CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201277Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA:	**201-277**
Submission Date:	**3/2/2011; 3/8/2011**
Brand Name:	**Gadavist**
Generic Name:	**Gadobutrol Injection**
Formulations:	**Intravenous solution** **1.0 mmol Gd/mL (604.72 Gadovist mg/mL)**
Route of Administration:	**Intravenous injection**
Dosing Regimen:	**0.1 mmol/kg**
Indication:	**For intravenous use in diagnostic MRI in adults and children (2 years of age and older) to detect and visualize areas with disrupted blood brain barrier and/or abnormal vascularity of the central nervous system (CNS)**
Sponsor:	**Bayer HealthCare Pharmaceuticals, Inc.**
Type of Submission:	**Response to the agency's recommendation & the proposed labeling**
Relevant IND:	**IND 56,410**
OCP Division:	**DCP-V**
ORM Division:	**DMIP**
Reviewer:	**Christy S. John, Ph.D.**
Team Leader:	**Young Moon Choi, Ph.D.**

Reference ID: 2917352

SUMMARY

Gadovist (gadobutrol injection) is a gadolinium based contrast agent. The proposed indication is for intravenous use in diagnostic magnetic resonance imaging (MRI) in adults and children (2 years of age and older) to detect and visualize areas with disrupted blood brain barrier (BBB) and/or abnormal vascularity of the central nervous system (CNS).

Gadobutrol exhibits linear pharmacokinetics with increasing dose. The elimination half-life of gadobutrol is about 2 hours. Gadobutrol is not metabolized and primarily excreted unchanged in urine by glomerular filtration. The urinary excretion is nearly complete 12 hours after administration. Protein binding is negligible.

In a dedicated pharmacokinetic study in patients with renal impairment, the elimination of gadobutrol is significantly prolonged in relation to the extent of renal impairment. The elimination half-life in patients with severe renal impairment increased to 18 hrs as compared to about two hours for patients with normal renal function, and the systemic exposure of gadobutrol in patients with severe renal impairment is about ten fold higher than patients with normal renal function (comparison based on cross study). Gadolinium chelates can undergo dissociation in-vivo and release free gadolinium and cause a debilitating adverse effect called as Nephrogenic Sysetmic Fibrosis (NSF). Due to prolonged retention in the systemic circulation of gadolinium based contrast agents (GBCAs) in patients with renal impairment, the NSF risk seems to be the highest in patients with severe renal impairment (GFR <30ml/min). Therefore, it is recommended in the box warning (for all GBCAs) to avoid the use in patients with renal impairment. If gadobutrol must be used in patients with severe renal impairment, one-third dose (0.03 mmol/kg) be used. The dose reduction is not recommended in patients with mild to moderate renal impairments.

The applicant did not agree with the agency's recommendation about the dose reduction to 0.03 mmol/kg, and on 3/2/2011, submitted a rationale of the appropriateness of the dose of 0.1 mmol/kg for the patients with severe renal impairment. The rationale is based mainly on efficacy and safety as follows: *(Refer to the Attachment 1 of the present review; page 5-10.)*

- Potential loss of efficacy; Volume of distribution is not different in the patients with renal impairment from that in healthy volunteer, and the initial concentration is reduced significantly if 1/3 dose is used. Hence the efficacy may be compromised.

- Gadavist is classified as a low NSF risk gadolinium based contrast agent (GBCA) based on physicochemical properties and the supportive safety data for 0.1 - 0.3 mmol/kg dose from 4500 patients in clinical trial and 6.5 million post marketing usage.

- Concerns on the labeling complication and potential misuse of the dose
- No precedence for use of 0.03 mmol/kg

RECOMMENDATION

The Office of Clinical Pharmacology (OCP), DCP 5 has reviewed the applicant's response to the agency's labeling recommendation. OCP finds that the applicant's rationale is reasonable and recommends the dose 0.1 mmol/kg to be used in the patients with severe renal impairment. Therefore, the applicant's proposed labeling on 3/8/2011 is acceptable from a clinical pharmacology perspective except minor modification on effective numbers under 12.3 Pharmacokinetics, Special Populations. *(Refer to the Attachment 2 of the present review; page 21; the yellow highlighted area is the agency's recommendation).*

ATTACHMENT 1: The applicant's rationale for 0.1 mmol/kg dose for the patients with severe renal impairment

ATTACHMENT 2: The labeling recommendation

ATTACHMENT 1: The applicant's rationale for 0.1 mmol/kg dose for the patients with severe renal impairment

Bayer appreciates the continuous dialogue with the Division and shares the same goal as FDA in ensuring the safe use of Gadobutrol in all patient populations, particularly in patients with severe renal impairment.

It is our understanding that FDA's recommendation for dosing of Gadobutrol at 0.03 mmol/kg is based on pharmacokinetic modeling of AUC estimating a 10-fold higher exposure in patients with severe renal impairment compared to patients with normal renal function. It appears, therefore, that this recommended dosing is based on the assumption that this higher exposure in patients with severe renal impairment may correlate with a higher potential risk of NSF in these patients.

Bayer has evaluated the available evidence and has concerns with FDA's proposed dose recommendation from a number of perspectives:

1. Pharmacokinetic Properties of GBCAs
2. Efficacy
3. Pharmacokinetics/Safety
4. Labeling/Regulatory Precedence

Many of the topics raised below apply to not only Gadobutrol but also to the class of GBCAs, particularly those with CNS indications (MultiHance, ProHance, Magnevist, Omniscan, OptiMARK) and also those considered to be lower-risk GBCAs[1] with CNS indications (MultiHance, ProHance).

1. Pharmacokinetic Properties of GBCAs

The pharmacokinetic (PK) profile of all extracellular GBCAs is similar. This PK profile is characterized by rapid distribution out of the vascular into the extracellular space (defined as volume of distribution) and fast elimination from blood and body by renal filtration. With respect to efficacy, the concentration in blood and the region of interest during the early post-injection phase (first 15-20 min p.i.) is relevant and this is dependent on the dose and the volume of distribution. The volume of distribution is not different in subjects with renal impairment compared to healthy subjects, regardless of degree of renal impairment. In contrast, elimination time is based on the glomerular filtration rate (GFR), which is a measure of renal function. As renal function decreases, the terminal half life and AUC increase. The above PK properties are applicable for all extracellular GBCAs.

2. Efficacy

From an efficacy perspective, Bayer's primary concern relates to patients with severe renal impairment who receive a GBCA dose of 0.03 mmol/kg, as that dose has not been shown to have the same efficacy as a 0.1 mmol/kg dose. In addition to being statistically

[1] Lower-risk GBCAs defined as GBCAs approved in the United States without a contraindication in patients with chronic, severe kidney disease or acute kidney injury. In Europe, low risk GBCAs include all macrocyclic GBCAs (Gadobutrol, ProHance, and Dotarem)

lower than a dose of 0.1 mmol/kg, in order to achieve the desired imaging (i.e. lesion visualization), a second GBCA dose may be necessary to properly visualize their lesions.

2.1. The efficacy of Gadobutrol and other extracellular GBCAs is independent of renal status (see above). Efficacy for contrast-enhanced MRI is driven by C_{max} and concentrations at early time points (15-20 min p.i.). As shown in our Phase 1 studies, these concentrations are dependent on dose and the volume of distribution. As the volume of distribution is not influenced by renal function, the plasma and consequently the lesion concentration in the region of interest (at MRI relevant time points) is directly related to the administered dose. This holds true for all extracellular GBCAs (similar C_{max} and time to C_{max} values, independent of the GBCA).

2.2. In line with the dose dependent differences shown in Phase 1 studies (with respect to the achieved concentrations after iv injection), our Phase 2 Study 308200, a dose of 0.1 mmol/kg showed significant improvement over the 0.03 mmol/kg dose:

- For contrast enhancement according to the average reader, a statistically significant improvement in favor of the 0.1 mmol/kg BW dose as compared with the 0.03 mmol/kg BW dose was found (95% CI: -1.171, -0.424). In addition, although clinical relevance between doses was not specifically defined for this study, lesion contrast enhancement based on the average reader was 82% improved for the 0.1 mmol/kg BW dose than for the 0.03 mmol/kg BW dose, which was a clinically meaningful improvement.
- For border delineation according to the average reader, a statistically significant improvement in favor of the 0.1 mmol/kg BW dose as compared with the 0.03 mmol/kg BW dose was found (95% CI: -0.619, -0.17). This difference was also clinically relevant, representing a 143% improvement with the 0.1 mmol/kg BW dose compared with the 0.03 mmol/kg BW dose.
- For internal morphology according to the average reader, a statistically significant improvement in favor of the 0.1 mmol/kg BW dose as compared with the 0.03 mmol/kg BW dose was found (95% CI: -0.581, -0.181). This difference was also clinically meaningful, representing a 73% improvement for the 0.1 mmol/kg dose over the 0.03 mmol/kg BW dose.
- For number of lesions, neither comparison provided a statistically significant difference (confidence intervals of the differences included the value 0).

2.3. The clinical use of a 0.03 mmol/kg dose in patients (i.e. only 30% of the recommended 0.1 mmol/kg dose) with severe renal impairment will likely result in some non-diagnostic images and require these severely-renally impaired patients to receive an additional GBCA dose, which could potentially increase their overall gadolinium exposure beyond 0.1 mmol/kg.

2.4. The PK parameters relating to efficacy are demonstrably lower for a dose of 0.03 compared to 0.1 mmol/kg (see figure below). These PK results are consistent with findings from our Phase 2 dose ranging study.

Reference ID: 2917352

2.5. Pivotal studies conducted with MultiHance and used to support their approval in the US evaluated a 0.05 mmol/kg dose, and this dose was not found to be efficacious. On page 12 of the Medical Officer's review of MultiHance, dated August 27, 2004, the following was concluded with regards to the efficacy of MultiHance at doses of 0.1 and 0.05 mmol/kg for CNS imaging:

"On a by lesion analysis the 0.05 mmol/kg dose produces results that are inconsistent from reader to reader… Efficacy has been demonstrated for the 0.1 mmol/kg dose, but not for the 0.05 mmol/kg dose."

(reference: FDA Medical Review - MultiHance).

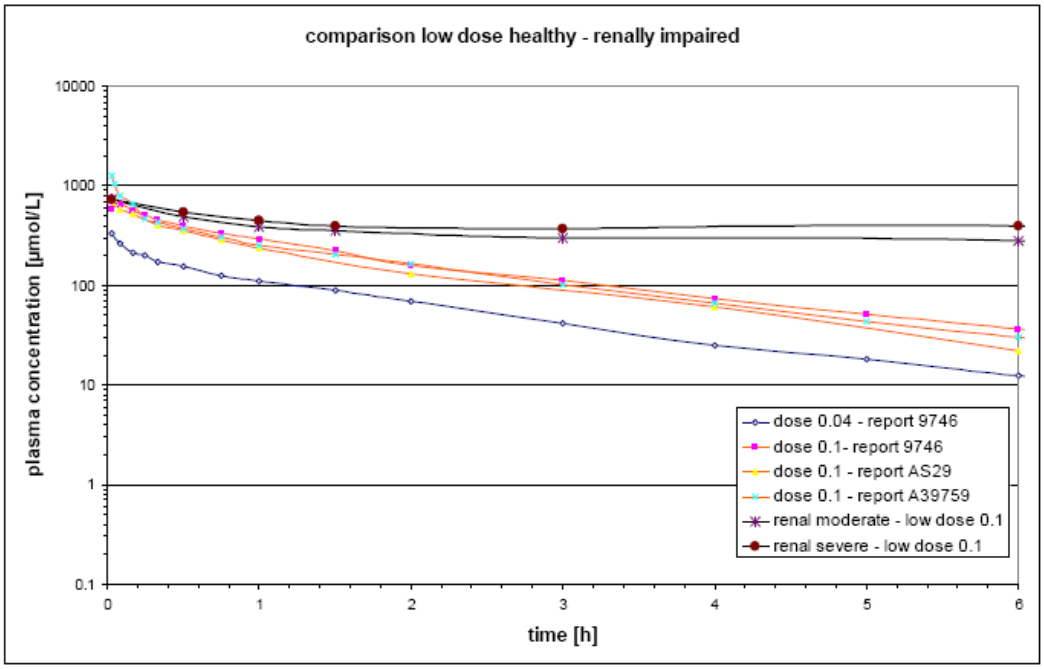
3. Pharmacokinetics and Safety

Patients with severe renal impairment have an increased exposure compared to normal patients, and a potential link to an increased risk of NSF. The extensive physico-chemical, non-clinical, clinical and post-marketing data for Gadobutrol support the safety of a dose of 0.1 mmol/kg in the at-risk patient population.

3.1. We understand that a non-MEM simulation was performed by FDA and simulated AUC values are the basis to recommend a dose of 0.03 mmol/kg for patients with severe renal impairment. FDA performed a simulation based upon the data from both dose groups (0.1 and 0.3 mmol/kg) for patients with renal impairment, and AUC was normalized for a dose of 0.1 mmol/kg for the high dose group. Non-MEM data for healthy adult was taken from the submission, a simulation was performed, and exposure was calculated for a dose of 0.03 mmol/kg. FDA recommends a dose reduction based on about a 10-fold exposure in patients with severe renal impairment and the associated safety risk.

Mean plasma concentrations of Gadobutrol for different doses in healthy and renally impaired subjects are given in the figure below. The graph demonstrates that plasma concentrations in healthy and renally impaired subjects receiving the same dose (0.1 mmol/kg) are similar during the first 30 minutes (distribution phase), the time frame used to acquire diagnostic images. Only at later time points (when most of the drug is already eliminated from blood and body) plasma concentrations in healthy subjects decline faster than in renally-impaired patients, yielding the differences in AUC. Furthermore, the figure clearly shows the relevant difference in plasma concentration after a dose of 0.04 mmol/kg, which is dose proportionally lower (by at least a factor 2.5) than after the standard clinical dose of 0.1 mmol/kg.

Reference ID: 2917352



3.2. The safety of Gadobutrol has been demonstrated across more than 4500 patients in clinical trials and 6.5 million patients in post-marketing experience. This experience includes the worldwide use of a standard dose of 0.1 mmol/kg in all patient populations, with most countries permitting an additional 0.2 mmol/kg dose to be administered if needed.

3.3. All available physico-chemical and non-clinical data supports classification of Gadobutrol as a lower-risk[1] GBCA for NSF at a dose of 0.1 mmol/kg, including:

- High stability due to macrocyclic structure
- No detectable release of gadolinium in non-clinical studies
- No skin lesions in rat models
- No long-term gadolinium retention detectable

4. Labeling/Regulatory Precedence

Currently, all GBCAs with CNS indications are approved in the US to be dosed at 0.1 mmol/kg, regardless of renal impairment status. The recommendation of a lower dose in patients with severe renal impairment for Gadobutrol without data suggesting any differential PK, physico-chemical, non-clinical, clinical or post-marketing data versus other lower-risk GBCAs does not appear to be warranted. Additionally, as clinicians are familiar with GBCAs labeled for doses as high as 0.3 mmol/kg, an unfamiliar dose of 0.03 mmol/kg could be misread and result in a 0.3 mmol/kg dose (i.e. 3 times higher than

the recommended dose of 0.1 mmol/kg and 10 times higher than a dose of 0.03 mmol/kg) being erroneously administered.

4.1. As presented by Dr. Stinson at the FDA Advisory Committee (Slide 2), the dose recommended in all adult patients for GBCAs with CNS indications is 0.1 mmol/kg. This same 0.1 mmol/kg dose is recommended in patients with severe renal impairment for GBCAs approved for use for this indication in this patient population (MultiHance, ProHance). In the absence of differentiating pharmacokinetic or safety data, the recommendation of a Gadobutrol dose that is 70% lower, while maintaining a dose of 0.1 mmol/kg for other GBCAs, does not appear to be warranted.

4.2. Bayer's objective in all of our proposed educational materials, labels, packaging and dosing charts is to highlight for health care providers that the recommended dose is 0.1 mL/kg (0.1 mmol/kg), or half the volume compared to other GBCAs. We view this communication as key to ensuring the correct dose of Gadobutrol is administered to patients. Recommending a lower dose for patients with severe renal impairment significantly complicates these educational efforts. Patients with normal renal function will receive 50% of the volume of other GBCAs, while patients with severe renal impairment will receive 15% of the volume of other GBCAs.

- Adding an additional column to a Gadobutrol dosing chart has the potential to increase confusion due to multiple values for each weight, while a note regarding dosing in patients with severe renal impairment at the bottom of the dosing chart has the potential to be missed.

4.3. As clinicians are familiar with GBCAs labeled for doses as high as 0.3 mmol/kg, an unfamiliar dose of 0.03 mmol/kg could result in a 0.3 mmol/kg dose (i.e. 3 times higher than the recommended dose of 0.1 mmol/kg and 10 times higher than a dose of 0.03 mmol/kg) being erroneously administered.

4.4. In December 2010, FDA approved new labeling for all GBCAs with regards to NSF. Among the lower-risk GBCAs (those without a contraindication), the dose of 0.1 mmol/kg was reaffirmed by FDA for both patients with normal renal function as well as those with severe renal impairment. Bayer is not aware of any new published research or data that has become available since December 2010 that would support a recommendation of 0.03 mmol/kg in these patients. Recommending a lower dose of 0.03 mmol/kg for Gadobutrol without data suggesting a differential risk versus other lower-risk GBCAs (such as ProHance and MultiHance) appears to be inconsistent with the December 2010 labeling changes.

5. Recommendation

5.1. The dose of 0.1 mmol/kg in patients with severe renal impairment is supported by:

- pivotal clinical studies demonstrating efficacy at a dose of 0.1 mmol/kg

Reference ID: 2917352

- pharmacokinetic analyses in patients with renal impairment demonstrating similar gadolinium concentrations at the time window relevant for CE-MRI, independent of the renal function
- significant clinical and post-marketing experience demonstrating safety at this dose

5.2. Without differentiating PK, non-clinical, clinical or post-marketing data compared to other GBCAs, regulatory precedence set by FDA in December 2010 in supporting the dose of 0.1 mmol/kg in both patients with either normal or impaired renal function for the other lower-risk GBCAs, a dose of 0.1 mmol/kg should be recommended for Gadobutrol in both of these patient populations.

Reference ID: 2917352

ATTACHMENT 2: The labeling recommendation

15 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTY S JOHN
03/11/2011

YOUNG M CHOI
03/11/2011
I concur.

CLINICAL PHARMACOLOGY REVIEW

NDA:	**201-277**
Submission Date:	**May 14, 2010**
Brand Name:	**Gadovist 1.0**
Generic Name:	**Gadobutrol Injection**
Formulations:	**Intravenous solution** **1.0 mmol Gd/mL (604.72 Gadovist mg/mL)**
Route of Administration:	**Intravenous injection**
Dosing Regimen:	**0.1 mmol/kg**
Indication:	**For intravenous use in diagnostic MRI in adults and children (2 years of age and older) to detect and visualize areas with disrupted blood brain barrier and/or abnormal vascularity of the central nervous system (CNS)**
Sponsor:	**Bayer HealthCare Pharmaceuticals, Inc.**
Type of Submission:	**Original NDA; 1S**
Relevant IND:	**IND 56,410**
OCP Division:	**DCP-V**
ORM Division:	**DMIP**
Reviewer:	**Christy S. John, Ph.D.**
Team Leader:	**Young Moon Choi, Ph.D.**

Reference ID: 2910496

Table of Contents

Reference ID: 2910496

1. EXECUTIVE SUMMARY

Gadovist (gadobutrol injection) is a gadolinium based contrast agent. The proposed indication is for intravenous use in diagnostic magnetic resonance imaging (MRI) in adults and children (2 years of age and older) to detect and visualize areas with disrupted blood brain barrier (BBB) and/or abnormal vascularity of the central nervous system (CNS).

Gadobutrol exhibits linear pharmacokinetics with increasing dose. The elimination half-life of gadobutrol is about 2 hours. Gadobutrol is not metabolized and primarily excreted unchanged in urine by glomerular filtration. The urinary excretion is nearly complete 12 hours after administration. Protein binding is negligible. The pharmacokinetics of gadobutrol was evaluated in 130 pediatric patients (age 2-17 years old) after IV administration of 0.1 mmol/kg. The pediatric study supports body weight based dosing similar to the adult population, i.e., 0.1 mmol/kg body weight.

