 Degree of contrast enhancement

A total of up to the 5 largest lesions will be selected and scored by the blinded readers.

The following 4-point scale will be used for lesion enhancement:

1 =	No	lesion is not enhanced
2 =	Moderate	lesion is weakly enhanced
3 =	Good	lesion is clearly enhanced
4 =	Excellent	lesion is clearly and brightly enhanced

The score for each lesion will be recorded in the eCRF. This will be evaluated according to Table 10-3.

10.2.1.5.2 Border delineation

Up to 5 of the largest lesions will be selected and scored by the blinded readers.

The following 4-point scale will be used for lesion delineation:

1 =	None	no or unclear delineation of the lesion boundaries
2 =	Moderate	some aspects of border delineation covered
3 =	Good	almost clear, but not complete delineation
4 =	Excellent	clear and complete delineation

The internal morphology score will be recorded into eCRF. This will be evaluated according to Table 10-3.

10.2.1.5.3 Internal morphology

Up to 5 of the largest lesions will be selected and scored by the blinded readers.

The following 3-point scale will be used for lesions:

1 =	Poor	the structure and internal morphology of the lesion is poorly visible
2 =	Moderate	the structure and internal morphology of the lesion is partially visible
3 =	Good	the structure and internal morphology of the lesion is sufficiently visible

The internal morphology score will be recorded into eCRF. This will be evaluated according to Table 10-3.

10.2.1.6 Secondary efficacy variables

10.2.1.6.1 Quantitative contrast enhancement estimation - AMENDED

Quantitative contrast enhancement estimation will be performed using an exploratory Overall Contrast Enhancement Estimation Algorithm. Descriptive statistics will be presented for each study drug (gadoterate and gadobutrol).

10.2.1.6.2 Diagnosis of Malignancy/Confidence in Diagnosis

The blinded readers will determine if the pathology detected in the combined image sets is benign or malignant. These scores will be matched with the final diagnosis of malignant or benign disease based on the final diagnosis provided by the Investigator.

The blinded readers will record in the eCRF his/her confidence in diagnosis for each patient for the combined unenhanced and gadobutrol-enhanced MR image sets, and the combined unenhanced and gadoterate-enhanced MR image sets separately.

Diagnostic confidence will be evaluated to determine the level of certainty that the blinded readers assign to a diagnosis. This is defined as the degree of confidence that the information on the images represents the true and complete clinical picture of a patient. The degree of confidence will be rated on a 4-point scale:

1 = Not confident

2 = Some what confident

3 = Confident

4 = Very confident

10.2.1.6.3 Image quality

The blinded readers will evaluate the relative image quality of the gadobutrol-enhanced T1w MR images and the gadoterate-enhanced T1w MR images. The assessment will be based on the overall subjective interpretation of the degree of contrast enhancement, border delineation, and internal morphology. These images will be presented in a paired fashion in a separate reading session. The gadobutrol and gadoterate images will be randomly assigned to either the left (image L) or right (image R) positions.

Image quality will be compared on a 5-point scale:

1 = Image R is worse
2 = Image R is slightly worse
3 = Image R is same
4 = Image R is slightly better
5 = Image R is better

10.2.1.6.4 Total number of lesions

For each image set, the blinded reader is to record the total number of lesions up to a maximum of 10 lesions.

10.3 Pharmacokinetics

Not applicable.

10.4 Safety

10.4.1 Adverse events

10.4.1.1 Definitions

Definition of adverse event (AE) and treatment emergent AEs

In this study, adverse events (AEs), defined as any untoward medical occurrence (i.e. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation patient after signing informed consent will be recorded.

A treatment emergent AE is defined as any AE that is reported after the patient has received at least one dose of study drug. Therefore, a TEAE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

Pathology identified on the MRI will not be considered a TEAE.

A surgical procedure that was planned prior to the start of the study by any physician treating the patient should not be recorded as a TEAE (however, the condition for which the surgery is required may be a TEAE).

In the following differentiation between medical history and TEAEs, the term "condition" may include abnormal e.g. physical examination findings, symptoms, diseases, laboratory results, ECG.

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present until signing of informed consent are recorded as medical history (e.g. seasonal allergy without acute complaints).
- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at *unchanged intensity*, are recorded as medical history (e.g. allergic pollinosis).
- Conditions that started or deteriorated after signing of informed consent will be documented as adverse events. This includes intercurrent illnesses.

Definition of serious AE (SAE) and treatment emergent serious (TESAE)

A SAE is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria (a – f) and a TESAE is any SAE that is reported after the patient has received at least one dose of study drug.

The criteria for both an SAE and a TESAE are:

a. Results in death
b. Is life-threatening

   The term 'life-threatening' in the definition refers to an event in which the patient was at risk of death at the time of the event, it does not refer to an event which hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

   A hospitalization or prolongation of hospitalization will not be regarded as a SAE or TESAE if at least one of the following exceptions is met:

   - The admission results in a hospital stay of less than 12 hours
   - The admission is pre-planned
     (e.g. elective or scheduled surgery arranged prior to the start of the study; admission is part of the study procedures as described in Section 9.2)
   - The admission is not associated with an AE
     (e.g. social hospitalization for purposes of respite care).

   However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of 'medically important' and as such may be reportable as a SAE / TESAE

dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

d. Results in persistent or significant disability / incapacity
   Disability means a substantial disruption of a person's ability to conduct normal life's functions.
e. Is a congenital anomaly / birth defect
f. Is another serious or important medical event as judged by the investigator

10.4.1.2 Classifications for adverse event assessment

All AEs /TEAEs will be assessed and documented by the investigator according to the categories detailed below.

10.4.1.2.1 Seriousness

For each AE / TEAE, the seriousness must be determined according to the criteria given in Section 10.4.1.1.