In a dedicated PK study in patients with renal impairment, the elimination of gadobutrol is significantly prolonged in relation to the extent of renal impairment. The elimination half-life in patients with severe renal impairment increased to 18 hrs as compared to about two hours for patients with normal renal function, and the systemic exposure of gadobutrol in patients with severe renal impairment is about ten fold higher than patients with normal renal function (comparison based on cross study). Gadolinium chelates can undergo dissociation in-vivo and release free gadolinium and cause a debilitating adverse effect called as Nephrogenic Sysetmic Fibrosis (NSF). Due to prolonged retention in the systemic circulation of gadolinium based contrast agents (GBCAs) in patients with renal impairment, the NSF risk seems to be the highest in patients with severe renal impairment (GFR <30ml/min). Therefore, it is recommended in the box warning (for all GBCAs) to avoid the use in patients with renal impairment. If gadobutrol must be used in patients with severe renal impairment, one-third dose (0.03 mmol/kg) be used. In patients requiring dialysis, gadobutrol appeared to be eliminated almost completely after three routine dialysis cycles. The effect of gadobutrol on QT prolongation appeared negligible. No formal drug-drug interaction studies were conducted with gadobutrol as it is to be used as single dose and not metabolized.

Overall, the NDA is acceptable. No post marketing studies are needed.

1.1. RECOMMENDATIONS

The Office of Clinical Pharmacology, DCP 5 has reviewed NDA 201-277 submitted on May 14, 2010. OCP finds this application acceptable provided mutually agreeable language on labeling can be reached.

1.2. PHASE IV COMMITMENTS

None

Reference ID: 2910496

1.3. CLINICAL PHARMACOLOGY FINDINGS

Gadobutrol is an extracellular MRI contrast agent that produces contrast enhancement (CE). When placed in a magnetic field, it produces the CE by shortening of the relaxation times of protons in plasma, referred to as relaxivity. Both T1 and T2 relaxation times were shortened. The T1 shortening effect tends to dominate and is dependent on concentration of gadobutrol. Visualization of normal and pathological tissue depends, in part, on the variations in the radiofrequency signal intensity that occur with differences in proton density, differences in the T1 relaxation times, and differences in the T2 relaxation times.

Gadovist belongs to the class of gadolinium based contrast agents (GBCAs). Gadolinium is tightly bound in a macrocyclic complex with a high stability in Gadovist chelate (Figure 1). The product is an aqueous formulation of gadobutrol, a neutral macrocyclic gadolinium chelate, which exhibits a low osmolality, low viscosity and a high paramagnetic effect (relaxivity).

The recommended dose of Gadovist 1.0 is 0.1 mL/kg body weight (0.1 mmol/kg). Gadovist 1.0 is recommended to be administered as an intravenous bolus injection, manually or by power injector, at a flow rate of approximately 2 mL/second. A flush of intravenous cannula with physiological saline solution after the injection is recommended.

The dose was selected based upon primary visualization scores (pharmacodynamic parameters such as contrast to noise ratio (CNR), contrast enhancement, tumor border delineation, and internal morphology of tumor). The 4 primary visualization efficacy variables were condensed to a composite visual score (CVS). The higher the CVS, the more effective the respective treatment. For the average reader, the lowest CVS value (1.43) was obtained for the 0.03 mmol/kg dose group and the highest CVS value (2.02) was obtained for the 0.1 mmol/kg (standard) dose group. A dose of 0.1 mmol/kg was identified as optimal dose that yielded appropriate CNR, contrast enhancement and tumor border delineation.

After intravenous bolus injection, plasma gadolinium concentrations decreased in a bi-exponential manner with a rapid distribution phase. The AUC and Cmax increased with the increasing doses of gadobutrol. The mean values for $t_{1/2}$, CL, $A_{g,ur}$ (amount of gadolinium excreted in urine, expressed as % amount), and CL_R were similar in the 0.1, 0.2, and 0.3 mmol/kg dose cohorts. After two intravenous injections of 0.1 mmol/kg of gadovist with a 30-min interval between injections, the mean value for AUC was similar to that after a single intravenous injection of 0.2 mmol/kg of gadovist. In contrast, the mean value for Cmax was about 70% of that after a single intravenous injection of 0.2 mmol/kg of gadobutrol. The urinary excretion of gadolinium was almost completed after 12 h post injection with a mean recovery between 90.4–99.3 % of the administered gadolinium dose. The renal clearance was almost identical to the total clearance. The elimination half life of gadobutrol was about 2 hours. Gadobutrol does not undergo

Reference ID: 2910496

metabolism and is excreted entirely in urine as parent compound. No formal drug-drug interaction studies were conducted with gadobutrol as gadobutrol is not metabolized.

Gender had no significant effect on the pharmacokinetics of gadobutrol.. Age had a moderate effect on the pharmacokinetics of gadobutrol in plasma. In healthy elderly men and women (>65 years of age) plasma clearance was reduced by approximately 25% and 35%, respectively, as compared with non-elderly subjects. A dose reduction is not necessary in elderly patients based on the relative safety.

The sponsor conducted a PK study in patients with renal impairment. Two different doses (0.1 mmol/kg and 0.3 mmol/kg) were studied. The creatinine clearance correlated well with the total clearance of gadobutrol from serum. This correlation between total serum clearance and renal clearance of gadobutrol indicates almost exclusive elimination of gadobutrol via the kidney. A combined analysis of patients from both dose groups (0.1 and 0.3 mmol/kg) shows that AUC increased about 10 fold in patients with severe renal impairment, 4-fold for moderate renal impairment patients and about 2 fold in patients with mild renal impairment. The elimination half-life also increased 2 fold, four fold and about ten-fold for patients with mild, moderate and severe renal impairments, respectively. Due to the well known risk of NSF, a Box warning to avoid use of gadobutrol in patients with impaired renal function is in the package insert for all GBCAs. If however, gadobutrol must be used in severe renal impaired patients, it is recommended that a 0.03 mmol/kg dose be used due to ten fold exposure increase in this group of patients. The dose reduction is not warranted in patients with mild to moderate renal impairments.

In patients requiring dialysis, gadobutrol appeared to be eliminated almost completely after three routine dialysis cycles.

The pharmacokinetics of gadobutrol was evaluated in 130 pediatric patients (age 2-17 years old) after IV administration of 0.1 mmol/kg. In the pediatric population the pharmacokinetics of gadobutrol were adequately described using a two-compartment model with elimination from the central compartment. Body weight was the major covariate to scale the PK parameters. A cross-study comparison showed that exposure in age group 2-6 years old was about 30% lower than adults or adolescents aged 12-17 years. In all pediatric patients, more than 94 % of the dose was excreted with urine at 6 hours after administration, indicating the same mechanism (glomerular filtration) of excretion as adults. The technical adequacy of images for the three age groups was acceptable. Sixty eight to seventy one percent of images received excellent ratings from the readers. For contrast quality, 93-100% of the images received excellent ratings. These results supports the body weight based dosing to the pediatric population age 2 to 17 years similar to the adult population, i.e., 0.1 mmol/kg.

The sponsor conducted a TQT study to determine the effect of three doses of gadovist (0.03, 0.1 and 0.3 mmol/kg) in the presence of a positive control of moxyfloxacin. There was no clinically significant prolongation in QTc.

Reference ID: 2910496

In summary, the application is acceptable from clinical pharmacology perspective. There are no most marketing requirements/commitments necessary. The labeling changes have been recommended.

2. Question-Based Review:
2.1 General attributes

Gadobutrol injection was first approved in February 1998 for the indication "Contrast enhancement in cranial and spinal MRI" in Switzerland followed by approvals in Australia, Canada, European Union (EU) and several other countries. Following the initial approvals of gadobutrol for use in cranial and spinal MRIs, Gadobutrol was approved for contrast enhancement in magnetic resonance angiography (MRA) in 2003 EU and other countries and CE MRI of the liver and kidneys in 2007 (EU and other countries).

Gadovist, the aqueous solution of gadobutrol, is a gadolinium (Gd)-based extracellular contrast agent (GBCA) for magnetic resonance imaging (MRI). As in other extracellular magnetic resonance (MR) contrast agents, Gadovist contains the paramagnetic metal gadolinium (Gd3+), a rare earth element responsible for the shortening of relaxation times (T1 and T2) of hydrogen protons. On T1 weighted MR sequences, a significant increase in signal intensity is seen in tissues where gadobutrol is present. The Gadovist molecule contains gadolinium in a firmly bound, electrically neutral, macrocyclic complex of very high kinetic and thermodynamic stability.

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Gadovist belongs to the class of gadolinium based extracellular contrast agents like gadopentate dimeglumine (Magnevist). Gadolinium is tightly bound in a macrocyclic complex (Figure 1) with a high stability in Gadovist chelate. The product is an aqueous formulation of gadobutrol, a neutral macrocyclic gadolinium chelate, which exhibits a low osmolality, low viscosity and a high paramagnetic effect (relaxivity). Due to its unique physicochemical properties, Gadovist can be formulated in double the concentration of all other currently commercially available gadolinium (Gd) agents, i.e. as a 1.0 M (1.0 mmol Gd/mL) formulation.

Reference ID: 2910496

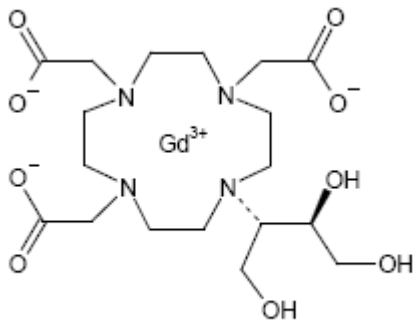


Figure 1. Chemical Structure of Gadobuterol

The drug product Gadovist is a (b) (4) clear, colorless (b) (4) solution. Gadovist is provided in a concentration of 1.0 mmol/mL of gadobutrol (formulation code number SH L 562 BB). Each mL of this formulation contains 604.720 mg of gadobutrol. Gadovist will be presented in (b) (4)

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

In MRI, visualization of normal and pathological tissue depends in part on variations in the radiofrequency signal intensity that occur with:

- Differences in proton density
- Differences of the spin-lattice or longitudinal relaxation times (T1)
- Differences in the spin-spin or transverse relaxation time (T2)

When placed in a magnetic field, Gadovist 1.0 shortens the T1 and T2 relaxation times. The extent of decreases in T1 and T2 relaxation times, and therefore the amount of signal enhancement obtained from Gadovist 1.0, is based upon several factors including the concentration of Gadovist 1.0 in the tissue, the field strength of the MRI system, and the relative ratio of the longitudinal and transverse relaxation times. At the recommended dose, the T1 shortening effect is observed with greatest sensitivity in T1-weighted magnetic resonance sequences. In T2-weighted sequences the induction of local magnetic field inhomogeneities by the large magnetic moment of gadolinium and at high concentrations (during bolus injection) leads to a signal decrease.

2.1.3 What are the proposed dosage and route of administration?

The recommended dose of Gadovist 1.0 is 0.1 mL/kg body weight (0.1 mmol/kg). Gadovist 1.0 is recommended to be administered as an intravenous bolus injection, manually or by power injector, at a flow rate of approximately 2 mL/second. A flush of intravenous cannula with physiological saline solution after the injection is recommended.

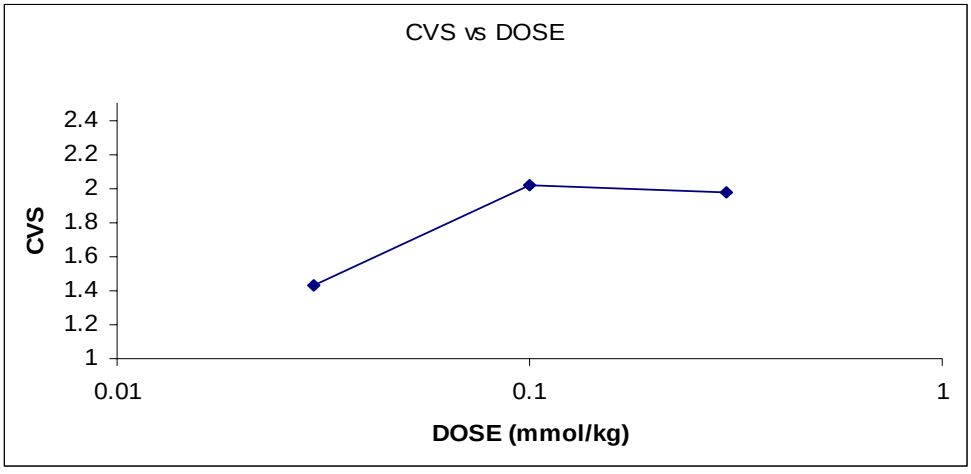
2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

To support the proposed indication, the sponsor conducted two pivotal clinical trials and eleven clinical pharmacology studies. The clinical pharmacology studies include dose-finding study, pharmacokinetic evaluation after single or repeated intravenous administration of gadobutrol, PK evaluation in patients with renal impairment, thorough QT (TQT) study, safety and PK evaluation in pediatric subjects (2 to 17 years), and evaluation of the effect of endogenous factors such as age and body weight based on pooled data consisting of all phase 1 studies in healthy adults.

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

The dose was selected based upon a Phase 2 dose finding study. The studied doses were 0.03, 0.1 and 0.3 mmol/kg. The dose was selected based on primary visualization scores (pharmacodynamic parameters such as contrast to noise ratio (CNR), contrast enhancement, tumor border delineation, and internal morphology of tumor). The four primary visualization efficacy variables were condensed to a composite visual score (CVS). The higher the CVS, the treatment was considered the more effective. For the average reader, the lowest CVS value (1.43) was obtained for the 0.03 mmol/kg dose group and the highest CVS value (2.02) was obtained for the 0.1 mmol/kg (standard) dose group (Figure 2). A dose of 0.1 mmol/kg was identified as optimal dose that yielded appropriate CNR, contrast enhancement and tumor border delineation.



Reference ID: 2910496

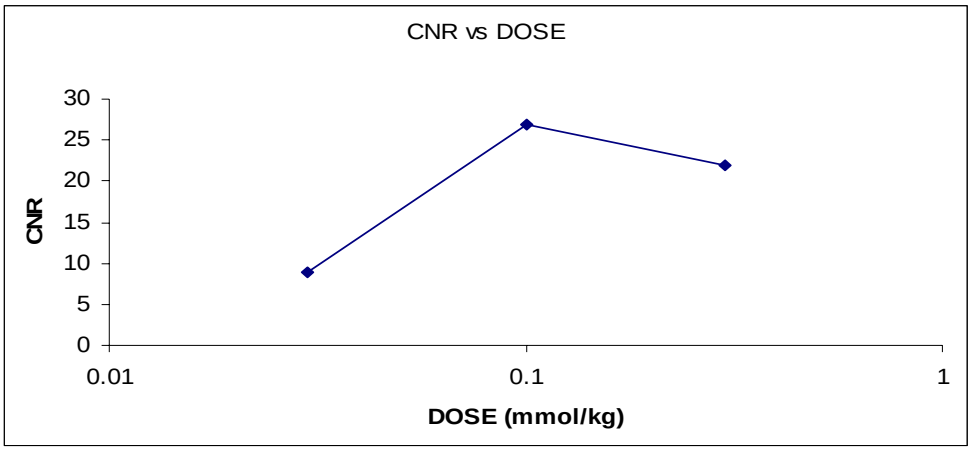


Figure 2. Dose-Response (CVS and CNR) Curves for Gadobutrol

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

The plasma/serum and urine gadolinium (Gd)-concentrations were measured by inductively coupled plasma-atomic emission spectrometry (ICP-AES) or inductively coupled plasma-mass spectrometry (ICP-MS), and plasma and urinary metabolites were investigated using high-performance liquid chromatography (HPLC) or HPLC combined with ICP-AES. The plasma/serum and urine drug concentration is expressed as the concentration of Gd in µmol/L. Gadolinium is the "signal producing" element, and one molecule of gadobutrol contains one Gd.

2.2.4 Exposure-response
2.2.4.1 What are the characteristics of the exposure-response relationships (dose response, concentration-response) for efficacy?
Two pivotal phase 3 trials were conducted as follows:

A multi-institutional (13 sites in USA, 15 sites in Germany, 12 sites in Japan and others), randomized, double-blind, phase III study was conducted. The objectives of this study were to demonstrate the superiority of combined unenhanced and gadobutrol-enhanced magnetic resonance imaging (MRI) compared to unenhanced MRI based on the evaluation of the degree of contrast enhancement, assessment of border delineation and internal morphology of lesions.

Additionally, a noninferiority study was conducted. In this study, the combined unenhanced and gadobutrol-enhanced magnetic resonance imaging (MRI) was compared to unenhanced MRI based on the evaluation of the total number of lesions detected. The objectives of this study were to demonstrate noninferiority of gadobutrol compared to gadoteridol for degree of contrast enhancement, assessment of border delineation, internal morphology of lesions and total number of lesions detected.

Primary efficacy variables

Combined unenhanced/gadobutrol-enhanced vs. unenhanced: Results

The four primary efficacy variables were contrast enhancement, border delineation, internal morphology, and number of lesions, as assessed by the blinded readers. For contrast enhancement, border delineation, and internal morphology, the improvement in scores from unenhanced to combined unenhanced/gadobutrol-enhanced was statistically significant for the average reader, as well as for the 3 individual readers (P<0.0001 in all cases). The mean contrast enhancement average reader score increased from 0.97 unenhanced to 2.26 (Table I) combined unenhanced/enhanced (using a scale of 1 = no enhancement to 4 = excellent enhancement). The mean differences were very consistent across the 3 readers, with all 3 readers demonstrating increases of between 1.06 and 1.59 units on the 4-unit scale. The mean border delineation average reader score increased from 1.98 unenhanced to 2.58 combined unenhanced/enhanced (using a scale of 1 = no or unclear delineation to 4 = excellent delineation). The mean differences were consistent across the 3 readers, with all 3 readers demonstrating increases of between 0.43 and 0.72 units on the 4-unit scale.

Table I. Summary of Contrast Enhancement: Blinded readers-combined unenhanced/gadobutrol-enhanced vs. combined unenhanced /gadoteridol enhanced

Reader	Image Set	No. of Subjects	Mean	Median	SD	Min	Max	95% CI Lower Limit	95% CI Upper Limit	P-Value
1	Unenhanced	314	0.94	1.0	0.14	0.5	1.3			
	Combined	314	2.21	2.1	0.57	0.0	3.6			
	Difference	314	1.26	1.1	0.61	-1.0	2.9	1.197	1.332	<.0001
2	Unenhanced	314	1.01	1.0	0.28	0.0	2.5			
	Combined	314	2.60	2.5	0.70	0.0	4.0			
	Difference	314	1.59	1.4	0.77	-1.0	3.4	1.503	1.673	<.0001
3	Unenhanced	312	0.96	1.0	0.16	0.5	1.5			
	Combined	312	2.02	1.9	0.46	1.0	3.3			
	Difference	312	1.06	1.0	0.51	-0.4	2.8	1.002	1.117	<.0001
Average	Unenhanced	316	0.97	1.0	0.15	0.0	1.5			
	Combined	316	2.26	2.2	0.52	0.0	3.5			
	Difference	316	1.29	1.2	0.56	-1.0	2.8	1.228	1.351	<.0001

Scale: 1 = no, 2 = moderate, 3 = good, 4 = excellent. Zero scores are due to the zero-filled averaging used when different numbers of lesions were detected by different modalities in order for the averages to be based on the same number of scores.

CI = confidence interval; Combined = combined unenhanced and enhanced; Max = maximum; Min = minimum; SD = standard deviation.

The mean internal morphology average reader score increased from 1.32 unenhanced to 1.93 combined unenhanced/enhanced (using a scale of 1 = poor visibility to 3 = good visibility). The mean differences for the 3 blinded readers, while all showing statistically significant increases, had some variability across the readers, with mean changes of 0.62, 0.82, and 0.41 for readers 1, 2, and 3, respectively.

For the number of lesions, there was a high level of variability across the 3 readers. In

particular, reader 2 had a higher mean number of lesions for both the unenhanced and combined unenhanced/enhanced modalities. Reader 2 also had much more variability within his assessments than there was for readers 1 and 3. As a result, the variability in the average reader change from unenhanced to combined unenhanced/enhanced was higher than anticipated in the protocol. There was a mean increase of 0.17 lesions, with a 95% confidence interval of (-0.439, 0.780).

The lower limit of this confidence interval, -0.439, was slightly lower than the prespecified noninferiority margin of -0.35. However, this was mainly driven by the high standard deviation from reader 2. For readers 1 and 3, the lower limits of the confidence intervals were above the prespecified value of -0.35.

Based upon the observed data, a nonparametric analysis was performed where the lesion counts were replaced by a categorical variable. For the average reader, the number of lesions detected was equal for the 2 modalities for 20.8% of the subjects, higher for combined unenhanced/gadobutrol-enhanced in 44.0% of subjects, and higher for unenhanced in 35.1% of the subjects. The difference between combined unenhanced/gadobutrol-enhanced and, unenhanced was 8.9%, and the 95% confidence interval was (-0.5%, 18.4%). Using the noninferiority margin of -10%, which was prespecified as the noninferiority margin for the categorical variables, noninferiority was demonstrated for gadobutrol. Noninferiority was demonstrated for all 3 blinded readers as well.

Table II shows summary of border delineation. Blinded readers combined unenhanced/ gadobutrol-enhanced vs. combined unenhanced /gadoteridol enhanced. For all 3 individual readers, the change in scores from unenhanced to combined unenhanced/enhanced was again statistically significant ($P<0.0001$ in all cases). The mean border delineation average reader score increased from 1.98 unenhanced to 2.58 combined unenhanced/enhanced. The mean differences were consistent across the 3 readers, with all 3 readers demonstrating increases of between 0.43 and 0.72 units on the 4-unit scale. These results demonstrate that border delineation was statistically significantly superior after administration of gadobutrol as compared to the unenhanced values.

Reference ID: 2910496

Table II. Summary of border delineation: Blinded readers-combined unenhanced/ gadobutrol-enhanced vs. combined unenhanced /gadoteridol enhanced

Reader	Image Set	No. of Subjects	Mean	Median	SD	Min	Max	95% CI Lower Limit	95% CI Upper Limit	P-Value
1	Unenhanced	314	2.03	2.1	0.37	0.9	3.3			
	Combined	314	2.70	2.7	0.53	0.0	3.9			
	Difference	314	0.67	0.6	0.66	-2.0	2.6	0.599	0.745	<.0001
2	Unenhanced	314	2.19	2.3	0.49	0.0	3.2			
	Combined	314	2.91	3.0	0.60	0.0	4.0			
	Difference	314	0.72	0.7	0.78	-2.0	3.0	0.632	0.805	<.0001
3	Unenhanced	312	1.73	1.8	0.32	0.6	2.6			
	Combined	312	2.16	2.2	0.35	1.0	3.3			
	Difference	312	0.43	0.4	0.50	-1.0	2.3	0.373	0.485	<.0001
Average	Unenhanced	316	1.98	2.0	0.30	0.0	2.5			
	Combined	316	2.58	2.6	0.43	0.0	3.5			
	Difference	316	0.60	0.6	0.53	-2.0	3.0	0.537	0.654	<.0001

Scale: 1 = none, 2 = moderate, 3 = good, 4 = excellent. Zero scores are due to the zero-filled averaging used when different numbers of lesions were detected by different modalities in order for the averages to be based on the same number of scores.

CI = confidence interval; Combined = Combined unenhanced and enhanced; Max = maximum; Min = minimum; SD = standard deviation.

Similarly, visualization of the number of tumors and internal morphology improved significantly for combined enhanced gadobutrol over enunhanced image reads by three blinded readers.

Combined unenhanced/gadobutrol-enhanced vs. combined unenhanced/gadoteridol enhanced

For all 3 individual readers, the contrast enhancement, border delineation, and internal morphology scores were extremely similar for the 2 agents. The noninferiority of gadobutrol to gadoteridol was proven for each parameter.

For the average reader, as well as for all 3 individual readers, the numbers of lesions seen were very similar for the 2 agents. However, as mentioned previously, the variability for reader 2 was much higher than for the other 2 readers, which resulted in higher than expected variability for the average reader. The 95% confidence interval for the difference between gadobutrol and gadoteridol was (-0.601, 0.622). The lower limit of this interval was lower than the prespecified noninferiority margin of -0.35.

The results of the nonparametric analysis for the number of lesions show for the average reader, the difference between gadobutrol and gadoteridol was 8.3%, and the 95% confidence interval was (-0.9%, 17.6%). Using the prespecified noninferiority margin of -10%, noninferiority of gadobutrol to gadoteridol was demonstrated. Noninferiority was demonstrated for all 3 blinded readers as well.

Results for the blinded reader analysis of contrast enhancement are shown in Table III.

For the average reader, as well as for all 3 individual readers, the contrast enhancement scores were extremely similar for the 2 agents. The average reader score was 2.28 for gadobutrol, and 2.24 for gadoteridol; the 95% confidence interval for this difference was (0.004, 0.078). Since the lower limit of the confidence interval was 0.004, which is greater than the prespecified noninferiority margin of -0.35, noninferiority of gadobutrol to gadoteridol was proven.

Table III. Summary of Contrast Enhancement: Enhanced Gadobutrol vs enhanced gadoteridol

Reader	Image Set (Combined)	No. of Subjects	Mean	Median	SD	Min	Max	95% CI Lower Limit	95% CI Upper Limit
1	Gadobutrol	314	2.22	2.1	0.56	0.0	3.7		
	Gadoteridol	314	2.17	2.1	0.53	1.0	3.6		
	Difference	314	0.05	0.0	0.42	-2.0	1.6	0.005	0.098
2	Gadobutrol	313	2.67	2.5	0.69	0.5	4.0		
	Gadoteridol	313	2.60	2.5	0.72	0.0	4.0		
	Difference	313	0.06	0.0	0.56	-2.0	2.0	0.000	0.124
3	Gadobutrol	312	1.98	1.9	0.45	1.0	3.3		
	Gadoteridol	312	1.95	1.9	0.46	0.9	3.5		
	Difference	312	0.03	0.0	0.42	-1.5	1.9	-0.018	0.076
Average	Gadobutrol	315	2.28	2.2	0.51	0.0	3.3		
	Gadoteridol	315	2.24	2.1	0.49	0.0	3.5		
	Difference	315	0.04	0.0	0.33	-2.0	1.0	0.004	0.078

Scale: 1 = no, 2 = moderate, 3 = good, 4 = excellent. Zero scores are due to the zero-filled averaging used when different numbers of lesions were detected by different modalities in order for the averages to be based on the same number of scores.

CI = confidence interval; Combined = combined unenhanced and enhanced; Max = maximum; Min = minimum; SD = standard deviation.

The sponsor was able to show superiority in gadobutrol enhanced images as compared to unenhanced images (without contrast agent). The sponsor also successfully demonstrated the noninferiority of gadobutrol as compared to approved agent gadoteridol.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose response, concentration-response) for safety?

Information relevant for exposure-response for safety is derived from the following studies:

- Study 308200, the main dose-finding study, which supports the choice of the proposed 0.1 mmol/kg dose.

- Study 95062 which assessed the pharmacokinetics of gadobutrol 1.0 M in renally impaired patients and demonstrated that renal impairment does not affect the pharmacokinetics of gadobutrol 1.0 M after injection of doses up to 0.3 mmol/kg.

Reference ID: 2910496

- Study 310788 that assessed the pharmacokinetics of gadobutrol 1.0 M in pediatric patients and demonstrated that BW-adjusted dose proposed for adults is also appropriate for pediatric patients aged 2 to 17 years.

Safety results are summarized below:
Seventy nine (35.1%) of subjects in the gadobutrol group reported at least one AE; 52 (22.9%) of subjects in the comparator group reported at least one AE in the same time frame.

The incidence of subjects with AEs was similar among dose groups, (36.8%, 36.7%, 31.3% for 0.3, 0.1, and 0.03 mmol/kg respectively). The most commonly reported AEs for gadobutrol were headache, (8.0%), dizziness, (2.2%), and nausea and diarrhea, (both 1.8%). Four subjects who received gadobutrol experienced severe intensity AEs; 2 subjects who received comparator experienced severe AEs. Twenty two (9.8%) of subjects experienced drug related AEs, (5-7.4%, 12-13.3%, and 5- 7.5% in the 0.3, 0.1, and 0.03 mmol/kg dose groups respectively); 5.7% of subjects receiving comparator drug experienced drug related AEs

Headache was the most common drug related AS, reported with similar frequency among groups, (2.9%, 3.3%, and 3.0% in the 0.3, 0.1, and 0.03 mmol/kg dose groups respectively).

There were no deaths or discontinuations from the study due to an AE; one subject in the gadobutrol and one subject in comparator group experienced an SAE, not drug related. Mean changes in clinical chemistry and hematology parameters were not clinically relevant; one subject in each dose group experienced a change in clinical chemistry parameters, not drug related Vital sign changes showed no notable differences between dose groups and were not considered to be related to study drug.

One subject in the 0.03 mmol/kg group had EKG change of ST segment depression; one subject had an increase (≥60 msec) in QT interval according to Fridericia's method.

2.2.4.3 Does gadobutrol prolong the QT or QTc interval?

No. A formal review request was sent out to IRT for QTc Study. The review team concluded that there was no clinically significant increase in QTc after administration of gadobuterol (0.1 to 0.5 mmol/kg). For a brief description of the TQT study please refer to Individual Study Review in appendix (Study 21381; Page 49 in the present review)

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?
What are the characteristics of exposure-response relationship? How was an optimal dose selected for best contrast?

Reference ID: 2910496

For the optimal dose selection, the sponsor conducted a multi-center, double-blind, randomized, controlled, parallel group, dose comparison study. The corresponding blinded image were evaluated following a single intravenous injection of three different doses of gadobutrol 1.0 molar (Gadovist®) in patients with known or highly suspected focal blood brain barrier disturbances and/or abnormal vascularity of the central nervous system. The study compared three different doses of gadobutrol 1.0 M for the determination of safety and efficacy in patients for central nervous system (CNS) imaging. [See the individual study report in 4. Appendices: Report A40524 / Phase 2 Study 308200: " Multi-center, double-blind, randomized, parallel group, dose comparison study with corresponding blinded image evaluation following a single intravenous injection of three different doses of gadobutrol 1.0 molar (Gadovist®) in patients with known or highly suspected focal blood brain barrier disturbances and/or abnormality of the central nervous system"]

The objective of this study was to determine a safe and effective dose of gadobutrol 1.0 molar based on evaluation of the following:
• Raw number of lesions detected in precontrast and combined precontrast and postcontrast magnetic resonance imaging (MRI), assessment of border delineation, degree of contrast enhancement, and internal morphology of lesions.
• The maximum Contrast-to-Noise Ratio (CNR) between white and gray matter with gadobutrol perfusion MRI.

The secondary objectives of this study were:
• To evaluate the proportion of all enhanced lesions detected and matched.
• To evaluate the proportion of all lesions detected and matched with gadobutrol MRI.
• To evaluate quantitative and qualitative parameters of perfusion MRI (uncorrected/ corrected cerebral blood volume [CBV], cerebral blood flow [CBF], time to peak [TTP], mean transit time [MTT], permeability factor [PF]).
• To evaluate/describe the alteration of perfusion parameters in CNS lesions and in particular that this was associated with different tumor grades of malignancy and to determine the usefulness of these parameters for evaluation of tumor grades.
• To evaluate the CNR of lesion/gray matter and lesion/white matter with gadobutrol perfusion MRI.
• To evaluate diagnosis and confidence in diagnosis.
• To assess the safety profile of gadobutrol after intravenous administration.

Three MRIs were obtained on each subject: unenhanced MRI, gadobutrol-enhanced MRI consisting of perfusion and steady-state MRI; and comparator-enhanced MRI consisting of steady-state MRI only. The CNR in white and gray matter, uncorrected and corrected CBV, CBF, TTP, MTT, and PF were evaluated by blinded readers and compared to histopathology, where applicable. The unenhanced MRI, combined unenhanced and gadobutrol-enhanced MRI, and combined unenhanced and comparator-enhanced MRI were evaluated by clinical study investigators and 3 independent blinded readers. To allow exact matching of lesions throughout the different imaging sequences, an independent radiologist (lesion tracker) performed 'lesion tracking' based only on the

Reference ID: 2910496

available CNS diagrams, separate from the investigator image and blinded image evaluations.

The 229 subjects were randomized to 1 of the 3 gadobutrol dose groups, including 69 subjects in the 0.3 mmol/kg group, 90 subjects in the 0.1 mmol/kg group, and 70 subjects in the 0.03 mmol/kg group. Twelve (5.2%) of the 229 subjects were withdrawn prematurely from the study. Two (0.9%) subjects, both in the 0.1 mmol/kg dose group, were withdrawn from the study after receiving gadobutrol and before receiving comparator—1 subject due to an AE (endocranial hypertension and brain edema) and 1 subject due to other reasons. Four (1.7%) subjects were withdrawn after receiving comparator and before receiving gadobutrol—1 subject due to a protocol deviation, 1 subject due to loss to follow-up, and 2 subjects due to other reasons. The other 6 subjects who received study drug and were withdrawn from the study prematurely were withdrawn after receiving both gadobutrol and comparator, including 2 subjects who withdrew consent, 1 who was lost to follow-up, and 3 for other reasons. The efficacy analysis sets included the full analysis set (FAS) and the per protocol set (PPS). A total of 206 subjects comprised the FAS, which included data from all subjects for whom case report form (CRF) entries and images were available for unenhanced MRI, combined unenhanced and gadobutrol-enhanced MRI, and combined unenhanced and comparator-enhanced MRI. A total of 173 subjects were included in the PPS, which included all subjects in the FAS with valid images who received ±10% of the intended dose of study drug and had no major protocol or MRI procedure deviations. The PPS was used for the primary efficacy analyses. Subjects who received any amount of study drug were included in the safety analysis set (SAS), which comprised 229 subjects overall (225 subjects received gadobutrol and 227 subjects received OptiMARK).

The four primary visualization efficacy variables were condensed to a composite score, the CVS. The higher the CVS, the more effective the respective treatment. For the average reader, the lowest CVS value (1.43) was obtained for the 0.03 mmol/kg dose group and the highest CVS value (2.02) was obtained for the 0.1 mmol/kg (standard) dose group (Table IV). The difference in CVS between these 2 dose groups was statistically significant ($p = 0.003$) in favor of the 0.1 mmol/kg dose. CVS values appeared to plateau with the 0.1 mmol/kg dose; ie, the highest dose group 0.3 mmol/kg showed no further increase in CVS (1.98) compared with 0.1 mmol/kg. The difference in CVS between the standard and the highest dose was not statistically significant ($p = 0.844$). Scores for 2 of the 3 the individual blinded readers were similar to those of the average reader scores. Increasing the dose of gadobutrol did not significantly increase the number of lesions detected between the unenhanced and the enhanced MRI, as was expected.

Reference ID: 2910496

Table IV. Categorical Visualization Score for three different dose groups

Dose (mmol/kg)	Rate	Total Lesions	Lesions Detected	Border Delineation	Internal Morphology	Contrast Enhancement	CVS	CVS StD	T-test P-value
0.3 (N=56)	Precontrast	261	4.66	2.42	1.62	1.00	1.98	1.20	
0.3	Pre + Post	271	4.85	3.07	2.40	2.77	1.98	1.20	
									0.844
0.1 (N=55)	Precontrast	273	4.96	2.41	1.60	1.00	2.02	1.04	
0.1	Pre + Post	270	4.92	3.09	2.50	2.78	2.02	1.04	
									0.003
0.03 (N=61)	Precontrast	347	5.69	2.50	1.73	1.00	1.43	1.07	
0.03	Pre + Post	346	5.67	2.78	2.23	2.01	1.43	1.07	

CVS = Contrast Visualization Score; N = number of subjects in dose group; Pre = precontrast; Post = postcontrast; StD = standard deviation

Statistically significant differences between the 0.03 and 0.1 mmol/kg dose groups were observed for every reader for contrast enhancement and for 2 of 3 readers for border delineation and internal morphology (Table IV). Mean CNR values were higher for the 0.1 (27.0) and 0.3 (22.2) mmol/kg dose groups compared with the 0.03 mmol/kg dose group (9.42). There was no statistically significant difference between the 0.03 and 0.1 mmol/kg dose groups or between the 0.1 and 0.3 mmol/kg dose groups. Secondary efficacy variables included lesion detection (all matched lesions and contrast enhanced matched lesions), diagnosis and confidence in diagnosis, perfusion parameters (maps and artifacts), evaluation of tumor grade, and CNR of lesion/gray matter and lesion/white matter.

The results of the analyses of secondary efficacy variables provided variable support of the results of the primary efficacy analysis. For one of the blinded readers, there was a statistically significant difference between the low and standard doses ($p = 0.03$) and between the standard and high doses ($p = 0.02$) in favor of the 0.1 mmol/kg dose with respect to the accuracy comparison of low-standard gadobutrol doses (0.03 and 0.1 mmol/kg) and the accuracy comparison of the standard-high gadobutrol doses (0.1 and 0.3 mmol/kg) using detection of all matched lesions. For the other 2 blinded readers, there was no significant difference between the 0.03 and 0.1 mmol/kg doses or between the 0.1 and 0.3 mmol/kg doses. For 2 of 3 readers, there was a statistically significant difference between the low and standard doses ($p = 0.02$) and between the standard and high doses ($p = 0.02$ and $p = 0.04$) in favor of the standard (0.1 mmol/kg) dose with respect to the accuracy comparison of low-standard gadobutrol doses (0.03 and 0.1 mmol/kg) and standard-high gadobutrol doses (0.1 and 0.3 mmol/kg) using detection of enhanced matched lesions. For the remaining 2 blinded readers (one for low-standard comparison and the other for standard-high comparison), there was no significant difference between the 0.03 and 0.1 mmol/kg doses or between the 0.1 and 0.3 mmol/kg doses.

Lesion Contrast Enhancement:
The average of the findings for the 3 blinded readers is summarized in Table V. There was a statistically significant difference (95% CI: -1.171, -0.424) between the 0.03 and 0.1 mmol/kg doses in favor of the 0.1 mmol/kg dose according to the average reader with regard to lesion contrast enhancement (Table V). In addition, although clinical significance between doses was not specifically defined for this study, lesion contrast enhancement based on the average reader was 82% better for the 0.1 mmol/kg dose than for the 0.03 mmol/kg dose, which was a clinically meaningful improvement. There was no significant difference between the 0.1 and 0.3 mmol/kg doses.
Table V. Lesion Contrast Enhancement for three dose groups

Dose (mmol/kg)	Rate	No. of Subjects	Mean	Median	StD	Min, Max	Dose Difference (Lower, Upper)
0.3	Precontrast	53	1.00	1.00	0.00	1, 1	
0.3	Pre + Post	53	2.79	3.20	1.15	1, 4	
0.3	Difference	53	1.79	2.20	1.15	0, 3	
							-0.011 (-0.436, 0.414)
0.1	Precontrast	55	1.00	1.00	0.03	1, 1	
0.1	Pre + Post	55	2.78	3.11	1.08	1, 4	
0.1	Difference	55	1.78	2.11	1.07	0, 3	
							-0.797 (-1.171, -0.424)
0.03	Precontrast	58	1.00	1.00	0.00	1, 1	
0.03	Pre + Post	58	1.98	1.86	0.93	1, 4	
0.03	Difference	58	0.98	0.86	0.93	0, 3	

Max = maximum; Min = minimum; Pre = precontrast; Post = postcontrast; StD = standard deviation
Scale: 1=None 2=Moderate 3=Good 4=Excellent
Confidence intervals are asymptotic confidence intervals adjusted for clustering.