10.4.1.2.2 Intensity

The intensity of an AE / TEAE is classified according to the following categories:

- Mild
- Moderate
- Severe

10.4.1.2.3 Causal relationship

The assessment of the causal relationship between an AE / TEAE and the administration of treatment is a decision to be made by the investigator, who is a qualified physician, based on all information available at the time of the completion of the CRF.

Causality should be assessed separately for each study treatment as detailed in the CRF. If the investigator feels that the event cannot be firmly attributed to one of the study treatments (e.g. owing to a suspected underlying interaction), the same assessment will be documented for each study treatment.

The assessment is based on the question whether there was a "reasonable causal relationship" to the study treatment in question.

Possible answers are "yes" or "no"

An assessment of "no" would include:

1. The existence of a highly likely alternative explanation, e.g. mechanical bleeding at surgical site.

or

2. Non-plausibility, e.g. the patient is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration.

An assessment of "yes" indicates that that the TEAE is reasonably associated with the use of the study treatment.

10.4.1.2.4 Other specific treatment(s) of AEs / TEAEs

- None
- Remedial drug therapy
- Other

10.4.1.2.5 Outcome

The outcome of the AEs / TEAEs is to be documented as follows:

- Recovered/resolved
- Recovering/resolving
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Fatal
- Unknown

10.4.1.3 Assessments and documentation of adverse events

The investigator must record on the respective CRF pages all adverse events occurring in the period between the signing of the informed consent and the end of the follow-up phase; all SAEs/TESAEs must be followed to resolution. After the end of the follow-up phase there is no requirement to actively collect TEAEs including deaths. The type of information that should be assessed and recorded by the investigator for each TEAE is listed in Section 10.4.1.2.

10.4.1.4 Expected TEAEs

Known TEAEs of radiographic or MRI contrast media may occur following administration of gadobutrol. The majority of TEAEs occur within 30 minutes of administration; this is the minimum period during which the patient should be under continuous supervision. The most common TEAEs after administration of gadobutrol are nausea, headache and dizziness. Other TEAEs that may occur include (but are not limited to) taste perversion, paresthesia, vomiting,

hypersensitivity reactions, dyspnea, erythema, pruritus, rash, injection site reactions and feeling hot.

For IV injection of gadobutrol, the routine precautions and supervision should be used as with any other radiographic or MRI contrast medium. In very rare cases, severe anaphylactoid reactions or shock may occur. Familiarity with the practice of emergency procedures is essential for prompt, efficient action in the event of post injection TEAEs. Appropriate emergency staff, drugs, and instruments (eg, endotracheal tube and ventilator) must be readily available. Symptoms such as itching skin, or a coughing fit may be the first signs of an anaphylactoid reaction. Administration of the contrast medium must be discontinued immediately, and any complications treated according to generally accepted clinical guidelines.

The adverse event rate and general safety profile of gadobutrol is comparable to other Gd-based, approved MRI contrast agents (eg, gadoterate).

10.4.1.5 Reporting of serious adverse events

The definitions of SAEs /TESAEs are given in Section 10.4.1.1. Each SAE /TESAE must be followed up until resolution or stabilization by submission of updated reports to the designated recipient.

“Death” should not be recorded as a SAE /TESAE on the SAE /TEAE page. Instead, “death” is the outcome of underlying SAE /TESAE (s).

For all SAEs the sponsor has to carry out a separate assessment for expectedness, seriousness and causal relationship to study drug.

Investigator’s notification of the sponsor

All investigators will be thoroughly instructed and trained on all relevant aspects of the investigator’s reporting obligations for SAEs / TESAEs. This information, including all relevant contact details, is summarized in the investigator site file. This information will be updated as needed.

The investigator must report immediately (within 24 hours of the investigator’s awareness) all SAEs / TESAEs occurring during the observation period defined in Section 10.4.1.3 to the recipient detailed in the instructions for SAE / TESAE reporting included in the Investigator File. For this, a SAE / TEAE page in the CRF as well as the complementary pages provided in the Investigator File must be completed for each SAE /TESAE.

All SAEs occurring after the protocol-defined observation period will be processed by the sponsor according to all applicable regulations.

Notification of the IECs / IRBs

Notification of the IECs / IRBs about all relevant events (e.g. TESAE s, suspected, unexpected, serious adverse reactions [SUSARs]) will be performed by the sponsor/CRO and/or by the investigator according to all applicable regulations.

Notification of the authorities

The processing and reporting of all relevant events (e.g. TESAE s, SUSARs) to the authorities will be done by the sponsor according to all applicable regulations.

Sponsor's notification of the investigational site

The sponsor/CRO will inform all investigational sites about reported relevant events (e.g. SUSARs) according to all applicable regulations.

10.4.1.6 Expected adverse events

For this study, the applicable reference documents are the current versions of the package insert/SmPC for each imaging agent.

The expectedness of TEAEs will be determined by the sponsor according to the applicable reference document and according to all local regulations.

10.5 Prospective blinded image evaluation and centralized procedures

Diagnostic efficacy will be evaluated by prospective evaluations of the blinded images in a centralized manner. The blinded readers will be independent radiologists who have not been involved in the clinical study. They will be blinded to all patient history and will not have any information about the study center, detailed information about the sequence parameters, the application of the contrast agent, or the study protocol. Further details on blinded image evaluation and centralized procedures will be provided in the Image Review Charter by GCIS.

10.5.1 Image handling and preparation

All image sets that are required in this protocol will be provided electronically in DICOM format by the centers.

The images will be sent to the image core laboratory GCIS, Berlin, where the images will be prepared for evaluation. Received images will be reviewed by the core laboratory for quality control with regard to clinical appropriateness and protocol adherence. If an issue is found, the core laboratory or its representative will contact the investigator and attempt to correct it for future patients.