CONTRAST-TO-NOISE RATIO (CNR):
CNR is a variable derived from the signal intensity (SI) measurement, which was performed using a centralized procedure by an independent radiologist.
CNR between white and gray matter in the perfusion imaging is defined as the SI difference between white and gray matter divided by the standard deviation of the SI of white matter and was calculated according to the following formula:

$$CNR = (SI_{white} - SI_{gray}) / SD_{white}$$

where, SI_{white} = the SI in the Region of Interest (ROI) in the white matter of the hemisphere contralateral to a lesion

SI_{gray} = the SI in the ROI in the gray matter of the hemisphere contralateral to a lesion
SD_{white} = standard deviation of the SI of the white matter

The derived variable CNR is summarized by gadobutrol dose group in Table VI. CNR values were higher for the 0.1 and 0.3 mmol/kg dose groups compared with the lowest dose group (0.03 mmol/kg). There was no statistically significantly difference between the 0.03 and 0.1 mmol/kg dose groups or between the 0.1 and 0.3 mmol/kg dose groups.

Reference ID: 2910496

Table VI. Contrast to Noise Ratio for Three Different Dose Groups

Dose (mmol/kg)	No. of Subjects	Mean	Median	StD	Min, Max	Dose Difference (Lower, Upper)
0.3	55	22.2	17	15.2	3, 70	
						4.7421 (-15.86, 25.347)
0.1	56	27.0	14	75.6	4, 573	
						17.54 (-37.11, 2.022)
0.03	60	9.42	7	11.4	-21, 77	

Max = maximum; Min = minimum; StD = standard deviation
For each subject, mean of the CNRs for the 6 maps is used.

2.2.5 Pharmacokinetic characteristics of the drug and its major metabolites

2.2.5.1 What are the single dose and multiple dose PK parameters?

The mean primary pharmacokinetic parameters of gadovist after a single intravenous injection of 0.1, 0.2, or 0.3 mmol/kg of gadovist (gadovist 1.0 M) or two intravenous injections of 0.1 mmol/kg of gadovist with a 30-min interval between injections at a rate of 2 mL/sec are summarized in the Table VII (compartment model independent method).

Table VII. Primary pharmacokinetic parameters for gadovist

Parameters	Unit	0.1 mmol/kg (n=8)	0.2 mmol/kg (n=8)	0.3 mmol/kg (n=8)	0.1+0.1 mmol/kg (n=7)
AUC	µmol-h/L	1026(13%)	2008(12.5%)	2812(10.6%)	2070(14.3%)
Cmax	µmol/L	1218(48%)	2508(36.2%)	3586(36.7%)	1792(15.9%)
CL	mL/min/kg	1.63(13.0%)	1.66(12.6%)	1.78(10.8%)	1.61(14.3%)
$T_{1/2}$	hr	1.82(12%)	1.77(11.8%)	1.82(10.2%)	1.78(17.2%)
Ag,ur	%	91.8(14.7%)	99.2(5.75%)	101(9.04%)	94.8(3.74%)

(CV); Ag,ur = total amount excreted in urine

Plasma gadolinium concentrations increased proportionally with an increase in dose from 0.1 to 0.3 mmol/kg.

After intravenous bolus injection, plasma gadolinium concentrations decreased generally in a bi-exponential manner with a rapid distribution phase followed by a relatively slower elimination phase. The mean values for t1/2, CL, Ag,ur (amount of gadolinium excreted in urine, expressed as % amount), and CLR were similar in the 0.1, 0.2, and 0.3 mmol/kg dose cohorts. After two intravenous injections of 0.1 mmol/kg of gadovist with a 30-min interval between injections, the mean value for AUC was similar to that after a single intravenous injection of 0.2 mmol/kg of gadovist. In contrast, the mean value for Cmax was about 70% of that after a single intravenous injection of 0.2 mmol/kg of SH L 562

Reference ID: 2910496

BB. The urinary excretion of gadolinium was almost completed after 12 h post injection with a mean recovery between 90.4–99.3 % of the administered gadolinium dose. The mean overall recoveries up to 72 hr after intravenous injection were 91.8–101% of the administered gadolinium dose. The renal clearance was almost identical to the total clearance.

Figure 3 shows the plasma Gd concentration-time profile and the relationship between the systemic exposure (AUC) and dose after intravenous
administration of this product as single doses of 0.1, 0.2, or 0.3 mmol/kg or at a divided dose of 0.2 mmol/kg two times at an interval of 30 minutes, respectively

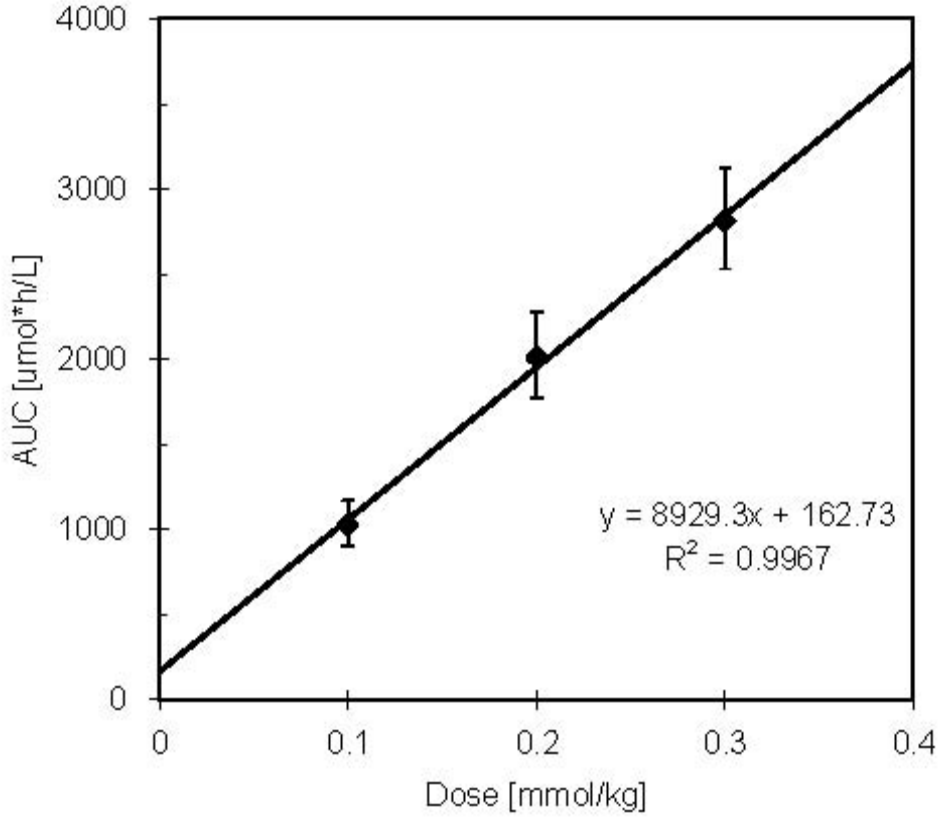


Figure 3. Dose linearity between exposure and dose for intravenous administration

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?
There is no direct comparison with the PK of gadobutrol in healthy volunteers and patients for MRI.

2.2.5.3 What are the characteristics of drug absorption?
Not applicable as gadobuterol is to be used as single intravenous injection.

2.2.5.4 What are the characteristics of drug distribution?

After intravenous administration of 0.1 mmol/kg of gadobutrol, it is rapidly distributed in the extra cellular space. There is negligible binding to plasma proteins.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?
The renal route appeared a major elimination route of the gadobutrol. The urinary excretion of gadolinium was almost completed after 12 h post injection with a mean recovery between 90.4–99.3 % of the administered gadolinium dose. The mean overall recoveries up to 72 hr after intravenous injection were 91.8–101% of the administered gadolinium dose. The renal clearance was almost identical to the total clearance.

2.2.5.6 What are the characteristics of drug metabolism?
Gadovist does not undergo metabolism and is excreted in urine in 97-100% over 72 hour period.

2.2.5.7 What are the characteristics of drug excretion?
Gadobutrol is excreted in an unchanged from via the kidneys. Gadobutrol is eliminated from plasma with a mean terminal half-life of 1.81 hours (1.33 – 2.13 hours). See 2.2.5.1.

2.2.5.8 Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?
See 2.2.5.1. The PK of gadobutrol is linear in the dose range from 0.1 to 0.3 mmol/kg.

2.2.5.9 How do the PK parameters change with time following chronic dosing?
Not applicable as gadobutrol is to be used as single use.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

The CV (%) of PK parameters appeared 5-17 %, except Cmax (15 – 48 %) .
It is expected that the Cmax after IV administration is a function of sampling time and also function of bolus injection rate.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The effect of age and gender on the pharmacokinetics of gadobutrol was investigated during a Phase I study in non-elderly (45 y) and elderly (> 65 y) healthy men and women following single bolus intravenous administration of 0.1 mmol/kg. There was no

Reference ID: 2910496

clinically relevant effect on the pharmacokinetics in relation to gender. The results indicate that the effect of gender on clearance can be accounted for by the difference in body weight between genders and thus by the administered total dose.

In contrast, a statistically significant effect was seen with age. In healthy elderly men and women plasma clearance was reduced by approximately 25% and 35%, respectively, as compared with non-elderly subjects paralleled by an increase in systemic exposure by 33% (men) and 54% (women) and in the terminal half-life by approximately 33% and 58%, respectively (Table VIII). There is no dose adjustment necessary for elderly patients as the exposure is not substantially decreased and this would not compromise the diagnostically useful image.

Table VIII. Pharmacokinetic parameters of gadobutrol for non-elderly men and women as compared to elderly (>65 years) men and women

Parameter	unit	Non-elderly men (N=8)		Elderly men (N=8)	
		Geo. mean (%CV)	Range	Geo. mean (%CV)	Range
AUC	mcmol·h/L	891 (20.8%)	703 – 1249	1183 (12.4%)	894 – 1294
CL	L/h	8.88 (22.0%)	6.36 – 12.9	6.68 (7.25%)	6.14 – 7.47
CL/kg	L/h/kg	0.112 (20.8%)	0.0801 – 0.142	0.0845 (12.4%)	0.0773 – 0.112
$t_{1/2}$	h	2.12 (14.1%)	1.75 – 2.82	2.81 (8.55%)	2.34 – 2.98

Parameter	unit	Non–elderly women (N=8)		Elderly women (N=7)	
		Geo. mean (%CV)	Range	Geo. mean (%CV)	Range
AUC	mcmol·h/L	849 (12.7%)	667 – 974	1306 (20.1%)	986 – 1589
CL	L/h	7.76 (14.4%)	6.56 – 9.51	4.85 (14.2%)	4.34 – 6.05
CL/kg	L/h/kg	0.118 (12.7%)	0.103 – 0.150	0.0766 (20.1%)	0.0629 – 0.101
$t_{1/2}$	h	1.81 (8.26%)	1.68 – 2.14	2.86 (14.8%)	2.33 – 3.72

AUC = area under the drug concentration vs. time curve from time 0 to the last data point >LLOQ
CL = total body clearance of drug
CL/kg = total body clearance of drug, normalized to bodyweight
LLOQ = lower limit of quantification
$t_{1/2}$ = half-life associated with terminal slope

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Pediatric patients:
According to Agency's Pediatric Decision Tree, it is reasonable to assume that the progression of disease (CNS tumors) is the same in adults and pediatric population. It is also reasonable to assume similar concentration-response for gadobutrol in pediatric and adults patients. In this context, the PK data in pediatric population could be extrapolated to the efficacy of gadobutrol in this population, instead of an efficacy trial. Therefore, the sponsor conducted a study in pediatric patients to evaluate the pharmacokinetics of Gadovist 1.0 in plasma at the standard dose of 0.1 mmol/kg in children of different age and to evaluate quantitatively the renal excretion of gadolinium/Gadovist 1.0 within a

Reference ID: 2910496

predefined collection period as well as to evaluate the safety and tolerability of Gadovist 1.0 at the standard dose of 0.1 mmol/kg in children. In addition, a qualitative image evaluation of Gadovist 1.0 at the standard dose of 0.1 mmol/kg in children following MRI of brain, spine, liver and kidneys or MRA was also performed. This study was designed to be a multicenter and open-label study in pediatric patients aged 2-17 years (3 age groups: 2-6, 7-11, and 12-17 years) who were routinely scheduled for a Gd-enhanced MRI examination. Of the 140 enrolled patients, 2 patients were considered dropouts as they never received any study drug. Another 3 patients had to be excluded from the PPS due to major protocol deviation. Further 5 patients had to be excluded from the final PK analysis set based on the gadolinium (Gd) concentration measurements (implausible PK profile, high Gd concentration already at baseline). The pharmacokinetics of gadobutrol were evaluated after intravenous administration of Gadovist to 130 pediatric patients at a dose of 0.1 mmol/kg. The injection rate was 0.8-3 mL/sec. Blood was collected before and at intervals up to 8 hours after administration to measure the plasma Gd concentration by a validated ICP-MS method with a lower limit of quantification of 0.0636 µmol/L. In suitable/capable patients urine was quantitatively collected over 6 hours p.i.

Table IX. Pharmacokinetic profiles or pediatric (2-17 year old) subjects as compared to adult for 0.1 mmol of gadobutrol intravenous administration.

Parameter	Age Group	Median estimate	2.5th percentile	97.5th percentile
			of parameter distribution	
CL [L/h]	**All ages (2-17 years)**	**3.24**	**1.53**	**6.62**
	2-6 years	2.07	1.45	3.83
	7-11 years	3.28	1.81	5.93
	12-17 years	4.90	2.52	7.37
CL/kg [L/h/kg]	**All ages (2-17 years)**	**0.10**	**0.05**	**0.17**
	2-6 years	0.13	0.09	0.17
	7-11 years	0.10	0.05	0.17
	12-17 years	0.09	0.05	0.10
Vss [L]	**All ages (2-17 years)**	**5.96**	**3.27**	**13.2**
	2-6 years	3.83	3.24	6.33
	7-11 years	5.98	4.06	11.69
	12-17 years	10.02	5.16	14.12
Vss/kg [L/kg]	**All ages (2-17 years)**	**0.20**	**0.12**	**0.28**
	2-6 years	0.24	0.20	0.28
	7-11 years	0.19	0.14	0.23
	12-17 years	0.18	0.092	0.23
AUC [µmol*h/L]	**All ages (2-17 years)**	**999**	**590**	**1808**
	2-6 years	815	494	1167
	7-11 years	969	590	2163
	12-17 years	1167	925	1808
$t_{1/2}$ [h]	**All ages (2-17 years)**	**1.69**	**1.34**	**2.32**
	2-6 years	1.75	1.34	2.30
	7-11 years	1.61	1.17	2.62
	12-17 years	1.65	1.42	2.23
MRT [h]	**All ages (2-17 years)**	**1.94**	**1.24**	**2.99**
	2-6 years	1.88	1.24	2.77
	7-11 years	1.83	1.03	3.37
	12-17 years	2.03	1.57	2.99

Gadobutrol pharmacokinetics in the pediatric population aged 2 to 17 years can be adequately described by an open two-compartment model with elimination from the central compartment. Body weight was the major covariate to scale the PK parameters total body clearance (CL) and central volume of distribution (V1) using an allometric model. Inter-individual variability of CL and V1 was moderate with 18.5% and 28.6%, respectively.

Adjustment of CL to body weight was superior compared to adjustment to calculated body surface area (BSA). Neither age nor gender were found to be additional independent parameters affecting the pharmacokinetics of gadobutrol in the pediatric population aged 2 to 17 years. Due to the non-linear relationship between body weight and gadobutrol clearance, there was a small difference in the median AUC in young children aged 2 to 6 years (815 µmol/h) when compared to the median AUC in adolescents aged 12 to 17

years (1167 µmol/h), when the same nominal dose of 0.1 mmol/kg gadobutrol was administered. The distribution of parameter values, however, largely overlapped. Simulations based on the final population PK model applying different body weights showed minor differences in median Gd plasma concentrations within 30 min post injection. Thus, comparable gadolinium concentrations during the initial phase relevant for MRI are predicted to be achieved with body weight-based dosing in the pediatric population aged 2 to 17 years. In all pediatric patients (2-17y) more than 94% (arithmetic mean) of the administered dose was excreted with urine already after a period of about 6 hours. This finding confirms the assumption that in the pediatric population aged 2 to 17 years gadobutrol is rapidly excreted from the body via glomerular filtration, similar to adults.

2.3.2.2 Renal impairment

The sponsor conducted a study to evaluate the safety and tolerability of 1.0 molar gadobutrol administered intravenously at a dose of 0.1 and 0.3 mmol/kg in patients with impaired renal function or patients on dialysis.

The aim of this clinical study was to evaluate the safety and pharmacokinetic profile of gadobutrol in these patients. The primary variable for patients with impaired renal function was the change in creatinine clearance when post-injection values were compared to pre-injection values. For patients on dialysis, the primary variable was the decrease of serum gadobutrol content with each post-injectional dialysis session.

Gadobutrolis excreted primarily through kidneys. The individual patient's creatinine clearance as a marker of renal impairment, correlated well with the total clearance of gadobutrol from serum. This correlation between total serum clearance and renal clearance of gadobutrol was indicative for an almost exclusive elimination of gadobutrol via the kidney. Two doses were studied (0.1 mmol/kg and 0.3 mmol/kg in patients with renal impairment. A composite graph for both doses showed that the creatinine clearance is linearly dependent on renal function (Figure 4). Therefore, as expected, the clearance of gadobutrol in decreased in patients with renal impairment and AUC is increased

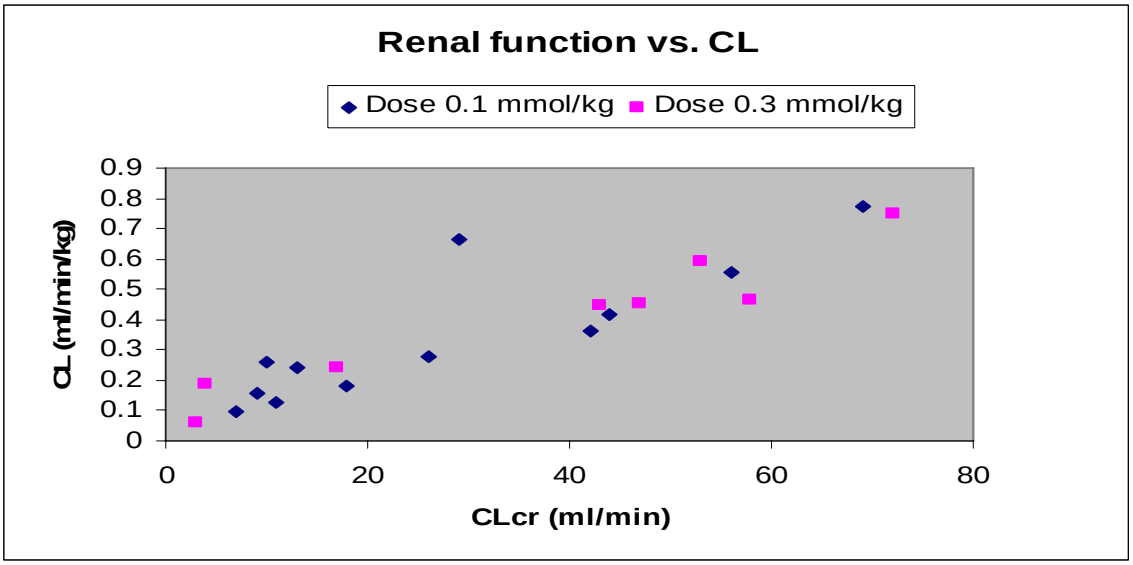


Figure 4. Relationship between creatinine clearance and total clearance for gadovist for two doses.

The data for all patients with renal impairment was reanalyzed based on the classification in renal guidance. A combined analysis of patients from both dose groups (0.1 and 0.3 mmol/kg) shows that AUC increased about 10 fold in patients with severe renal impairment, 4-fold for moderate renal impairment patients and about 2 fold in patients with mild renal impairment. The elimination half-life also increased 2 fold, four fold and about ten-fold for patients with mild, moderate and severe renal impairment patients, respectively. The data for healthy patients used was from a cross comparison study. These estimates are based on a cross study comparison with healthy adults as the renal study did not include healthy volunteers.