An audit trail will be maintained.

All software for the image processing is standardized.

10.5.2 Blinded reading evaluations

The blinded image evaluations will be performed centrally at the image core laboratory by independent radiologists experienced in CNS imaging who are not involved in the clinical portion of the study. A core-lab generated blinded read eCRF will be used to ensure that the images and the diagnostic findings are properly aligned and to ensure that all questions are answered by the blinded readers.

The blinded read will be in three sessions. The first session will score the lesion variables for unenhanced and combined Agent 1 and a determination of malignant disease and confidence.

Two weeks later – the same blinded read procedure will be followed for Agent 2.

At a third session, the blinded readers will score a paired presentation of the t1w enhanced images for image preference.

Additional details will be provided in the Image Review Charter by GCIS.

In case one of the readers cannot continue the reading (e.g. illness), a new reader will be selected and trained. A separate blinded reading manual contains the details.

Training will be provided for the reader before the blinded image evaluation in the completion of the eCRF, in the operation of the imaging work station (eg, window and leveling controls), and in the specific protocol language, such as the definition of the scores used for the imaging variables and image quality. A refresher training session may be provided prior to each reading session.

Refresher training sessions may be provided as applicable. Reading sessions will be usually conducted in a remote setting (web based) with each reviewer separated from each other In case reading sessions will be conducted at centralized facilities it will be ensured that readers are monitored by GCIS staff or qualified external personnel.

A core lab representative might be present at the time of the blinded read to answer technical questions initiated by the readers such as use of equipment or completion of eCRFs. All interactions will be documented. All personnel present during a reading session will be blinded to image modality assignment and other clinical data and will be subject to the applicable financial disclosure. The identity and the relationship to the sponsor of such personnel will be recorded.

Exceptionally a case may be re-opened and re-evaluated due to any circumstance that is significantly impacting the correct reading process or interpretation of study images, e.g., erroneous completion of a case, any non-compliance issues, and additional site information delivered after the time of the original reading or technical issues. The responsible Imaging Clinician will review such cases before authorizing a re-evaluation of the case, and only data that is directly affected by the respective error or circumstances should be subject to a reassessment by the Independent Central Reader. A thorough explanation and documentation will be provided within the Image Evaluation Summary Report.

Complete re-reads of all images and cases may only be permitted prior to the primary analysis when a reader has to be replaced due to non-compliance or systematic errors.

If cases have to be re-assessed it will be documented in the audit trail. This documentation is enforced by the image evaluation module (IEM) system.

The blinded image evaluations may take place in parallel with the conduct of the clinical trial.

10.5.3 Technical prerequisites for blinded readings

10.5.3.1 Blinded image evaluation system

Blinded image evaluations will be conducted using full fidelity digital images. The system type and workstation details will be documented in an Imaging Review Charter provided by the core laboratory and maintained in the sponsor's TMF.

The number of screens needed for the blinded image evaluation will be adapted to the different reading parts.

Standard functions at the image visualization system will be available to the reader during the review sessions, eg.:

- Ability to change the image brightness and contrast (level/window) of all image material and screens
- Ability to move through the images of one set
- Ability of image zoom and move

10.5.3.2 Electronic CRF design

An eCRF will be used for the electronic data capture of the evaluation results by the blinded readers during the reading sessions as discussed in Section 10.5.2. The eCRF application allows for a logical progression design with a built-in plausibility check according to the user requirements document, forcing the readers to answer the appropriate questions and auto-checking for missing data. Once the blinded reader has completed a case, no further changes can be made by the blinded reader. This process facilitates the efficient and timely completion of the digital based image review.

Each eCRF is developed based on the annotated CRF created by the sponsor following the requirements of the central destination database.

Adequate data transfer to the sponsor's database is guaranteed and will be tested prior to the start of the blinded image evaluation.

The plausibility check built into the eCRF will guarantee that:

- All entries will be made and checked according to logical plausibility
- The next case to be evaluated can only be started after the entries for the current case have been finished.

All data required by the protocol are to be entered into the eCRF. A trained monitor from the core laboratory may be available to assist the reader in entering his/her appropriate answers into the eCRF fields.

Once the reader has completed the appropriate section of the eCRF, he or she will be asked to enter a password in order to approve the eCRF case record. After approval, the entry pages are locked and no further changes can be made. The eCRF will be signed by the blinded reader immediately after each case.

All evaluations will be stored in the sponsor's central study destination database for analysis.

10.5.4 Randomization of image material

Each image set from a single patient will be assigned separate randomization numbers for each session.

10.5.4.1 Independent blinded reader training

All readers will undergo training prior to the start of the blinded image evaluations. Training will be provided by the core laboratory, GCIS. The training sessions will include a review of the appropriate study guidelines, a review of the image display software, a review of the eCRF, and a review of teaching and training cases. A record of the training sessions will be maintained, with signatures and dates of the blinded readers and the personnel performing the training. The training session data and images will be archived along with the images from the blinded evaluations.

Teaching cases comprised of images not included in the actual image evaluation sessions will be reviewed with the readers, noting presentation of various radiologic findings. Additionally, the blinded readers will conduct a "mock" blinded image evaluation on training cases that will not be part of the study data. The training image evaluations will be identical to the actual image evaluations in process and will allow the blinded readers to work with the image review software and the eCRF. The training session will be conducted prior to the start of the actual blinded image evaluations. Results of the training sessions will be conjointly reviewed with the readers prior to the start of the actual blinded image evaluations.

10.5.4.2 Blinded image evaluation of the MRI

The blinded image evaluations are described in detail in the IRC.

All readers will be completely blinded with regard to patient data, clinical information, center-related and imaging-related information as well as details of the study protocol.