Table X. Phamacokinetic parameter (AUC) for patients with renal impairment vs healthy volunteers

	Mild RI CrCL (60-90 ml/min) N=2	**Moderate RI CrCL (30-59 ml/min) N=7**	**Severe RI CrCL (<30 ml/min) N=11**	**Healthy N=55**
AUC* (µmolh/L)	**2153-2221**	**4947±3917**	**12090±9954**	**1244±155**
FOLD INCREASE vs HEALTHY	**1.75**	**4**	**10**	

Reference ID: 2910496

The recovery of gadobutrol in urine of patients with mild and moderate renal impairment was complete within the study period of 72 hours p.i. In patients with severe renal impairment (creatinine clearance < 30 mL/min), the recovery of gadobutrol was less complete within the study period of 120 hours p.i. due to the extremely prolonged elimination half-life (up to 44.4 h).

PATIENTS ON DIALYSIS:
For the patients on dialysis, the decrease of serum gadobutrol content with each dialysis session served as primary variable. The serum gadobutrol content after each dialysis session is displayed as percentage recovery of gadobutrol in Table XI.

Table XI. % Recovery of gadovist with time for two different doses in dialysis patients

treatment	time of dialysis	serum SH L 562 BB content recovered [%]					
		mean	SD	minimum	median	maximum	Σ
0.1 mmol/kg BW	day of exam.	71.98	12.91	50.40	76.00	82.80	5
	48 hours p.i.	97.13	2.22	94.70	97.25	99.30	4[a]
	96 hours p.i.	98.80	0.63	98.10	98.60	99.60	5
0.3 mmol/kg BW	day of exam.	65.07	13.96	48.50	66.25	78.70	6
	48 hours p.i.	91.45	4.42	85.50	92.55	96.00	6
	96 hours p.i.	97.37	2.27	94.30	98.10	99.80	6[b]
	168 hours p.i.	99.60	–	99.60	99.60	99.60	1

In patients treated with 0.1 mmol/kg, recovery of gadobutrol ranged between a minimum of 98.1 % and a maximum of 99.6% after the third dialysis session at 96 hours p.i. For patients treated with 0.3 mmol/kg, recovery ranged between a minimum of 94.3% and a maximum of 99.8% after the third dialysis session at 96 hours p.i. Total recovery of gadobutrol, increased continuously with each dialysis and was nearly complete after the third dialysis session at 96 hours p.i. (98.1 % to 99.6% recovery).

For patients treated with 0.3 mmol/kg, total recovery of gadobutrol, increased continuously with each dialysis and was nearly complete after the third dialysis session at 96 hours p.i. (94.3% to 99.8% recovery). One patient (no. 10028) received a further dialysis at 168 hours p.i.; total recovery of gadobutrol summed up to 99.6% after this fourth dialysis session.

2.3.2.3 Hepatic impairment
There was no study performed in patients with hepatic impairment using gadobutrol as per discussion with the Division.

2.3.2.4 What pregnancy and lactation use information is there in the application?
There are no adequate and well-controlled studies in pregnant women using gadobutrol and no data on the use of gadobutrol in nursing mothers.

Reference ID: 2910496

2.4.1
EXTRINSIC FACTORS

2.4.2 Drug-drug interactions
2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?
Not known.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?
Not known.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?
Not known.

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?
Not known.

2.4.2.5 Are there other metabolic/transporter pathways that may be important?
Not known.

2.4.2.6 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?
The label does not specify co-administration of another drug.

2.4.2.7 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?
No formal drug-drug interaction studies were conducted with gadobutrol as it is to be used as single dose and not metabolized.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Not applicable as the formulation is for IV administration

2.5.2 What is the composition of the to-be-marketed formulation?

The qualitative and quantitative composition of 1 mL Gadovist solution is described in Table XII below:

Reference ID: 2910496

Table XII. Gadovist Composition of 1 mL Gadovist solution

No.	Name of Ingredient	Unit	Function	Refer to Standards
Active substances:				
1.	Gadobutrol	604.720 mg	Active ingredient	(b) (4)
Excipients:				
1.	Calcium sodium butrol (Calcobutrol sodium)	(b) (4)		
2.	Trometamol	(b) (4)		USP
3.	Hydrochloric acid. (b) (4)			USP
4.	Water for injection			USP

2.5.3 What moieties should be assessed in bioequivalence studies?
Not applicable.

2.5.4 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?
Not applicable.

2.5.5 Has the applicant developed an appropriate dissolution method and specification that will assure in vivo performance and quality of the product?
Not applicable.

2.6 ANALYTICAL SECTION

2.6.1 Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

Gadobutrol does not undergo any metabolism.

2.6.2 Were the analytical procedures used to determine drug concentrations in this NDA acceptable?
Yes.
The plasma/serum and urine gadolinium (Gd)-concentrations were measured by inductively coupled plasma-atomic emission spectrometry (ICP-AES) or inductively coupled plasma-mass spectrometry (ICP-MS), and plasma and urinary metabolites were investigated using high-performance liquid chromatography (HPLC) or HPLC combined

Reference ID: 2910496

with ICP-AES. The plasma/serum and urine drug concentration is expressed as the concentration of Gd in μmol/L. Gadolinium is the "signal producing" element, and one molecule of gadobutrol contains one Gd. Thus, the gadolinium concentration directly reflects the gadobutrol concentration. The calibration curves were linear over the range of 1.00 μg/mL to 500 μg/mL, using a plasma volume of 100 μL. The assay was regarded as valid for human plasma samples in the investigated concentration range from 1.00 μg/mL to 500 μg/mL. Accuracy and precision of determination of Gd at the lower limit of quantification (LLOQ) were very high with a low % CV (2% for intra-run and 3.6% for inter-run).

Reference ID: 2910496

3. DETAILED LABELING RECOMMENDATIONS

The labeling recommendation is as follows:

14 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

Reference ID: 2910496

4 APPENDICES

4.1. Proposed Package Insert (Original and Annotated): Not attached (Please refer to the above 3. Detailed labeling recommendation)

4.2 INDIVIDUAL STUDY REVIEW:

RENAL IMPAIRMENT STUDY:

Study objectives (STUDY REPORT B0245)
To evaluate the safety and tolerability of 1.0 molar SH L 562 BB administered intravenously at a dose of 0.1 and 0.3 mmol/kg BW in patients with impaired renal function or dialysis undergoing MR-investigation for any indication, and evaluation of the pharmacokinetic profile of SH L 562 BB in these patients.

The aim of the present clinical study was to evaluate the safety of 1 molar SH L 562 BB administered intravenously at a dose of 0.1 or 0.3 mmol/kg BW in patients with impaired renal function or on dialysis undergoing M R-investigation for any indication, and evaluation of the pharmacokinetic profile of SH L 562 BB in these patients. The primary variable for patients with impaired renal function was the change in creatinine clearance when post-injection values were compared to pre-injection values. For patients on dialysis, the primary variable was the decrease of serum SH L 562 BB content with each post-injection dialysis session.

The fate of SH L 562 BB in the body is governed by its physico-chemical properties, i.e., low molecular weight and high hydrophilicity. Due to the negligible plasma protein binding of SH L 562 BB, no change in the volume of distribution was expected in patients with renal impairment. This assumption was supported by the results for the volume of distribution at steady state (Vss) of SH L 562 BB. Even in patients with impaired renal function *(group* 2) Vss did not change, documenting that plasma protein binding of SH L 562 BB was negligible. The mean V ss and the corresponding standard deviations in patients with mild *(group* 1; 0.1 mmol/kg BW: 0.20 ± 0.042 L/kg and 0.3 mmol/kg BW: 0.22 ± 0.046 L/kg) or severe renal impairment *(group* 2; 0.1 mmol/kg BW: 0.22 ± 0.042 L/kg and 0.3 mmol/kg BW: 0.24 ± 0.017 L/kg) were comparable to those in healthy volunteers (0.2 L/kg).

The individual patient's creatinine clearance as a marker of renal impairment, correlated very well with the total clearance of SH L 562 BB from serum. This correlation between total serum clearance and renal clearance of SH L 562 BB was indicative for an almost exclusive elimination of SH L 562 BB via the kidney governed by the individual glomerular filtration rate. A decreasing total clearance of SH L 562 BB resulted in an increasing elimination half-life (t 1/2 , ß) of up to 9 h (0.1 mmol/kg BW) and of up to 7.6 h (0.3 mmol/kg BW) in patients with mild renal impairment *(group* 1). In the group of patients with severe renal impairment *(group* 2), the maxima of elimination half-life were 23 h (0.1 mmol/kg BW) and 44.4 h (0.3 mmol/kg BW). Under both treatments, i.e., 0.1 and 0.3 mmol/kg BW, the recovery of SH L 562 BB in urine of patients with mild renal impairment (creatinine c1earance < 80 and > 30 mL/min; *group* 1) was complete within the study period of 72 hours p.i. In patients with severe renal impairment (creatinine clearance < 30 mLlmin; *group* 2), the recovery of SH L 562 BB was less complete within the study period of 120 hours p.i. due to the extremely prolonged elimination half-life (up

to 44.4 h). The PK parameters for patients with two different renal function groups are shown in Table XIII-XVII.

Table XIII. Area under serum concentration in Group 1 (creatinine clearance <80 and >30) and Group 2 (creatinine clearance <30 ml/min)

treatment	patient group	area under the serum–concentration time curve [µmol/L*h]					
		mean	SD	minimum	median	maximum	Σ
0.1 mmol/kg BW	group 1	4015	1818	2153	3494	6420	6
	group 2	11531	4255	6819	10680	17800	5
0.3 mmol/kg BW	group 1	10339	2466	6664	10940	13780	6
	group 2	45677	34576	20860	31000	85170	3

Table XIV. Total Clearance in Group 1 (creatinine clearance <80 and >30) and Group 2 (creatinine clearance <30 ml/min)

treatment	patient group	total clearance from serum [mL/(min*kg)]					
		mean	SD	minimum	median	maximum	Σ
0.1 mmol/kg BW	group 1	0.49	0.21	0.26	0.49	0.77	6
	group 2	0.16	0.058	0.094	0.16	0.24	5
0.3 mmol/kg BW	group 1	0.51	0.14	0.36	0.46	0.75	6
	group 2	0.15	0.091	0.059	0.16	0.24	3

Table XV. Elimination half-life in Group 1 (creatinine clearance <80 and >30) and Group 2 (creatinine clearance <30 ml/min)

treatment	patient group	half–life of elimination [h]					
		mean	SD	minimum	median	maximum	Σ
0.1 mmol/kg BW	group 1	5.81	2.41	3.03	4.94	8.98	6
	group 2	17.60	6.16	8.79	18.02	23.32	5
0.3 mmol/kg BW	group 1	5.32	1.43	3.74	4.99	7.58	6
	group 2	24.79	17.40	11.33	18.59	44.44	3

Table XVI. Recovery of SH L562BB from renal elimination in Group 1 (creatinine clearance <80 and >30) and Group 2 (creatinine clearance <30 ml/min)

treatment	patient group	SH L 562 BB content recovered [%]					
		mean	SD	minimum	median	maximum	Σ
0.1 mmol/kg BW	group 1	104.7	13.7	86.4	102.5	126.1	6
	group 2	77.3	7.4	64.5	79.9	83.6	5
0.3 mmol/kg BW	group 1	92.8	9.1	84.3	90.6	110.1	6
	group 2	76.5	25.6	47.2	88.2	94.2	3

PATIENTS ON DIALYSIS:

Serum SH L 562 BB content
In patients on dialysis, the decrease of serum SH L 562 BB content with each dialysis session served as primary variable. The serum gadobutrol content after each dialysis session is displayed as percentage recovery of SH L 562 BB in Table XVII.

treatment	time of dialysis	serum SH L 562 BB content recovered [%]					
		mean	SD	minimum	median	maximum	Σ
0.1 mmol/kg BW	day of exam.	71.98	12.91	50.40	76.00	82.80	5
	48 hours p.i.	97.13	2.22	94.70	97.25	99.30	4[a]
	96 hours p.i.	98.80	0.63	98.10	98.60	99.60	5
0.3 mmol/kg BW	day of exam.	65.07	13.96	48.50	66.25	78.70	6
	48 hours p.i.	91.45	4.42	85.50	92.55	96.00	6
	96 hours p.i.	97.37	2.27	94.30	98.10	99.80	6[b]
	168 hours p.i.	99.60	–	99.60	99.60	99.60	1

• Summary
In patients treated with 0.1 mmol/kg BW, recovery of SH L 562 BB ranged between a minimum of 98.1 % and a maximum of 99.6% after the third dialysis session at 96 hours p.i. For patients treated with 0.3 mmol/kg BW, recovery ranged between a minimum of 94.3% and a maximum of 99.8% after the third dialysis session at 96 hours p.i.

• Patients treated with 0.1 mmol/kg BW
Total recovery of SH L 562 BB, increased continuously with each dialysis and was nearly complete after the third dialysis session at 96 hours p.i. (98.1 % to 99.6% recovery).

• Patients treated with 0.3 mmol/kg BW
Total recovery of SH L 562 BB (see text table 11), increased continuously with each dialysis and was nearly complete after the third dialysis session at 96 hours p.i. (94.3% to 99.8% recovery). One patient (no. 10028) received a further dialysis at 168 hours p.i.; total recovery of gadobutrol summed up to 99.6% after this fourth dialysis session.

ANALYTICAL METHODS:
The plasma/serum and urine gadolinium (Gd)-concentrations were measured by inductively coupled plasma-atomic emission spectrometry (ICP-AES) or inductively coupled plasma-mass spectrometry (ICP-MS), and plasma and urinary metabolites were investigated using high-performance liquid chromatography (HPLC) or HPLC combined with ICP-AES. The plasma/serum and urine drug concentration is expressed as the concentration of Gd in μmol/L. Gadolinium is the "signal producing" element, and one molecule of gadobutrol contains one Gd. Thus, the gadolinium concentration directly reflects the gadobutrol concentration.

Study No A39759

Title: Phase I, single-center, randomized, placebo-controlled, single-blind, dose-escalation study to assess the pharmacokinetics and safety of SH L 562 BB (gadobutrol 1.0 molar) 0.1, 0.2, 0.3 or 0.1 + 0.1 mmol/kg bw in Japanese healthy male subjects

Objective: The objective of this study was to evaluate the PK and safety of injection of SH562BB in healthy Japanese male subjects (healthy men ages 20-40 years).

Number of subjects: Eight subjects per treatment (40 subjects total) were planned. 8 subjects were included in the placebo and SH562BB 0.1, 0.2 and 0.3 mmol/kg groups, 7 subjects were included in 0.10.1 mmol/kg.

PK RESULTS: The mean primary pharmacokinetic parameters of gadobutrol after a single intravenous injection of 0.1, 0.2, or 0.3 mmol/kg of SH L 562 BB (gadobutrol 1.0 M) or two intravenous injections of 0.1 mmol/kg of SH L 562 BB with a 30-min interval between injections at a rate of 2 mL/sec are summarized in the Table XVIII (compartment model independent method).

Plasma gadolinium concentrations increased proportionally with an increase in dose from 0.1 to 0.3 mmol/kg. The mean values for AUC/D remained constant within the investigated dose range, as indicated by the range of values from 9.35 to 10.2 kg · h/L. This was also true for the mean values of Cmax/D, as indicated by the range of values from 11.9 to 12.5 kg/L.

After intravenous bolus injection, plasma gadolinium concentrations decreased generally in a bi-exponential manner with a rapid distribution phase followed by a relatively slower elimination phase. The mean values for t1/2, CL, AE,ur, and CLR were similar in the

0.1, 0.2, and 0.3 mmol/kg dose cohorts. After two intravenous injections of 0.1 mmol/kg of SH L 562 BB with a 30-min interval between injections, the mean value for AUC was similar to that after a single intravenous injection of 0.2 mmol/kg of SH L 562 BB. In contrast, the mean value for Cmax was about 70% of that after a single intravenous injection of 0.2 mmol/kg of SH L 562 BB. The urinary excretion of gadolinium was almost completed after 12 h post injection with a mean recovery between 90.4–99.3 % of the administered gadolinium dose. The mean overall recoveries up to 72 hr after intravenous injection were 91.8–101% of the administered gadolinium dose. The renal clearance was almost identical to the total clearance.

Table XVIII. Primary pharmacokinetic parameters of gadobutrol after a single intravenous injection of 0.1, 0.2, or 0.3 mmol/kg of SH L 562 BB or two intravenous injections of 0.1 mmol/kg of SH L 562 BB with a 30-min interval between injections (Compartment model independent method)

Parameters	Unit	0.1 mmol/kg (n = 8)	0.2 mmol/kg (n = 8)	0.3 mmol/kg (n = 8)	0.1 + 0.1 mmol/kg (n = 7)
AUC	µmol·h/L	1026 (13.0%)	2008 (12.5%)	2812 (10.6%)	2070 (14.3%)
AUC/D	kg·h/L	10.2 (13.0%)	10.0 (12.6%)	9.35 (10.8%)	10.3 (14.3%)
C_{max}	µmol/L	1218 (48.0%)	2508 (36.2%)	3586 (36.7%)	1792 (15.9%)
C_{max}/D	kg/L	12.2 (48.1%)	12.5 (36.5%)	11.9 (36.6%)	8.95 (15.9%)
$t_{1/2}$	h	1.82 (12.0%)	1.77 (11.8%)	1.82 (10.2%)	1.78 (17.2%)
CL	mL/min/kg	1.63 (13.0%)	1.66 (12.6%)	1.78 (10.8%)	1.61 (14.3%)
$A_{E,ur}$	%	91.8 (14.7%)	99.2 (5.75%)	101 (9.04%)	94.8 (3.74%)
CL_R	mL/min/kg	1.49 (15.1%)	1.65 (11.8%)	1.79 (8.29%)	1.53 (16.6%)

Because previous investigation showed that gadobutrol does not undergo biotransformation in humans, the concentration of gadolinium represents the concentration of gadobutrol in the study samples. Values are geometric means with geometric coefficients of variation (%) in parentheses. n = number of subjects; AUC = area under the plasma concentration–time curve from 0 h data point up to infinity; AUC/D = AUC divided by dose; Cmax = maximal plasma concentration; Cmax/D = Cmax divided by dose; t1/2 = terminal elimination half-life; CL = total clearance; Ag,ur = amount of gadolinium excreted into urine, expressed as % of dose; CLR = renal clearance.

Safety Results:
A total of 40 subjects received at least one injection of the investigational product. Of these, one subject in the 0.1 + 0.1 mmol/kg of SH L 562 BB treatment group did not receive a second injection because of adverse events (AEs) that developed after the first injection. Other subjects received the investigational product as planned. The mean ± SD (minimum–maximum) amounts (mL) of the investigational product injected in the placebo (saline) and 0.1, 0.2, 0.3, and 0.1 + 0.1 mmol/kg of SH L 562 BB groups were

13.4 ± 5.5 (5.3–21.0), 6.5 ± 0.7 (5.4–7.5), 11.8 ± 1.1 (10.6–14.0), 17.7 ± 1.7 (14.4–20.1), and 12.7 ± 2.9 (6.0–15.4), respectively.

Of the 40 subjects who received the investigational product (SH L 562 BB or placebo) at least once, 8 (20%) reported at least one AE. AEs were reported in 0 (0%), 0 (0%), 1 (12.5%), 3 (37.5%), and 4 (50.0%) subjects in the placebo and 0.1, 0.2, 0.3, and 0.1 + 0.1 mmol/kg of SH L 562 BB groups, respectively. The most common (developed in 2 or more subjects) AEs in preferred term (reported term) were urticaria (wheal) in 3 subjects and rhinorrhoea (nasal discharge) in 2. All AEs were judged by the investigator as unlikely, possibly, probably, or definitely related to the study drug. AEs judged as possibly, probably, or definitely related to the study drug were reported in 0 (0%), 0 (0%), 1 (12.5%), 3 (37.5%), and 2 (25.0%) subjects in the placebo and 0.1, 0.2, 0.3, and 0.1 + 0.1 mmol/kg of SH L 562 BB groups, respectively. Most AEs were judged by the investigator as mild in intensity. Two AEs (anaphylactoid reaction and vomiting) were rated as moderate. None of the subjects had a severe AE, and no deaths occurred. One subject had an anaphylactoid reaction, which was rated by the sponsor as a serious AE.

Conclusions:
Systemic exposure to gadolinium increased in proportion to increases in single intravenous doses of SH L 562 BB ranging from 0.1 to 0.3 mmol/kg. No difference in systemic exposure was observed after intravenous administration of 0.2 mmol/kg of SH L 562 BB in a single dose or in 2 doses with a 30-min interval between doses. Gadolinium is almost completely excreted via the renal route. SH L 562 BB was well tolerated at doses up to 0.3 mmol/kg administered as single injections and at a dose of 0.2 mmol/kg administered as 2 injections (0.1 mmol/kg each) in healthy Japanese men.

STUDY B000 PROTOCOL ME97113:
Safety, tolerability and pharmacokinetics of gadobutrol 1 molar in a dose range of 0.3 - 1.5 mmol/kg bw (SH L 562 BB) in healthy volunteers.

Forty-eight male volunteers with an average age ranging from 28.8 years (0.3 mmol/kg BW gadobutrol group) to 36.7 years (1.25 mmol/kg BW gadobutrol group). Their mean height and weight were from 178.3 cm (1.25 mmol/kg BW gadobutrol group) to 184.7 cm (0.5 mmol/kg BW gadobutrol group) and 72.5 kg (1.5 mmol/kg BW gadobutrol group) to 78.8 kg (0.5 mmol/kg BW gadobutrol group), respectively. Regarding the mean BMI, the means ranged from 22.4 kg/m2 (0.3 mmol/kg BW gadobutrol group) to 23.8 kg/m2 (1.0 mmol/kg BW gadobutrol group). All volunteers were Caucasians with the exception of one who was of mixed origin.

Study objectives
1) To evaluate the safety and tolerability of increasing dose levels of gadobutrol 1.0 molar in healthy volunteers
2) To obtain pharmacokinetic data on gadobutrol 1.0 molar after administration of dose level 0.3 mmol/kg BW

Study Design: The study was designed as a double-blind, randomized (only within a dosage level), independent group comparison, comparing a maximum of 6 dose levels of gadobutrol 1.0 molar and placebo (0.9% normal saline solution). The dose levels investigated were 0.3, 0.5, 0.75, 1.0, 1.25 and 1.5 mmol gadobutrol/kg BW. For each dose level, two volunteers were treated with placebo. After completion of the entire trial, all data from the placebo volunteers were pooled in one group.

In each dose level, six volunteers received gadobutrol 1.0 molar and two volunteers received placebo. The treatments were performed on two consecutive days (2 blocks of 4 volunteers each). The study drugs were injected intravenously as a fast bolus via injector pump: at dose level 0.3 mmol/kg at a rate of 5 mL/sec., at dose levels 0.5, 0.75 and 1 mmol/kg at a rate of 2 mL/sec. and at dose levels 1.25 and 1.5 mmol/kg at a rate of 1 mL/sec. For each volunteer, a complete physical examination was performed during the pre study examination and was repeated 7 days after study drug administration. Laboratory tests, vital sign measurements, ECG documentation and body temperature measurements were performed regularly after injection. In addition, partial oxygen saturation (O2 saturation) was monitored for up to 1 hour and cardiac rhythm for up to 2 hours postinjection. Adverse events were monitored for a period of 7 days after administration.

The blood samples were drawn at the start of administration as time point 0 (t=0) blood (about 4.5 mL) were taken at the following time points: before dosing (-15 minutes) and 2, 5, 10, 15, 20, 30, and 45 minutes and at 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24 and 48 hours after study drug injection.

Just before injection, each volunteer emptied his bladder, and an aliquot of this specimen (10 mL) was stored for pharmacokinetic analysis (baseline). Urine was collected quantitatively for a three-day period after administration of gadobutrol during the following collection intervals: 0-2, 2-4, 4-6, 6-12, 12-24, 24-48, and 48-72 hours after study drug administration. The actual urine collection time was recorded in the appropriate CRF. The volume of the urine voided in each collection interval was measured and recorded in the appropriate CRF.

The pharmacokinetic parameters were calculated for each individual volunteer using compartment model independent and compartment model dependent methods. WinNonlin Version 3.0 (Pharsight Cooperation, 1999) running on a personal computer (Pentium II 400 mHz, Window NT 4.0) was used instead of the planned software TOPFIT.

Compartment model independent Method
The pharmacokinetic parameter estimates of gadobutrol obtained with the compartment model independent methods are given in Table XIX. The mean (SD) value for the terminal disposition half-life in the serum was t1/2 = 2.01 (0.23) hours. The mean (SD) values of observed Cmax and AUC were 2563(832) µmoL/L and 3645 (423) h.µmoL/L, respectively. The mean (SD) values of total clearance, renal clearance, mean residence time after intravenous bolus injection and steady-state volume of distribution were CL = 1.39 (0.14) mL/min/kg, CLr = 1.39 (0.16) mL/min/kg, MRT = 2.35 (0.21) hours and Vss = 0.194 (0.017) L/kg, respectively.

Compartment model dependent approach
The details of pharmacokinetic analysis of WinNonlin output are presented in the Table XX. The mean (SD) values of key pharmacokinetic parameters gadobutrol obtained with the compartment model dependent methods and a weighting factor of 1/y are given in Table XXIV. The mean (SD) values for the disposition half-life determined were t1/2□2 = 1.76 (0.20) hours. The mean (SD) values of estimated AUC were 3555 (403) h. µmoL /L. The mean (SD) values of total clearance, mean residence time after intravenous bolus injection and steady-state volume of distribution were CL = 1.42 (0.14) mL/min/kg, MRTiv = 2.25 (0.19) h and Vss = 0.191 (0.019) L/kg, respectively.

Table XIX: Pharmacokinetic parameters of gadobutrol after rapid intravenous injection of 0.3 mmoL/kg (compartment model dependent method – two compartment model)

Volunteer	AUC	t1/2λ1	t1/2λ2	Vc	Vss	CL	MRTiv
	h•µmoL/L	h	h	L/kg	L/kg	mL/min/kg	h
2	3447.5	0.250	1.69	0.122	0.189	1.45	2.17
3	3279.9	0.475	1.84	0.152	0.205	1.52	2.24
4	3310.2	0.068	1.45	0.081	0.177	1.51	1.96
6	3722.6	0.045	1.66	0.054	0.179	1.34	2.22
7	3268.3	0.471	2.02	0.153	0.221	1.53	2.41
	(3391.9)	(0.806)	(2.49)	(0.174)	(0.268)	(1.47)	(2.57)
8	4298.7	0.356	1.89	0.130	0.174	1.16	2.49
	(4450.6)	(1.255)	(3.135)	(0.155)	(0.215)	(1.12)	(2.79)
Mean	3554.5	0.278	1.76	0.115	0.191	1.42	2.25
SD	402.6	0.190	0.20	0.040	0.019	0.14	0.19
%CV	11.3	68.6	11.6	34.7	9.85	10.2	8.33

Table XX Pharmacokinetic parameters of gadobutrol after rapid intravenous injection of 0.3 mmoL/kg (compartment model independent method – two compartment model)

Volunteer	AUC (0-12)	AUC	Cmax	t1/2λz	Vss	CL	MRTiv	CLr
	h•µmoL/L	h•µmoL/L	µmoL/L	h	L/kg	mL/min/kg	h	mL/min/kg
2	3484.7	3519.1	2339.2	1.89	0.190	1.42	2.23	1.37
3	3317.1	3350.9	2000.5	1.94	0.203	1.49	2.27	1.49
4	3362.1	3380.0	2998.8	1.65	0.179	1.48	2.02	1.50
6	3786.5	3849.0	4050.9	2.13	0.195	1.30	2.50	1.36
7	3295.7	3353.4	1840.8	2.26	0.221	1.49	2.47	1.54
8	4338.9	4416.0	2147.5	2.21	0.176	1.13	2.60	1.11
Mean	3597.5	3644.7	2562.9	2.01	0.194	1.39	2.35	1.39
SD	405.8	422.7	832.4	0.23	0.017	0.14	0.21	0.16
%CV	11.3	11.6	32.5	11.4	8.53	10.4	9.1	11.3

RESULTS OF PK AND SAFETY:

Gadobutrol is a new extracellular Gd chelate-based contrast medium for MR angiography which is available in two concentrations: 0.5 and 1 molar. Clinical studies on gadobutrol were performed in volunteers and patients; however, with regard to the higher concentration, safety data are only available for a single injection up to 0.5 mmol gadobutrol /kg BW. The aim of this study was to assess the safety and tolerability of gadobutrol 1 molar at higher doses. Therefore, young healthy male volunteers were selected as a study population. Increasing doses of gadobutrol 1 molar were administered starting with a dose of 0.3 mmol/kg BW which has already been tested; the highest dose in this study was 1.5 mmol/kg BW. Gadobutrol 1 molar was given as a single bolus injection. Based on experience, the number of volunteers examined at each dose level was limited to eight. As the study was designed as a placebo-controlled, double-blind, interindividual comparison, the small sample size was considered sufficient to assess safety. The safety assessment included the incidence of adverse events, clinical laboratory tests, evaluation of physical examination, vital signs and cardiac rhythm. Safety data were obtained immediately prior to study drug administration and at multiple times during the 3-day postinjection observation period. Poststudy examinations were performed 1 week after study drug administration. Forty-eight volunteers were included in the study. Overall, gadobutrol 1 molar had a good safety profile. All volunteers were in good general health at the completion of the study.

As with other contrast media, local tolerance indicators, i.e. paresthesia and vasodilatation, occurred following the administration of gadobutrol 1 molar. There was no evidence of a dose-dependency of these symptoms. Paresthesia was also reported by 3 volunteers receiving placebo. The different injection schemes given in this study had no influence on the incidence of these adverse events. Another known local tolerance indicator, pain at the injection side, was not reported by the volunteers. Standard laboratory tests (hematology, blood coagulation, clinical chemistry and urinalysis) were performed. With regard to hematology, a transient, dose-related effect following administration of gadobutrol was seen for some white blood cell parameters. There was a decrease in the mean total leukocyte count within the first 30 minutes after drug administration. The differential count revealed a decrease in mean lymphocytes at the same time. The values returned to baseline values within 6 hours. From statistical point of view, these differences were significant. However, both mean and individual values never reached any clinically relevant range. This observation may be explained by shifting of lymphocytes (migration and recirculation) due to the contrast material administration. The laboratory evaluation revealed no effect of gadobutrol 1 molar on routine serum chemistry. Based on pharmacokinetic data in animals and humans, gadobutrol is excreted via the kidneys. The plasma half-life of gadobutrol is about 1.8 hour in humans. Following an intravenous injection of gadobutrol, the highest amount of the dose is excreted within 12 hours; only a small amount (< 2.4%) of the dose is excreted beyond this time point. Renal function was a target for safety assessment. Renal-specific serum parameters as well as qualitative and quantitative urine parameters were determined. In addition, creatinine clearance as an indicator for theglomerular filtration rate was used. Creatinine clearance was predicted by the Cockroft-Gault equation at screening (baseline

value) and was measured over a total period of 48 hours after administration. The assessment of creatinine clearance largely depends on correct urine sampling. Although the volunteers were carefully instructed about the test procedure and the collection of urine was supervised and monitored as closely as possible, incomplete urine collection has to be assumed in several volunteers, particularly in volunteers on gadobutrol treatment. This assumption is supported by the data on urine specific gravity. For this parameter, dose group 1.25 mmol gadobutrol /kg BW showed the largest interindividual variation in values. Considering an average daily urine volume of at least 1000 mL, the 24-hour volume measured in volunteers nos. 34 and 39 clearly fell below this value (805 mL and 793 mL, respectively). Furthermore, the correlation made between diuresis [volume (mL) calculated per min] and urine specific gravity indicates that sampling errors may have occurred, at least in the highest dose groups. Thus, the data on creatinine clearance after CM injection have to be interpreted carefully. Considering the mean creatinine clearance values determined from each urine collection period following injection of gadobutrol 1 molar, no differences were observed between the gadobutrol groups and the placebo group with respect to the first shorter collections (0-2h, 2-4h and 4-6h). In the subsequent longer collection (6-12h), no difference between both treatments was also observed. However, during the longest, nocturnal collection (12-24h), a significant (p value = 0.0005) decrease in clearance values was observed in four of six gadobutrol dose groups (0.3, 0.75, 1.25 and 1.5 mmol Gd/kg) as compared to the placebo group. The lowest value was present in volunteers of dose group 1.25 mmol gadobutrol /kg BW, the same dose group where errors in urine sampling were assumed. In contrast, dose groups 0.5 and 1.0 mmol gadobutrol /kg BW showed higher clearance values, but a large interindividual variation was evident. The 24-hour creatinine clearance is assumed to be a true and constant value; there were no differences in 0-24h and 24-48h collections between the treatments. As a creatinine clearance > 80 mL/min per 1.73 m2 body surface is generally considered normal and reduced values may indicate renal damage; only individual values below this range are discussed. There were several volunteers in both treatments who showed reduced values, mostly at one single collection and, in particular, at the 12-24h collection. For the overall 24-hour collection, five volunteers showed values < 80 mL/min for the first 24-hour collection, and eight volunteers had such values for the second 24-hour collection. In this period, two volunteers on placebo showed reduced values. These individual abnormal values are not considered clinically relevant, because other markers for glomerular filtration such as creatinine, urea, Cystatin C and ß2-microglobulin did not show any changes indicative of renal damage. In particular, this applies to volunteer no. 37 (dose group 1.25 mmol gadobutrol /kg BW) whose 0-24h (time point 01:00:01:00) creatinine clearance was 61.88 mL/min. There were no signs of tubular dysfunction after administration of gadobutrol 1 molar (α1-microglobulin, urine albumin). Overall, laboratory results on renal function did not show any signs of renal damage following injection of gadobutrol 1 molar applied in doses up to 1.5 mmol gadobutrol /kg BW in any volunteer. Considering the results on 12-24h creatinine clearance obtained in this study, a transient influence of gadobutrol on the glomerular filtration rate cannot be completely ruled out.

There was no clinically significant effect of any dose of gadobutrol 1 molar on systolic and diastolic blood pressure. However, mean values for heart rate increased at the

immediate post-dose time points in the higher dose groups (0.75 to 1.5 mmol gadobutrol /kg BW). The maximal increase was observed at the highest dose of 1.5 mmol Gd/kg: from 55.83 b/min at baseline to 78.83 b/min at 2.5 min postinjection. These changes could partly be attributed to nervousness associated with the examination procedure, but may also be related to the CM administration. Although these changes were statistically remarkable ($p< 0.5$), they are not considered to be clinically meaningful. A 12-lead ECG was continuously recorded during injection and up to 30 seconds after the end of injection (planned time 00:00:02:00); thus, the maximal online ECG recording was about 2 minutes and 30 seconds. In addition, standard 12-lead ECG was performed at multiple times postinjection. Manual re-analysis of ECG data was made by one single reader who was blinded to the treatment. For online ECG recording, there was a significant difference ($p = 0.0158$) found between the treatment groups and the placebo group regarding the QTcB. In total, there were 3 volunteers (8.3%) with QTcB values >500 msec values and 10 volunteers (27.8%) with changes in QTcB >60 msec in the treatment groups as compared to 0 and 1 (8.3%) respectively in the placebo group. All of these volunteers except 1 (volunteer 11 in the 0.5 mmol/kg BW gadobutrol group) were in the 3 highest dosing groups (1.0 to 1.5 mmol/kg BW gadobutrol). There were no QTcB values >500 msec nor changes in QTcB >60 msec in the 0.3 and 0.75 mmol/kg BW gadobutrol groups. In the 1.5 mmol/kg BW gadobutrol group, 4 out of 6 volunteers (66.7%) had changes in QTcB >60 msec. In addition to the changes at online ECG recording, one volunteer (41 in the 1.5 mmol/kg BW gadobutrol group) had continued changes in QTcB up to an maximum increased value of about 112 at 2 hours postinjection; he also had an isolated change in QTcB >60 msec at 24 hours postinjection. This volunteer did not report any adverse events.

PK RESULTS: A linear two compartment model adequately fitted the serum data for each volunteer. The pharmacokinetic parameter estimates of gadobutrol obtained with the compartment model independent and dependent methods were comparable in the estimates of Vss, CL and MRTiv. The mean estimates of $t1/2\lambda z$ (terminal phase half-life by model independent method) and $t1/2\lambda 2$ (disposition phase half-life, two compartment model) were slightly different (2.01 vs 1.76 h). This was due to the weighting factor, 1/y, used during compartment model based analysis. The predicted12 h value was consistently smaller than the observed 12 h value. Overall, across the entire 12-hour duration, the quality of regression fits with weighting factor 1/y was far better than when weighting factor of 1/y2 or uniform weight was tested. The choice of the weighting factor of 1/y in the compartment model dependent analysis was such that excessive influence of the early data points (time points < 1 h after injection) and the late data points (time points >6 hours after injection) on the parameter estimates was avoided. The delayed peak concentration (DPC) after rapid intravenous injection and with very early blood sampling procedures, is often observed in pharmacokinetic investigations, and the DPC phenomenon is attributed to finite mixing time anticipated under the physiologic conditions. The DPC phenomenon in the two volunteers, however, introduced a noticeable irregularity and high inter-volunteer variability in the parameter estimates of compartment model dependent pharmacokinetic analysis, especially in the estimate of the initial disposition half-life, $t1/2\lambda 1$. Because the DPC phenomenon is inconsistent with the pharmacokinetic compartment model used, the estimates of model dependent parameters,

after removal of the DPC phenomenon (achieved by exclusion of 2-min data points in volunteers 7 and 8), was considered appropriate. It was noted that the values of estimates of t1/2λ2 and t1/2λz tended to be higher in the volunteers who's initial serum disposition profile showed DPC phenomenon (volunteer nos. 7 & 8), or showed a relatively less pronounced initial disposition phase (volunteer 3 who has a small secondary rise after 10 min time point & volunteer no. 2). The estimates of AUC and total clearance are not influenced by the inter-volunteer differences in the initial disposition phase. The results of the pharmacokinetic analyses were examined along with the results of tolerability assessment, as an attempt to explore a possible relationship between pharmacokinetics and pharmacodynamics. The two volunteers who showed the DPC phenomenon had transient nausea immediately following the injection time. In the present study, over the five-fold dose range (6 dose groups over the range of 0.3 to 1.5mmol/kg), there is no dose-response relationship for the incidence of nausea at near injection time. The result of an earlier Phase 1 (Safety, Pharmacokinetics) study of gadobutrol (Five dose groups in the range between 0.04 to 0.4 mmol/kg, using a 0.5 Molar concentration of gadobutrol) were examined. In the earlier study, the DPC phenomenon was observed in all three dose groups in which pharmacokinetics were investigated (4 out of 8 volunteers in the 0.04 mmol/kg dose group, 5 out of 8 volunteers in 0.10 mmol/kg dose group, and 1 out of 8 volunteers in the 0.4 mmol/kg dose group). Therefore, it can be concluded that the DPC phenomenon is neither dependent on the concentration of the gadobutrol dosing solution nor on the dose of gadobutrol. In the earlier study, transient nausea immediately following the bolus injection was reported in 2 volunteers in the dose group 0.4 mmol/kg. One of the two volunteers showed the DPC phenomenon.

Nearly complete recovery of the dose in the urine indicates the importance of the kidneys in the disposition of gadobutrol. The value for renal clearance, 1.39 mL/min/kg (or about 103 mL/min), is similar to the glomerular filtration rate in healthy volunteers, suggesting that renal excretion is predominantly by glomerular filtration.

STUDY AS29:

Study objectives
To examine the safety, pharmacokinetics, and metabolism of SH L 562 A (gadobutrol injection 0.5 mol/l) following single intravenous administration to healthy adult male volunteers.