10.5.4.3 Quantitative contrast enhancement

Quantitative contrast enhancement estimation will be performed using an exploratory Overall Contrast Enhancement Estimation Algorithm. Results will be summarized by MRI modality using descriptive statistics and confidence intervals.

10.6 Appropriateness of procedures and measurements

The efficacy and safety measurements described above are widely used and generally accepted as reliable, accurate, and relevant.

The comparison of the study drug (gadobutrol) with an approved comparator product for noninferiority reflects a reliable clinical and scientific technique to determine efficacy and safety.

The blinded MRI reading procedure with independent radiologists is planned to minimize bias from the clinical study, because clinical investigators' diagnoses might be influenced by other clinical information they might have received about the patients.

The safety parameters evaluated in this study are routine clinical parameters and allow risk assessment of the investigational drug.

11. Statistical methods and determination of sample size

11.1 General considerations

11.2 Statistical and analytical plans

11.2.1 General considerations

The primary efficacy analyses of the 3 primary efficacy variables (visualization) will be done using the average (arithmetic mean) of the values of the 3 blinded readers. The analysis of these variables and the analyses of the secondary efficacy variables will also be performed on the data from the 3 blinded readers individually.

For border delineation, contrast enhancement, and internal morphology, there will be multiple values for each patient (ratings for multiple lesions). The average (arithmetic mean) of these ratings will be used for the primary and secondary analyses. To avoid using a scoring system that rates the detection of fewer but more well-visualized lesions over the detection of more lesions, some of which may be not so well visualized, the analysis will be performed using zero-filled averages of the ratings for each patient.

In cases where the scans detect different number of lesions, enough zeros will be included with the scores for the modalities which detected fewer lesions to make the average for each modality based on the same number of scores. This zero-filled average will always reward the detection of extra lesions.

Demographic variables (age, race, sex, etc.) will be summarized using frequency tables and descriptive statistics.

Safety variables will be summarized using descriptive statistics and frequency tables.

All confidence intervals will be 2-sided, 95% intervals.

Statistical tests for superiority will be 2-tailed, using the 0.05 level of significance. Any statistical tests used for noninferiority will be one sided tests using the 0.025 level of significance.

11.3 Analysis sets

11.3.1 Definition of efficacy analysis set

Analyses of efficacy data will be performed using data from all patients for whom eCRF entries and images are available for unenhanced MRI, combined unenhanced and gadobutrol-enhanced MRI, and combined unenhanced and gadoterate-enhanced MRI. This population will be the full analysis set (FAS).

Efficacy analyses will also be performed using data from those patients from the FAS who also fulfill all major provisions of this protocol. This set will be the per protocol analysis set (PPS).

A patient will be excluded from the PPS for any one of the following reasons:

1. The patient received a dose of gadobutrol that was less than 90% or greater than 110% of the assigned dose.

2. The patient received a dose of gadoterate that was less than 90% or greater than 110% of the assigned dose.

3. An obvious error in the MRI procedure occurred either during the gadobutrol period or during the gadoterate period.

4. Pertinent images for the patient are damaged or lost.

11.3.1.1 Definition of safety analysis set

Analysis of safety data will be performed using all available data from all enrolled patients.

11.4 Variables and planned statistical analyses

11.4.1 Primary efficacy variables

The 3 primary analysis variables are:

- Lesion border delineation
- Degree of lesion contrast enhancement
- Lesion internal morphology

For the 3 variables, the average (arithmetic mean) lesion score will be calculated for each patient based on the scores for each individual lesions in a given patient.

11.4.1.1 Primary efficacy analysis - visualization parameters

The primary efficacy analysis is based on the data from the blinded readers' evaluation of 3 visualization parameters, which are evaluated in unenhanced and combined unenhanced and enhanced MR image sets.

A successful primary analysis is a demonstration of noninferiority for the difference between unenhanced and combined gadobutrol and unenhanced and combined gadoterate enhanced and unenhanced MRI to unenhanced MRI for the first 3 primary visualization parameters.

1. the contrast enhancement (measured on an ordinal 4-point scale);
2. the border delineation (measured on an ordinal 4-point scale);
3. the internal morphology (measured on an ordinal 3-point scale)

The analysis for three of these parameters (1, 2, and 3) will be performed on the mean of the values for the 3 blinded readers (blinded reader average). This analysis will be performed on the dataset including the patient average ratings for lesions.

For each parameter a noninferiority hypothesis will be considered, where the comparison will relate to a reasonable portion (c=0.2) of the difference between combined unenhanced and gadoterate mean to unenhanced. The goal is to show, that the loss in the visualization parameter (gadoterate - gadobutrol) is lower than a 0.2 times the combined gadoterate and unenhanced to unenhanced mean, which is equivalent to (gadobutrol – gadoterate) is greater than -0.2 times the combined gadoterate and unenhanced to unenhanced mean. "Mean" is the mean of the blinded reader averages.

The null and alternative hypotheses for noninferiority are:

H_0: (gadobutrol – gadoterate) $\leq$ - 0.2*(gadoterate – unenhanced), versus
~~K_0~~ H_1: (gadobutrol – gadoterate) $>$ - 0.2*(gadoterate – unenhanced),

where "(gadobutrol – gadoterate)" indicates the difference between combined unenhanced and gadobutrol mean to unenhanced mean minus the difference of combined unenhanced and gadoterate mean to unenhanced mean. The expression "(gadoterate – unenhanced)" indicates the difference between combined unenhanced and gadoterate mean to unenhanced mean.

The study is considered successful if all 3 hypotheses related with these co-primary target variables can be rejected each at a one-sided alpha of 0.025 or equivalently at a two-sided alpha of 0.05. Appropriate paired t-tests will be used.

No type I error adjustment for multiple comparisons is needed because tests on all 3 variables must be significant to demonstrate primary efficacy.

In addition 95% two-sided confidence intervals for the mean difference of the gadobutrol score and the gadoterate score will be calculated.

The primary analysis will be performed using data from evaluations from lesions.

11.4.2 Secondary efficacy variables

The secondary efficacy variables will be the evaluation of the detection of malignant disease. The evaluation of quantitative parameters will be performed by GCIS and image quality will be evaluated only by the blinded reader(s).

The secondary efficacy variables are the:

- Comparison of contrast enhancement utilizing an exploratory Overall Contrast Enhancement Estimation Algorithm.
- Number of lesions identified (up to 10)
- Identification of benign or malignant disease
- Confidence in diagnosis
- Image quality

11.4.2.1 Overall Contrast Enhancement Estimation Algorithm

Quantitative contrast enhancement estimation will be performed using an exploratory Overall Contrast Enhancement Estimation Algorithm. Results will be summarized by MRI modality using descriptive statistics and confidence intervals.

11.4.2.2 Number of lesions able to be identified

A confidence interval for the difference in the number of lesions detected by the 2 contrast agents will be constructed. Noninferiority of number of lesions detected will be demonstrated using confidence intervals based on the t-distribution with a noninferiority margin of 0.35.

11.4.2.3 Identification of benign or malignant disease

The investigator determines if the patient has benign or malignant disease.

The presence or absence of malignant disease in each patient for both contrast agents will be determined by the blinded readers, as well as the majority blinded reader (at least 2 of 3 readers), and compared to the investigators' assessment to calculate sensitivity and specificity for each drug.

Sensitivity, specificity, and accuracy for each drug will be compared using a McNemar's test with a noninferiority margin of 10 percent.

11.4.2.4 Confidence in diagnosis — AMENDED

Frequency tables for confidence responses (1-4) for patients will be constructed for combined unenhanced and gadoterate-enhanced MRI, and combined unenhanced and gadobutrol-enhanced MRI. Descriptive statistics for the combined unenhanced and gadobutrol and gadoterate enhanced

MRI and their difference will be generated. Confidence intervals for the differences will be generated.

11.4.2.5 Image quality

The blinded readers will evaluate relative image quality of gadobutrol and gadoterate as described in Section 10.2.1.6.3.

After the data are unblinded, the 5-point scale used by the blinded readers will be translated into the following scale:

-2 = Gadobutrol image is worse
-1 = Gadobutrol image is slightly worse
0 = Images are the same
1 = Gadobutrol image is slightly better
2 = Gadobutrol image is better

Frequency tables and descriptive statistics will be generated on these values, and the relative image qualities will be tested for equality using a Wilcoxon signed-rank test.

11.4.2.6 Analysis of safety variables — AMENDED

Frequencies of TEAE s will be tabulated by contrast agent and the proportions of patients exhibiting each TEAE will be displayed. Tabulations will also be made for the body system, intensity, and attribution corresponding to each TEAE. Separate tabulations will be made for serious TEAEs.

11.5 Determination of sample size

The determination of the sample size was based on the primary noninferiority test for the difference between unenhanced means and combined gadobutrol-enhanced and unenhanced means and combined gadobutrol-enhanced and unenhanced means to unenhanced means.

It considers all three primary efficacy visualization parameters.

1. the contrast enhancement
2. the border delineation
3. the internal morphology

For each parameter a non-inferiority hypothesis will be considered, where the comparison will relate to a reasonable portion of the difference between gadoterate and unenhanced. The goal is to show, that the loss in the visualization parameter (gadoterate - gadobutrol) is lower than a constant times the combined gadoterate and unenhanced to unenhanced.

The mean differences of combined gadobutrol and unenhanced to unenhanced, “(gadobutrol-unenhanced)”, observed in the pivotal study 310123 for these parameters will be used for power calculation (1.29, 0.60, 0.61).

The related statistical hypotheses read as follows:

- H_0: (gadobutrol - gadoterate) ≤ - 0.2*(gadoterate – unenhanced)

  vs.

- ~~K_0~~ H_1: (gadobutrol – gadoterate) > - 0.2*(gadoterate – unenhanced)

The study is considered successful if all 3 hypotheses related with these co-primary target variables can be rejected at a one-sided alpha of 0.025 or equivalently at a two-sided alpha of 0.05. Appropriate paired t-tests will be used.

Rejection of such a hypothesis means that it is demonstrated that gadobutrol (at reduced dose) preserves at least 80% of the effect gadoterate /Dotarem has compared to unenhanced images.

Enrolling 180 subjects allows for approximately 25% non-evaluable patients and guarantees 90% power for border delineation. For the remaining two variables the power will be close to 100% with this sample size. Hence also the overall power of this study will be 90%.

No type I error adjustment for multiple comparisons is needed because tests on all 3 variables must be significant to demonstrate primary efficacy.

12. Data handling and quality assurance

12.1 Data recording

The data collection tool for this study will be a validated electronic data capture system called RAVE. Subject data necessary for analysis and reporting will be entered/ transmitted into a validated database or data system (SAS).

Data required according to this protocol will be recorded by investigational site personnel via data entry into the internet based electronic data capture (EDC) software system RAVE, which has been licensed from Medidata Solutions Worldwide. RAVE has been validated by Medidata Solutions Worldwide for use in Bayer's clinical studies. RAVE allows for the application of software logic to set-up data entry screens and data checks to ensure the completeness and accuracy of the data entered by the site personnel. The logic has been extensively applied to ensure data are complete and reflect the clinical data requirements of the study. Data queries resulting from the application of the software logic are resolved by the site personnel. The data are stored at a secure host facility maintained by Medidata Solutions Worldwide, and transferred by the CRO to Bayer's internal computers via secure lines.