Administration of gadobutrol injection (0.5 mol Gd/l) commenced with 0.05 mmol Gd/kg in step 1, and the dose was raised in steps while confirming the safety until step 4, a dose of 0.40 mmol Gd/kg. Another group received physiological saline solution (0.9% sodium chloride) at the same volume as that of the active drug given in each step, and each step was carried out over the course of two trial days in four volunteers. The study drug, which was randomly allocated so as to be indistinguishable by the subjects and the Investigator, was injected using a syringe.

Randomization:

Four cases were randomized according to the body weight at admittance per a trial day of each step, and the study drug was allocated so that three cases would receive the active drug, while one case would receive physiological saline solution. The sealed key code was held by the Medical Officer and it was not opened until the completion of each trial step except when judged to be necessary for medical reasons by the Medical Officer and the Principal Investigator. The Medical Officer retained the key code of the drug randomization to be used in the event of an emergency.

Number of Subjects Number of cases: Per step, active drug group 6 subjects, placebo group 2 subjects

Total of 4 steps: active drug group 24 cases, placebo group 8 cases

Plasma Kinetics and Urinary analysis:
This agent disappeared from the plasma in a biphasic manner following administration in each administration group, and it was not detected in plasma 24 hours after administration (detection threshold is below 2.5 nmol/ml).

Analysis of both plasma pharmacokinetics and of the cumulative urinary excretion rates was performed by the non-linear least squares method in a two-compartment open model since this agent disappeared in a biphasic manner.

The cumulative urinary excretion rate constant was analyzed using the one-compartment open model by the non-linear least squares method.

The half lives of the distribution phases of each administration group were 4.84 minutes in the 0.05 mmol/kg administration group, 10.07 minutes in the 0.10 mmol/kg administration group, 6.10 minutes in the 0.20 mmol/kg administration group and 3.75 minutes in the 0.40 mmol/kg administration group. The half lives of the elimination phases were 1.40 hours in the 0.05 mmol/kg administration group, 1.42 hours in the 0.10 mmol/kg administration group, 1.26 hours in the 0.20 mmol/kg administration group and 1.20 hours in the 0.40 mmol/kg administration group.

The apparent distribution volumes (Vc) were 118.0 mL/kg in the 0.05 mmol/kg administration group, 154 ml/kg in the 0.10 mmol/kg administration group, 115 mL/kg in the 0.20 mmol/kg administration group and 77 mL/kg in the 0.40 mmol/kg administration group. The total clearance (Cltot) was 129 mL/hour/kg in the 0.05 mmol/kg administration group, 116 mL/hour/kg in the 0.10 mmol/kg administration group, 119 mL/hour/kg in the 0.20 mmol/kg administration group and 110 mL/hour/kg in the 0.40 mmol/kg administration group. The mean in vivo residence times (MRT) were 1.88 hour in the 0.05 mmol/kg administration group, 1.92 hour in the 0.10 mmol/kg administration group, 1.69 hour in the 0.20 mmol/kg administration group and 1.59 hour in the 0.40 mmol/kg administration group. None of these parameters exhibited dose dependence.

The area under the curve of the concentration in the blood (AUC) increased in a dose dependent fashion, showing linear pharmacokinetics (Table XXI). The average cumulative excretion rate in urine in each administration group reached over 90% of the dose within six hours after administration. The cumulative excretion rates in urine up to 48 hours after administration in each administration group reached 98.1% in the 0.05 mmol/kg administration group, 94.9% in the 0.10 mmol/kg administration group, 104.8% in the 0.20 mmol/kg administration group and 101.0% in the 0.40 mmol/kg administration group (Table XXII).

Metabolites in Urine

Urine excreted up to six hours after administration in the 0.40 mmol/kg administration group was combined and analyzed by high-performance liquid chromatography (HPLC). The chromatogram of urine exhibited a single peak identical with gadobutrol, and no metabolites were found.

Table XXI. Pharmacokinetic parameters of gadovist in healthy volunteers (dose range 0.05-0.4 mmol/kg)

Administration Group (dose: mmol/kg)	Step 1 (0.05)	Step 2 (0.10)	Step 3 (0.20)	Step 4 (0.40)
Half-Life of α Phase (min.)	4.84	10.07	6.10	3.75
Half-Life of β Phase (hour)	1.404	1.418	1.263	1.195
Apparent Distribution Volume Vc (ml/kg)	118	154	115	77
Clearance (ml/hour/kg)	129	116	119	110
AUC (nmol·hour/ml)	387.4	862.0	1681.8	3646.0
MRT (hour)	1.88	1.92	1.69	1.59

Table XXII. % Excretion of gadovist in healthy volunteers for different dose groups

Administration Group (Dose: mmol/kg)	Step 1 (0.05)	Step 2 (0.10)	Step 3 (0.20)	Step 4 (0.40)
Urinary Excretion Rate Kex	0.582	0.590	0.648	0.567
Half-Life (Hour)	1.34	1.18	1.07	1.22
Renal Clearance	1.19	1.10	1.25	1.11
Cumulative Urinary Excretion Rate (%)	98.1	94.9	104.8	101.0
Actual Cumulative Urinary Excretion Rate (%)	99.6	97.4	107.2	103.1

REVIEWER'S COMMENTS:

Single intravenous administration of 0.05, 0.10, 0.20 and 0.40 mmol/kg of SH L 562 A (gadobutrol injection) was given to 32 healthy adult male subjects, and the safety, pharmacokinetics and metabolism of this agent were examined. No anomalous changes were found in the vital signs or electrocardiograms. As the subjective and objective findings mild smell sensations etc were reported during the injection. All of them were transient, disappeared without treatment and were considered to be not clinically relevant. Dose dependency was not observed in the incidence. The aforementioned results led to the conclusion that the safety could be confirmed up to administration of 0.40 mmol/kg of this agent. The results of examining the pharmacokinetics indicated that this agent disappeared rapidly from the plasma following administration in all administration groups. It was confirmed to be excreted in the urine without undergoing metabolism.

STUDY 21381:

STUDY TITLE: Cardiovascular safety study of 0.1, 0.3 and 0.5 mmol/kg gadobutrol (Gadovist®) bolus injection in normal subjects following a randomized, cross-over design using placebo and a concurrent positive control

Study objectives
The objective of this study was to evaluate the electrocardiographic effects, especially a potential influence on cardiac repolarization, of gadobutrol. Gadobutrol was administered in normal subjects as a bolus (2 mL/sec) at doses of 0.1 mmol/kg (0.1 mL/kg), 0.3 mmol/kg (0.3 mL/kg), and 0.5 mmol/kg (0.5 mL/kg) using a power injector. QT measurements were compared with placebo (0.9% saline solution) as a negative control and to moxifloxacin 400 mg as a positive control.

Methodology:
This was a single-center, randomized, placebo-controlled, 5-period crossover, dose comparison study with a concurrent positive control. The design was double-blind for gadobutrol and placebo. Healthy male and female subjects qualifying for the study were randomized to the order of administration of study medication: 3 doses of gadobutrol (0.1, 0.3, and 0.5 mmol/kg), placebo (0.9% saline), and positive control (moxifloxacin, 400 mg) (5-period crossover). All subjects were to receive all 5 injections. There was a 4- to 14-day washout period between study injections.

During each study period, cardiac function was assessed by continuous 12-lead electrocardiogram (ECG) recordings over 23.5 hours (1.5 hours at baseline and 22 hours postinjection). Electrocardiogram recordings were evaluated offsite by independent cardiologists blinded to the 5 treatments (gadobutrol 0.1, 0.3 and 0.5 mmol/kg, placebo, positive control). Adverse events were monitored throughout the study. Other safety assessments included clinical laboratory tests (hematology and blood chemistry), vital signs, physical examination (including Mini-Mental Status Examination and upper extremities inspection), and conventional 12-lead ECG for onsite safety evaluation.

Blood samples were collected predose and at specified times over 24 hours postinjection for pharmacokinetic assessment.

TOTAL NUMBER OF SUBJECTS: Approximately 70 subjects were enrolled; 50 subjects finished the study with data.

MODE OF ADMIN: 0.07 mL/sec for 60 minutes

PRIMARY VARIABLE MEASURED:
The primary study variable was heart-rate corrected QT (QTc) interval. Three correction methods were used: Fridericia, Bazett and an individual correction factor based on regression analysis. The change from baseline in QTc interval for each subject was summarized using 2 approaches: (1) average change from baseline over measurements taken within 15 minutes postinjection (15-minute average) and (2) maximum change from baseline up to 22 hours postinjection (maximum value). The average change from baseline within 15 minutes postinjection in the Fridericia QTc interval was treated as the primary endpoint.
Other electrocardiogram variables:
• Uncorrected QT interval
• RR interval
• PR or PQ interval
• QRS interval
• Heart rate (derived from the beats used for QT measurement)
• ST segment (if abnormal, depression or elevation)
• Morphology of the T wave (normal/abnormal: if abnormal; flat, inverted, or biphasic)
• Abnormal U-waves (present/absent)
An additional analysis incorporating QT/RR hysteresis into QT interval correction was performed by an independent cardiologist after the study was completed and the data were unblinded

Statistical Method:
Study results were summarized by treatment using descriptive statistics. The primary analysis was performed using the "completers" analysis set, defined as subjects who received study drug in all 5 periods, had at least 1 evaluable QTc in each of the 5 baseline periods, and had at least 1 evaluable QTc in the first 15 minutes postinjection in each of the 5 periods. Selected secondary analyses and other safety analyses were performed using the "all-subjects" analysis set, defined as subjects with measurements from at least 1 treatment period. QTc change from baseline was analyzed using least-squares analysis of variance (ANOVA). Regardless of the result of the overall test of treatment difference across the 5 treatments, the placebo control was to be compared with each of the other 4 treatments individually as the primary interest of the study. Two-sided 95% confidence intervals for the difference were constructed for the following pairwise comparisons:

• Gadobutrol versus placebo (0.9% saline)
• Moxifloxacin 400 mg versus placebo

SYNOPSIS:
The trial was designed as a "thorough QT/QTc study," including a negative control and an accepted positive control, performed in accordance with an FDA preliminary concept paper (17 July 2003) for the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential of non-antiarrhythmic drugs. The study design is also consistent with the ICH E14 guidance (2005). According to the ICH E14 guidance, the QT/QTc prolongation threshold level of regulatory concern is around 5 msec as evidenced by an upper bound of the 95% confidence interval around the mean effect on QTc of 10 msec. A negative "thorough QT/QTc study" is one in which the upper bound of the 1-sided 95% confidence for the largest time-matched mean effect of the drug on the QTc interval excludes 10 msec. The guidance recommends presenting QT/QTc interval data both as analyses of central tendency (eg, means, medians) and categorical analyses. For categorical analyses, the guidance recommends multiple analyses using different limits, including absolute QTc interval (>450, >480, and >500 msec) and change from baseline in QTc interval (>30 and >60 msec). Both approaches were undertaken in this study, including an analysis of the more inclusive (conservative) categorical limits of ≥30 and ≥60 msec change from baseline, based on the draft ICH E14 guidance (2004).

PATIENT POPULATION: Sixty-four (64) subjects were randomized and received at least 1 dose of study medication (all-subjects analysis set). Fifty-six (56) subjects completed the study (all 5 treatment periods). Fifty-four (54) subjects were included in the completers analysis set. In the all-subjects analysis set, mean age was 34.2 years (range, 19 – 60 years). Most subjects (>80%) were less than 45 years of age. There were more males (54.7%) than females (45.3%). The majority of subjects were Black (54.7%). The treatment sequences were balanced with regard to demographic characteristics.

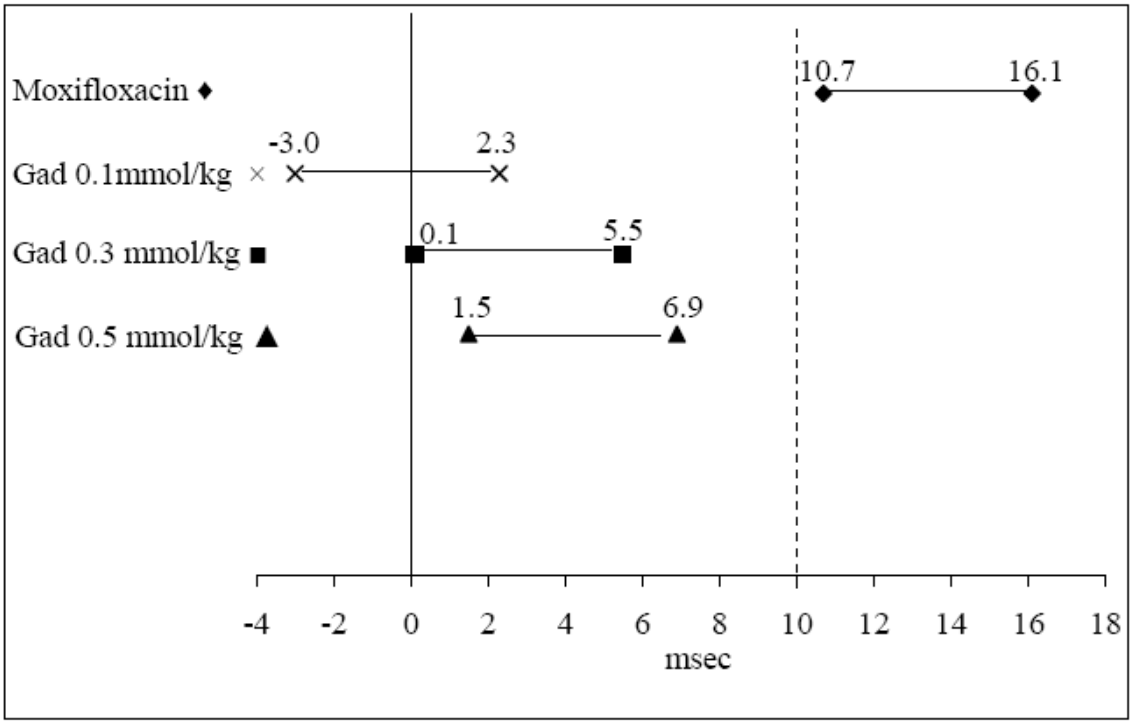
Table XXIII. Treatment Contrasts (Test Minus Placebo) for Fridericia QTc Interval (msec) Mean Change From Baseline –First 15-Minute Average: Completers (N=54)

	Gadobutrol 0.1 mmol/kg	Gadobutrol 0.3 mmol/kg	Gadobutrol 0.5 mmol/kg	Moxifloxacin
Treatment contrast	-0.3	2.8	4.2	13.4
95% confidence interval	-3.0, 2.3	0.1, 5.5	1.5, 6.9	10.7, 16.1

Test minus placebo: test = active drug (gadobutrol or moxifloxacin)
Mean change from baseline = mean of QTc values over first 15 minutes postinjection minus mean of QTc baseline values for each subject.
95% confidence interval calculated using an analysis of variance (ANOVA) model with subject, treatment and period as the main effects.

An overview of treatment contrasts (test minus placebo) for mean change from baseline for all QT/QTc variables (completers analysis set) is summarized in the table XXIII. For Fridericia QTc maximum value up to 22 hours postinjection (completers analysis), the treatment contrast (gadobutrol minus placebo) for mean change from baseline was around 5 msec for all doses (gadobutrol 0.5 mmol/kg = 5.2 msec), and the upper bound of the 2-sided 95% CI for each treatment contrast excluded 10 msec. For the other QT corrections, which were secondary endpoints, most treatment contrasts for mean change from baseline using both endpoints (15-minute average and maximum value) were around 5 msec and the 2-sided 95% CI upper bound excluded 10 msec. The Bazett's formula overcorrects at elevated heart rates and undercorrects at heart rates below 60 bpm and hence is not an ideal correction. The individual QT correction, based on linear QT-RR regression and using prebaseline and baseline data at rest and exercise, revealed unexpectedly higher QTc values than the Fridericia correction method. This may be explained in part by the elevated sympathicotonus throughout the prebaseline exercise. Following the injection of the hyperosmolar gadobutrol solution, heart rate was dose-dependently increased.

Figure 5. Test Minus Placebo Contrasts for Fridericia QTc Interval (msec) Mean Change From Baseline – First 15-Minute Average: Completers (N=54)



No subject experienced a ≥30 msec increase in Fridericia QTc following any gadobutrol dose based on the first 15-minute average assessment. For the maximum value assessment, the rate difference from placebo for subjects experiencing a ≥30 msec increase in Fridericia QTc was at least 4-fold higher following administration of moxifloxacin (46.3%) than following administration of gadobutrol: 0.1 mmol/kg (5.6%), 0.3 mmol/kg (5.6%), 0.5 mmol/kg (11.1%). No subject experienced a ≥60 msec increase

in Fridericia QTc following any treatment. No subject experienced a >450 msec 15-minute average Fridericia QTc following any gadobutrol dose. For the maximum value assessment, the percentages of subjects with a Fridericia QTc >450 msec was 7.4% for placebo; 9.3%, 5.6%, and 13.0% for gadobutrol 0.1, 0.3, and 0.5 mmol/kg, respectively; and 16.7% for moxifloxacin. One subject treated with moxifloxacin (1.9%) experienced a >480 msec Fridericia QTc maximum value.

Method Validation For Gd Concentration determination in Urine Samples: REPORT A44453 (December 2007):

A method for the determination of total gadolinium in human serum samples was validated at (b) (4) already in 1996. This validation was done in serum and with another gadolinium complex. The present validation was done in urine and the gadolinium complex was Gadobutrol. Due to the basic principles of the ICP/MS technique, the nature of the gadolinium containing molecule is only of secondary significance. The reason therefore is, that all organic structures are destroyed in the inductively coupled plasma source and only the isolated gadolinium ions are entering the instrument – independent from the original structure.

Therefore, only total gadolinium contents can be reported.

Purpose of the present validation is to demonstrate the validity of the gadolinium assay for Gadobutrol in urine samples. All samples were analyzed using an inductively coupled plasma as excitation source, combined with a mass spectrometer for mass selective detection (ICP/MS). Prior to measurement, the samples were diluted up to 8 mL with diluted nitric acid to obtain homogeneous samples in the appropriate concentration range. The monitored isotopes were ^{154}Gd (analyte) and (b) (4) (internal standard). All results are reported as µg gadolinium / mL urine. A summary on the validation results is given in the following.

Selectivity
No serious interference on the analyte trace could be observed in all investigated blank human urine samples.
Linearity
The calibration curves were linear over the range of 1.00 µg/mL to 500 µg/mL, using a urine volume of 100 µL.
Accuracy and precision
A summary on the accuracy and precision data is given in the following:

Parameter	Result
Calibration range [µg/mL]	1.00 – 500
Defined LLOQ [µg/mL]	1.00
Required urine volume [mL]	0.100
r^2 (mean)[1]	0.99966
Inter-run accuracy[2] [% bias]	4.7
Inter-run precision[2] [C.V %]	3.8
Stability of urine samples	No stability problems observed
Stability of processed samples	No stability problems observed

1: Of the standard curves
2: At the low QC level

Stability testing: The stability was only investigated for the Gadobutrol solution, because the single element gadolinium standard as well as the single element (b) (4) standard are certified solutions with corresponding expiry dates. Stability of the analyte could be demonstrated at all investigated conditions (in solution, in processed samples and in matrix).

Recovery: The recovery was determined by comparison of the signals in urine samples versus the signals in the corresponding working solutions (mean values). The recovery showed values for the analyte ranging from 98.7 % to 100.5 %, and 97.4 % for the internal standard

Conclusion: The requirements for acceptance of the validation, as defined in the validation study plan RX027, were fulfilled. The assay can be regarded as valid for human urine samples in the investigated concentration range from 1.00 µg/mL to 500 µg/mL.

Reference Standards

Compound name	Identification
Gadolinium	CPI International, Single Element Gadolinium Standard 1000 ± 3µg/mL (Gd in 2% HNO_3), AAI in-house ID no. M1904
Gadobutrol	Bayer HealthCare, Gadobutrol Working Standard, purity 96.7%, batch no. AS2550, AAI in-house ID no. M1901
[redacted]	(b) (4)

Standard Solutions.