All access to the RAVE system is through a password-protected security system that is part of the RAVE software. All internal Bayer and external investigator site personnel as well as the CRO personnel seeking access must go through a thorough RAVE training process before they are granted access to RAVE for use in Bayer's clinical studies. Training records are maintained.

All personnel with access to the RAVE system are supported by a Service Desk staffed with trained personnel to answer questions and ensure access is maintained such that data entry can proceed in a timely manner.

The RAVE System contains a system-generated audit trail that captures any changes made to a data field, including who made the change, why the change was made and the date and time it was made. This information is available both at the investigator's site and at Bayer. Data entries made in the RAVE EDC screens are supported by source documents maintained for all subjects enrolled in this study.

Source documentation

The site must implement processes to ensure availability of all required source documentation. A source document checklist (not part of this protocol) will be used at the site to identify the source data for key data points collected and the monitor will work with the site to complete this.

It is the expectation of the sponsor that all data entered into the eCRF has source documentation available at the site.

Data recorded from screening failures

At minimum, the following data should be recorded in the CRF:

- Demographic information (patient number; year of birth / age; sex; if applicable race / ethnicity)
- Date of informed consent
- Relevant inclusion/exclusion criteria
- Reason for premature discontinuation
- Date of last visit.

These data will be transferred to the respective database.

For screening failures with a SAE / TESAE, the following data should be collected in the CRF in addition to the data specified above:

- All information related to the SAE / TESAE such as:
  - The SAE / TESAE itself
  - Concomitant medication
  - Medical history
  - Other information needed for SAE / TESAE complementary page

12.2 Monitoring

In accordance with applicable regulations, GCP, and sponsor's/CRO's procedures, monitors will contact the site prior to the start of the study to review with the site staff the protocol, study

requirements, and their responsibilities to satisfy regulatory, ethical, and sponsor's requirements. When reviewing data collection procedures, the discussion will also include identification and documentation of source data items.

The sponsor/designee will monitor the site activity to verify that the:

- Data are authentic, accurate and complete.
  Supporting data may be requested (example: blood glucose readings to support a diagnosis of diabetes).
- Safety and rights of patients are being protected
- Study is conducted in accordance with the currently approved protocol (including study treatment being used in accordance with the protocol)
- Any other study agreements, GCP, and all applicable regulatory requirements are met.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents. Details will be provided in the Monitoring Plan.

12.3 Data processing

Data will be collected as described in Section 12.1. Clinical data management will be performed in accordance with applicable sponsor's / CRO's standards and data cleaning procedures. This is applicable for data recorded on CRF as well as for data from other sources.

For data coding (e.g. AEs /TEAEs, medication), internationally recognized and accepted dictionaries will be used.

12.4 Missing data

Not applicable

12.5 Audit and inspection

To ensure compliance with GCP and regulatory requirements, a member of the sponsor's (or a designated CRO's) quality assurance unit may arrange to conduct an audit to assess the performance of the study at the study site and of the study documents originating there. The investigator/institution will be informed of the audit outcome.

In addition, inspections by regulatory health authority representatives and IEC(s)/IRB(s) are possible. The investigator should notify the sponsor immediately of any such inspection.

The investigator/institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study.

12.6 Archiving

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request.

Patient (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice. Where the archiving procedures do not meet the minimum timelines required by the sponsor (i.e.15 years after the end of study), alternative arrangements must be made to ensure the availability of the source documents for the required period.

The investigator/institution notifies the sponsor if the archival arrangements change (e.g. relocation or transfer of ownership).

The investigator site file is not to be destroyed without the sponsor's approval.

The contract with the investigator/institution will contain all regulations relevant for the study center.

13. Ethical and legal aspects

13.1 Investigator(s) and other study personnel

All other study personnel not included in this section are identified in a separate personnel list (not part of this clinical study protocol) as appropriate. This list will be updated as needed; an abbreviated version with personnel relevant for the centers will be available in each center's investigator site file.

Whenever the term 'investigator' is noted in the protocol text, it may refer to either the principal investigator at the site, or an appropriately qualified, trained and delegated individual of the investigational site.

The principal investigator of each center must sign the protocol signature page and must receive all required external approvals (e.g. health authority, ethics committee, sponsor) before patient recruitment may start at the respective center. Likewise, all amendments to the protocol must be signed by the principal investigator and must have received all required external approvals before coming into effect at the respective center.

A complete list of all participating centers and their investigators, as well as all required signature documents, will be maintained in the sponsor's study file.

The global sponsor of this study is identified on the title page of this protocol. If required by local law, local co-sponsors will be nominated; they will be identified on the respective country-specific signature pages.

13.2 Funding and financial disclosure

Funding

This study will be funded by its sponsor.

Financial disclosure

Each investigator (including principal and/or any sub investigators) who is directly involved in the treatment or evaluation of research patients has to provide a financial disclosure according to all applicable legal requirements. All relevant documentation will be filed in the trial master file.

13.3 Ethical and legal conduct of the study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by Good Clinical Practice (GCP) guidelines and the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IEC(s)/IRBs will be obtained for all participating centers/countries before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the IEC/IRB approval must be obtained and also forwarded to the sponsor. The responsible unit (e.g. IEC/IRB, head of the study center/medical institution) must supply to the sponsor, upon request, a list of the IEC/IRB members involved in the vote and a statement to confirm that the IEC/IRB is organized and operates according to GCP and applicable laws and regulations.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator or the sponsor may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial patients without prior IEC/IRB/sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IEC/IRB/head of medical institution/sponsor. Any deviations from the protocol must be explained and documented by the investigator.

13.4 Patient information and consent

All relevant information on the study will be summarized in an integrated patient information sheet and informed consent form provided by the sponsor or the study center. A sample patient information and informed consent form is provided as a document separate to this protocol.

Based on this patient information sheet, the investigator or designee will explain all relevant aspects of the study to each patient, prior to his/her entry into the study (i.e. before any examinations and procedures associated with the selection for the study are performed or any study-specific data is recorded on study-specific forms).

The investigator will also mention that written approval of the IRB/IEC has been obtained.

Each patient will be informed about the following aspects of premature withdrawal:

- Each patient has the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.
- The patient's data that have been collected until the time of withdrawal will be retained and statistically analyzed in accordance with the statistical analysis plan.
- Patient-specific data on the basis of material obtained before withdrawal may be generated after withdrawal (e.g. image reading, analysis of biological specimen such as blood, urine or tissues); these data would also be retained and statistically analyzed in accordance with the statistical analysis plan. The patient has the right to object to the generation and processing of this post-withdrawal data. The patient's oral objection may be documented in the patient's source data.

Each patient will have ample time and opportunity to ask questions.

Only if the patient voluntarily agrees to sign the informed consent form and has done so, may he/she enter the study. Additionally, the investigator will personally sign and date the form. The patient / legal representative or proxy consenter will receive a copy of the signed and dated form.

The signed informed consent statement is to remain in the investigator site file or, if locally required, in the patient's note/file of the medical institution.

In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or patient´s clinical record must clearly show that informed consent was obtained prior to these procedures.

The informed consent form and any other written information provided to patients will be revised whenever important new information becomes available that may be relevant to the patient's consent, or there is an amendment to the protocol that necessitates a change to the content of the patient information and / or the written informed consent form. The investigator will inform the patient of changes in a timely manner and will ask the patient to confirm his/her participation in the study by signing the revised informed consent form. Any revised written informed consent form and written information must receive the IEC/IRB`s approval / favorable opinion in advance of use.

13.5 Publication policy and use of data

The sponsor has made the information regarding the study protocol publicly available on the internet at www.clinicaltrials.gov.

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the sponsor who may utilize them in various ways, such as for submission to government regulatory authorities or disclosure to other investigators.

Regarding public disclosure of study results, the sponsor will fulfill its obligations according to all applicable laws and regulations. The sponsor is interested in the publication of the results of every study it performs.

The sponsor recognizes the right of the investigator to publish the results upon completion of the study. However, the investigator, whilst free to utilize study data derived from his/her center for scientific purposes, must obtain written consent of the sponsor on the intended publication manuscript before its submission. To this end, the investigator must send a draft of the publication manuscript to the sponsor within a time period specified in the contract. The sponsor will review the manuscript promptly and will discuss its content with the investigator to reach a mutually agreeable final manuscript.

13.6 Compensation for health damage of patients / insurance

The sponsor maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the country in which the study is performed.

13.7 Confidentiality

All records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Patient names will not be supplied to the sponsor. Only the patient number will be recorded in the CRF, and if the patient name appears on any other document (e.g. pathologist report), it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, the patients will be informed in writing that representatives of the sponsor, IEC/IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the patient’s identity will remain confidential.

The investigator will maintain a list to enable patients to be identified.

14. Reference list

Not applicable

15. Protocol amendments

15.1 Amendment 1 — 26 MAR 2019

Editorial note

In the sections on changes to the protocol text, all protocol sections affected by the respective amendment are detailed; the sequence of the sections follows the structure of the most recent previous protocol version. As applicable, changes to the protocol text are highlighted as follows:

- **Editing of an existing portion**: Comparative presentation of "old text" versus "new text", with "old text" referring to the most recent previous protocol version. Deletions are ~~crossed out~~ in the "old text". Additions are underlined in the "new text".

In general, correction of typos or omissions are not highlighted. However, throughout the protocol, the designation of the alternative hypothesis has been changed from K_0 to H_1 to align the protocol with the terminology used in the SAP and with the general standard for designation of the alternative hypothesis. It is not considered to be a protocol change but is a correction.

15.1.1 Overview of changes to the study

- Section 10.2.1.1 MRI Equipment —This section was changed to reflect changes in MRI field strength in common use and to permit either the previously specified 1.5 and the newer 3.0 field strength and to provide greater flexibility based on the study center's available MRI equipment.
- Section 10.2.1.2 Pulse sequences — This section was changed to recommend that T1w spin echo/FSE acquisition should be performed in 2D mode.
- Section 10.2.1.6.1 Quantitative contrast enhancement estimation — Up to 10 lesions" has to be removed because the quantitative contrast enhancement estimation algorithm will not be applied to a single lesion or up to 10 lesions, because it is a software evaluation result for a complete image.
- Section 11.4.2.4 Confidence in diagnosis — This section has been modified to clarify that frequency tables for confidence responses will not be constructed for unenhanced MRI alone.
- Section 11.4.2.6 Analysis of safety variables — This section was changed to remove the reference to McNemar's tests and/or related confidence intervals, reflecting a changed analysis plan.

15.1.2 Modification 1: Section 10.2.1.1 MRI equipment

The modified text is:

The procedure will be performed using either a 1.5 or a 3.0 Tesla MRI scanner that can perform the required pulse sequences (see Section 10.2.1.2) with a dedicated head coil. The manufacturer, model, software version, and field strength of the MRI device will be recorded in the eCRF. The same scanner and required pulse sequences must be used for both the gadoterate and gadobutrol enhanced MRI's.

The same field strength (either 1.5 or 3.0) must be used for both scans. Mixed field strength scans are not permitted.

In addition, T1w enhanced sequences must be performed at or near the same post-dose time point (4-10 mins) for each study drug (gadoterate and gadobutrol).

Affected sections: No other sections.

15.1.3 Modification 2: Section 10.2.1.2. Pulse Sequences

The modified text is:

The same parameter setting must be used for unenhanced T1w images and for contrast-enhanced T1w images in each patient. T1w spin echo/FSE acquisition should be performed in 2D mode. The required pulse sequences for gadobutrol and gadoterate are:

- Unenhanced (axial and sagittal image presentation for brain)
  - T1w spin-echo/FSE images of the whole brain - axial
  - Fluid Attenuated Inversion Recovery (FLAIR) of the whole brain – axial
  - Optional: T2w spin-echo images of the whole brain – sagittal or axial

- Contrast-enhanced (axial and coronal image presentation for brain)
  - T1w spin echo/ FSE images of the whole brain

- General considerations
  - The MR scanner should NOT be actively retuned after the unenhanced sequences

Deviations from the specified MRI procedure will be recorded in the eCRF.

Affected sections: No other sections.

15.1.4 Modification 3: Section 10.2.1.2.1 Sequence parameters for brain imaging

The modified text is:

The recommended sequence parameters for brain imaging is displayed below in Table: 10-2.

Table 10-2: Orientation parallel to the planum sphenoidale (only for axial)

	T2	SE/FSE T1	FLAIR
Plane	Sagittal or Axial	Axial or Coronal	Axial
Pulse Sequence	Spin echo/FSE	Spin echo/FSE	IR
Patient position	Supine	Supine	Supine
Coil	Head	Head	Head
Slice thick/spacing	3-5 skip 0-1.5	3-5 skip 0-1.5	3-5 skip 0-1.5
Frequency	≥256	≥256	≥256
Phase	≥256	≥256	≥128
Nex	≥2	≥2	≥1

Affected sections: No other sections.

15.1.5 Modification 4: Section 10.2.1.6.1 Quantitative contrast enhancement estimation

The modified text is:

Quantitative contrast enhancement estimation will be performed using an exploratory Overall Contrast Enhancement Estimation Algorithm. Descriptive statistics will be presented for each study drug (gadoterate and gadobutrol). ~~Results will be summarized by MRI modality using. Up to 10 lesions will be identified~~.

Affected sections: No other sections.

15.1.6 Modification 5: Section 11.4.2.4 Confidence in diagnosis

The modified text is:

Frequency tables for confidence responses (1-4) for patients will be constructed for ~~unenhanced MRI,~~ combined unenhanced and gadoterate-enhanced MRI, and combined unenhanced and gadobutrol-enhanced MRI. Descriptive statistics for the combined unenhanced and gadobutrol and gadoterate enhanced MRI and their difference ~~from unenhanced MRI~~ will be generated. Confidence intervals for the differences will be generated.

Affected sections: No other sections.

15.1.7 Modification 6: Section 11.4.2.6 Analysis of safety variables

The modified text is:

Frequencies of TEAE s will be tabulated by contrast agent and the proportions of patients exhibiting each TEAE will be displayed. Tabulations will also be made for the body system, intensity, and attribution corresponding to each TEAE. Separate tabulations will be made for serious TEAE s. ~~McNemar's tests and/or related confidence intervals will be used to assess the significance of the differences in incidence rates between the agents.~~

Affected sections: No other sections.

16. Appendices

Appendix 1: Volume of Gadobutrol 0.075 mmol/kg by Body Weight

Appendix 2: Volume of Gadoterate 0.1 mmol/kg by Body Weight

Appendix 1: Volume of Gadobutrol 0.075 mmol/kg by Body Weight

Body Weight (kg)	Volume of Gadobutrol (mL)	Body Weight (kg)	Volume of Gadobutrol (mL)
45	3.4	79	5.9
46	3.5	80	6
47	3.5	81	6.1
48	3.6	82	6.2
49	3.7	83	6.2
50	3.8	84	6.3
51	3.8	85	6.4
52	3.9	86	6.5
53	4	87	6.5
54	4.1	88	6.6
55	4.1	89	6.7
56	4.2	90	6.8
57	4.3	91	6.8
58	4.4	92	6.9
59	4.4	93	7
60	4.5	94	7.1
61	4.6	95	7.1
62	4.7	96	7.2
63	4.7	97	7.3
64	4.8	98	7.4
65	4.9	99	7.4
66	5	100	7.5
67	5	101	7.6
68	5.1	102	7.7
69	5.2	103	7.7
70	5.3	104	7.8
71	5.3	105	7.9
72	5.4	106	8
73	5.5	107	8
74	5.6	108	8.1
75	5.6	109	8.2
76	5.7	110	8.3
77	5.8	115	8.6
78	5.9	120	9

Appendix 2: Volume of Gadoterate 0.1 mmol/kg by Body Weight

Body Weight (kg)	Volume of Gadoterate (mL)	Body Weight (kg)	Volume of Gadoterate (mL)
45	9.0	79	15.8
46	9.2	80	16.0
47	9.4	81	16.2
48	9.6	82	16.4
49	9.8	83	16.6
50	10.0	84	16.8
51	10.2	85	17.0
52	10.4	86	17.2
53	10.6	87	17.4
54	10.8	88	17.6
55	11.0	89	17.8
56	11.2	90	18.0
57	11.4	91	18.2
58	11.6	92	18.4
59	11.8	93	18.6
60	12.0	94	18.8
61	12.2	95	19.0
62	12.4	96	19.2
63	12.6	97	19.4
64	12.8	98	19.6
65	13.0	99	19.8
66	13.2	100	20.0
67	13.4	101	20.2
68	13.6	102	20.4
69	13.8	103	20.6
70	14.0	104	20.8
71	14.2	105	21.0
72	14.4	106	21.2
73	14.6	107	21.4
74	14.8	108	21.6
75	15.0	109	21.8
76	15.2	110	22.0
77	15.4	115	23.0
78	15.6	120	24.0