Preparation of the Analyte Solutions:

A stock solution of the analyte was prepared in a volumetric flask by weighing 198.9 mg of the reference compound (Gadobutrol) and dissolving it in 10 mL demineralized water (SS-3). The details of preparation were as follows:

Analyte	**Weighing [mg]**	**AAI Code**	**diluted to, with demin. water**	**resulting solution*)**	**Label: Date of prep.**
Gadobutrol	198.9	M1901	10 mL	5000 ng/µL	SS2: 27 Nov 2007**)
Gadobutrol	198.9	M1901	10 mL	5000 ng/µL	SS3: 24 Jan 2008
Gadobutrol	198.9	M1901	10 mL	5000 ng/µL	SS4: 08 Apr 2008**)

*) solution refers to the amount of Gd within the Gadobutrol solution

**) used for stability testing in solution (132 days at refrigerator condition)

The stock solution SS1 (single element gadolinium standard, 1000 ng/µL) was used as supplied. The SS-1 stock solution was used for preparation of the calibration standards, the SS-2 stock solution was used for preparation of the QC samples. Working solutions of the analyte were prepared by diluting the stock solution with 0.5 M nitric acid. The standard solutions were stored in a refrigerator at 5°C ± 3°C.

Preparation of the Internal Standard Solutions

[redacted] (b) (4)

Calibration standards and quality control samples

Calibration standards were prepared freshly for each run by spiking 100 µL of the corresponding working solution to 100 µL human urine. The working solutions were prepared from stock solution SS-1 as described below.
Preparation of working solution and calibration standard

QC samples
The QC samples were prepared by spiking the corresponding gadobutrol working solution to blank human urine. The QC samples were prepared as 1 mL pools freshly for each run.

Volume [µL]	Working sol. [ng/µL] (label)	diluted to, with blank urine	Resulting in QC sample [µg/mL]*)
80	5000 (AQ-1)	1 mL	400
80	500 (AQ-2)	1 mL	40.0
60	50.0 (AQ-3)	1 mL	3.00
20	50.0 (AQ-3)	1 mL	1.00

*) 100 µL aliquots were used for analysis

Sample work-up
Using ICP/MS, extraction or derivatization of the samples is not necessary. Nevertheless, all samples had to be diluted up to approx. 8 mL to obtain homogeneous samples in the appropriate concentration range. Therefore 100 µL aliquots of urine were treated with 200 µL concentrated nitric acid (65%) and diluted up to approx. 8 mL with VL1. The diluted samples were introduced into the ICP/MS system using a nebulizer with peristaltic pump. After atomization and ionization in the plasma source, the ions were separated and detected in the mass-spectrometric part of the instrument. The area counts of gadolinium and internal standard were measured automatically 5 times by the Plasma Quad system. The mean was calculated automatically by the PQ Vision 4.3 software and used for further calculations. Measurements were performed in the peak jumping mode. The selected isotopes were 154Gd(analyte) and (b) (4) (internal standard).

ICP-MS Equipment and Experimental Conditions:

(b) (4)

Data Evaluation The peak counts of the analyte and the internal standard were calculated by the PQ-Vision 4.3 software system. The data were then transferred to the analytical database dbLabCal V3, a software developed by (b) (4). Gadolinium concentrations were evaluated using the internal standard method. The standard curvesy = a + bx were calculated from the peak count ratios (PAR) of gadolinium / internal standard and the nominal gadolinium concentrations using linear regression with 1/x2weighting. The measured peak count ratios of the QC and study samples were converted into concentrations using the following equation:

Analyte Concentration = Peak count ratio (analyte/IS)-a/b

a=intercept of corresponding standard curve
b=slope of corresponding standard curve

Accuracy was defined as

Bias (%) =100X (mean amount found-amount added)/amount added

Precision = CV(%)= 100X standard deviation/mean

Validation Procedure:

Calibration Model and Linearity A linear regression (y = a + bx) with 1/x2 weighting1 was used as calibration model. The suitability of the weighing factor had to be proved by use of the accuracy data from back-calculated calibration standards and the coefficient of

determination, obtained for the standard curves measured during the validation procedure.

Accuracy and Precision

Intra-run:

The intra-run accuracy and precision data were established by analyzing 6 QC sets within one validation run. The calculated mean concentrations relative to the spiked concentrations were used to express accuracy (as % bias = relative error). The precision was calculated from the same QC samples by means of standard deviation and coefficient of variation. The coefficients of variation (cv) and the relative error of the calculated concentrations must not exceed ± 15 %.

Inter-run
The inter-run accuracy and precision data were established by analyzing 18 QC-sets in 3 different runs on 3 different days. The coefficient of variation (cv) and the relative error of the calculated concentrations must not exceed ± 15 %.

Selectivity: Samples which contained no additives, as well as samples with added internal standard, generated from six different sources of blank matrix (urine) were analyzed. The selectivity of the method against matrix constituents had to be proved by the lack of interfering signals.

Lower Limit of Quantification (LLOQ):
The LLOQ is the lowest concentration on the standard curve, which can be measured with acceptable accuracy and precision. The accuracy and precision at the LLOQ was determined during the intra- and inter-run experiments by analyzing 6 replicates of the LLOQ-QC in each of the accuracy and precision runs. The coefficient of variation (cv) at the LLOQ and the relative error of its back-calculated concentrations must be within ± 20 %.

Effect of gadobutrol on plasma and serum calcium ion concentration (in vitro):

The sponsor conducted an in-vitro study to determine the effect of gadobuterol on serum/plasma calcium ion concentrations by different standard laboratory methods.

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

PEDIATRIC PK (STUDY REPORT A43735):

Objectives

The primary objective of this population pharmacokinetic evaluation was to evaluate the pharmacokinetics of gadobutrol in the pediatric population (aged 2 to 17 years). In detail, the aims of the population pharmacokinetic analysis were:

• to define a structural PK model for gadobutrol in the pediatric study 310788 [1] by using gadolinium (Gd) plasma concentrations.
• to characterize the inter-individual variability in the derived PK parameters of gadobutrol in this specific population
• if appropriate, to evaluate possible covariates influencing the PK of gadobutrol in the pediatric population.

Pharmacokinetic/pharmacodynamic models

130 patients with a total of 390 Gd plasma concentrations were included in the population pharmacokinetic analysis. Data were evaluated by means of non-linear mixed effects models using NONMEM. Gadobutrol pharmacokinetics in children aged 2 to 17 years can be adequately described by an open two-compartment model with elimination from the central compartment.

The population pharmacokinetic (PK) characteristics of gadobutrol were assessed using data from the pediatric study 310788, “Open-label multi-center study of magnetic resonance imaging (MRI) with 0.1 mmol/kg BW Gadovist (1.0 M) to assess pharmacokinetics, safety and tolerability in children”. A sparse sampling approach was applied to the pediatric population (age range of 2 to 17 years) enrolled in this study.

Gadovist® is an extracellular MR contrast agent. The active ingredient is gadobutrol, an electrically neutral, macrocyclic paramagnetic Gadolinium (Gd) chelate of low osmolarity and low viscosity, with a high paramagnetic effect (relaxivity). Like gadopentetate dimeglumine (Magnevist®) and most other extracellular MRI contrast agents, gadobutrol contains gadolinium (Gd3+), a rare earth element responsible for the shortening of relaxation times (T1 and T2) yielding in contrast-enhancement in MRI scans. Gadobutrol has been proven to be an effective contrast medium for all of the approved indications (MRI of brain, spine, liver, kidney or MRA). It exhibits an excellent safety profile, at least comparable to that of other marketed extracellular contrast media (ECCM) in the approved dose in adults.

The pharmacokinetic profile of gadobutrol and other extracellular contrast agents,

following i.v. injection, is characterized by fast distribution throughout the extracellular space and rapid (quantitative) elimination via the kidneys. The well established and dose-proportional pharmacokinetics of gadobutrol in adults, similar to most other available extracellular Gd-containing MR contrast media, are mainly defined by its physicochemical properties and the absence of any metabolism. Based on this knowledge, little difference in the pharmacokinetic behavior in the pediatric population (2 to 17 years) as compared to adults is expected, only. The proof of similarity of the pharmacokinetics of gadobutrol would allow the further extrapolation of efficacy for this pediatric population from available adult data.

In general, the PK analyses were exploratory and did not test a priori hypotheses. Graphical visualization and population PK modeling based on the non-linear mixed effects modeling program NONMEM was the principal analysis technique. Model components (structural fixed effect parameters, random effect parameters and potential covariates) were included in the model dependent on prediction improvement of the model using the likelihood ratio (LR) test, goodness of fit criteria and mechanistic plausibility.

The primary objective of this PK evaluation was to characterize the pharmacokinetics of gadobutrol in the pediatric population (age range 2 to 17 years) and to develop a population pharmacokinetic model to determine the main pharmacokinetic parameters, e.g. CL, Vss, AUC and half-life in pediatric patients after single intravenous injection of a dose of 0.1 mmol/kg body weight.

Furthermore, the potential influence of demographic and physiological covariates (e.g. age, gender, body weight, body surface area) on the main pharmacokinetic parameters was investigated within this patient population. This evaluation is confined to the population included in study 310788. The pediatric population pharmacokinetic evaluation comprised the following detailed activities:

• to define a structural PK model for gadobutrol in the pediatric study 310788 [1] by using gadolinium (Gd) plasma concentrations.
• to characterize the inter-individual variability in the derived PK parameters of gadobutrol in this specific population
• if appropriate, to evaluate possible covariates influencing the PK of gadobutrol

Table XXIV. Estimates of PK Parameters for pediatric population

Parameter	Age Group[a]	Median estimate	2.5th percentile of parameter distribution	97.5th percentile of parameter distribution
CL [L/h]	**All ages (2-17 years)**	**3.24**	**1.53**	**6.62**
	2-6 years	2.07	1.45	3.83
	7-11 years	3.28	1.81	5.93
	12-17 years	4.90	2.52	7.37
CL/kg [L/h/kg]	**All ages (2-17 years)**	**0.10**	**0.05**	**0.17**
	2-6 years	0.13	0.09	0.17
	7-11 years	0.10	0.05	0.17
	12-17 years	0.09	0.05	0.10
Vss [L]	**All ages (2-17 years)**	**5.96**	**3.27**	**13.2**
	2-6 years	3.83	3.24	6.33
	7-11 years	5.98	4.06	11.69
	12-17 years	10.02	5.16	14.12
Vss/kg [L/kg]	**All ages (2-17 years)**	**0.20**	**0.12**	**0.28**
	2-6 years	0.24	0.20	0.28
	7-11 years	0.19	0.14	0.23
	12-17 years	0.18	0.092	0.23
AUC [µmol*h/L][b]	**All ages (2-17 years)**	**999**	**590**	**1808**
	2-6 years	815	494	1167
	7-11 years	969	590	2163
	12-17 years	1167	925	1808
$t_{1/2}$ [h]	**All ages (2-17 years)**	**1.69**	**1.34**	**2.32**
	2-6 years	1.75	1.34	2.30
	7-11 years	1.61	1.17	2.62
	12-17 years	1.65	1.42	2.23
MRT [h]	**All ages (2-17 years)**	**1.94**	**1.24**	**2.99**
	2-6 years	1.88	1.24	2.77
	7-11 years	1.83	1.03	3.37
	12-17 years	2.03	1.57	2.99

[a]Age groups are continuous, i.e. ≥2 to <7 years, ≥7 to <12, ≥12.0 to <18.0 years
[b]Administered dose: 0.1 mmol/kg

Results:

Body weight was the major covariate to scale the PK parameters, total body clearance (CL) and central volume of distribution (V1), using an allometric model. Inter-individual variability of CL and V1 was moderate with 18.5% and 28.6%, respectively. Adjustment of CL to body weight was superior compared to adjustment to calculated body surface area (BSA). In addition to body weight, estimated glomerular filtration rate (GFR), normalized to 1.73 m² BSA, had a significant impact on gadobutrol clearance. A 1% change in estimated (normalized) GFR at baseline relative to the median estimated (normalized) GFR (132 mL/min/1.73 m²) lead to an 0.5% change (increase or decrease) in CL. Age was not found to be an additional independent parameter affecting the pharmacokinetics of gadobutrol in the pediatric population.

As the parameters of the PK model were found to be dependent on body weight, the non-normalized derived PK parameters such as VSS and AUC also vary along with weight. As clearance increases with body weight to a power of 0.75 only, AUC values are lower in patients with lower body weight than with higher body weight when the same body weight-proportional nominal dose of 0.1 mmol/kg is administered.

Body weight-normalized CL and VSS decreased from children aged 2 to 6 years compared to adolescents aged 12 to 17 years by approx. 30% and 25%, respectively (Table XXIV) . The latter one because of V2 not depending on body weight. Compared to the median AUC in adolescents, the median AUC in children aged between 2 and 6 years is decreased by 30%. However, the distributions of parameter values largely overlap. No impact of body weight on terminal half-life and mean residence time (MRT) was detected and therefore, no differences with respect to these parameters were observed in the pediatric population.

The parameters CL and V1 (central volume of distribution) increase with increasing body weight. An allometric approach was applied to scale both systemic clearance and central volume of distribution to individual body weight. The use of an allometric approach is also in line with two recent review articles encouraging this approach in children aged 2 years and older to relate pediatric to adult pharmacokinetics of drugs. It is widely accepted that body weight is related to clearance to a power of 0.75 and to distribution volume to a power of 1 (i.e. linear relationship). The advantage of the allometric (non-linear) model for clearance is in separating out the effects of growth (weight) and maturation (age). As discussed before, the body-weight-normalized glomerular filtration rate, reflecting the excretion mechanism of gadobutrol, is higher in young children exerting maximum levels around 2 years followed by a steady decrease to adult levels. The finding that estimated normalized GFR, also had a small but significant impact on gadobutrol pharmacokinetics further underlines the importance of individual renal function for gadobutrol elimination. However, it does not suggest any dose adaptation based on the studied pediatric population (2 to 17 years). Since no additional independent impact of age on the PK of gadobutrol was identified, there is no indication for dose

adaptation based on age in addition to body weight-based dosing. The fact that the PK of gadobutrol largely depends on body weight confirms the dosing based on individual body weight. While the allometric (non-linear) model of clearance predominantly affects the AUC and the elimination of gadobutrol (increasing AUC values with increasing weight), special consideration has to be given to the pharmacokinetics of gadobutrol in the imaging time window. The pharmacokinetics in the early post injection phase is mainly driven by distribution processes. Since the central volume of distribution is directly proportional to weight, body weight-based dosing is predicted to result in comparable drug concentrations in the early part of the concentration time-profile. The differences between the median simulated concentrations for different body weights are small and at maximum 20% at 20 min post injection comparing a 13 kg child of 2 years and a 65 kg adolescent.

Conclusion:
In the studied pediatric population the pharmacokinetics of gadobutrol were best described using a two-compartment model with elimination from central compartment. PK parameters such as CL, AUC and VSS increased with increasing body weight and thus - on average - with age. The observed differences in pharmacokinetic parameters (e.g. AUC) among children aged 2 to 6 years compared to adolescents aged 12 to 17 years due to the non-linear relationship between weight and clearance are minor.

Simulations based on the final population PK model applying different body weights showed minor differences in median Gd plasma concentrations within 20 and 30 min post injection, respectively. Thus, comparable plasma Gd concentrations within the time window relevant for MRI are predicted to be achieved with body weight-based dosing in the pediatric population aged 2 to 17 years.

STUDY REPORT 40982:
Pharmacokinetics of gadobutrol after a single bolus intravenous 0.1 mmol/kg body weight dose of Gadovist injection in healthy elderly and non-elderly men and women

OBJECTIVE: To determine safety and pharmacokinetics of gadobutrol after a single bolus intravenous 0.1 mmol/kg body weight dose of Gadovist in a group of healthy young (18–45 years) male and female as well as in elderly (≥65 years) male and female subjects.

DESIGN: Single-center, open-label, single-dose, single-treatment, parallel-group, nonrandomized study in which 32 subjects were enrolled into one of four groups (8 non-elderly male, 8 non-elderly female, 8 elderly male, 8 elderly female).

POPULATION: Healthy volunteers (male/female) aged either 18–45 or >65 years were recruited. The exclusion criteria were designed so as to exclude volunteers whose health might be put at risk by participation, or whose participation could jeopardize the result of the study.

DOSE: An IV injection of 0.1 mmol/kg of gadobutrol injected with a power injector at 2 mL/s.

PK EVALUATIONS:
Primary variables in the study were the area under the curve (AUC) for plasma gadobutrol concentration, clearance (CL), CL/kg and half-life of excretion (t½). Secondary variables were maximum concentration of gadobutrol (Cmax), AUC up to the last measurement (AUC(0-tlast)), mean residence time (MRT), apparent volumes of distribution during steady state and the terminal phase (Vss and Vz), amounts excreted into urine during the complete sampling period and between given time points (AE,ur and AE,ur(t1–t2)), renal and non-renal clearance values (CLR and CLNR) based on non-compartmental analysis. Additional secondary pharmacokinetic variables were AUC, t1/2 alpha, t1/2 beta, CL, central-compartment distribution volume (Vc), Vss and MRT based on a two-compartment model.

Table XXV. Primary pharmacokinetic parameters of gadobutrol in plasma (model independent)

Parameter	unit	Non-elderly men (N=8)		Elderly men (N=8)	
		Geo. mean (%CV)	Range	Geo. mean (%CV)	Range
AUC	mcmol·h/L	891 (20.8%)	703 – 1249	1183 (12.4%)	894 – 1294
CL	L/h	8.88 (22.0%)	6.36 – 12.9	6.68 (7.25%)	6.14 – 7.47
CL/kg	L/h/kg	0.112 (20.8%)	0.0801 – 0.142	0.0845 (12.4%)	0.0773 – 0.112
$t_{1/2}$	h	2.12 (14.1%)	1.75 – 2.82	2.81 (8.55%)	2.34 – 2.98

Parameter	unit	Non–elderly women (N=8)		Elderly women (N=7)	
		Geo. mean (%CV)	Range	Geo. mean (%CV)	Range
AUC	mcmol·h/L	849 (12.7%)	667 – 974	1306 (20.1%)	986 – 1589
CL	L/h	7.76 (14.4%)	6.56 – 9.51	4.85 (14.2%)	4.34 – 6.05
CL/kg	L/h/kg	0.118 (12.7%)	0.103 – 0.150	0.0766 (20.1%)	0.0629 – 0.101
$t_{1/2}$	h	1.81 (8.26%)	1.68 – 2.14	2.86 (14.8%)	2.33 – 3.72

AUC = area under the drug concentration vs. time curve from time 0 to the last data point >LLOQ
CL = total body clearance of drug
CL/kg = total body clearance of drug, normalized to bodyweight
LLOQ = lower limit of quantification
$t_{1/2}$ = half-life associated with terminal slope

Table XXVI. Secondary pharmacokinetic parameters of gadobutrol in plasma and urine (model independent)

Parameter	unit	Non-elderly men (N=8)		Elderly men (N=8)	
		Geo. mean (%CV)	Range	Geo. mean (%CV)	Range
C_{max}	mcmol/L	478 (27.9%)	288 – 681	502 (22.3%)	383 – 672
$AUC(0–t_{last})$	mcmol·h/L	891 (20.8%)	703 – 1249	1183 (12.5%)	893 –1294
MRT	h	2.79 (13.6%)	2.40 – 3.71	3.50 (9.59%)	2.97 – 3.82
V_{ss}	L	24.8 (20.0%)	18.8 – 38.0	23.4 (11.0%)	20.3 – 28.2
V_{ss} /kg	L/kg	0.313 (18.8%)	0.214 – 0.419	0.296 (8.08%)	0.258 – 0.333
V_z	L	27.1 (15.9%)	22.1 – 38.2	27.1 (8.89)	23.3 – 31.4
V_z / kg	L/kg	0.343 (15.5%)	0.252 – 0.421	0.343 (7.70%)	0.297 – 0.378
CL_R	L/h	9.35 (26.5%)	6.18 – 12.8	6.78 (8.89%)	5.95 – 7.70
CL_R / kg	L/h/kg	0.118 (26.3%)	0.0777 – 0.168	0.0857 (11.9%)	0.0775 – 0.114
CL_{NR}	L/h	0 *	0 – 0.539	0*	0 0.553
CL_{NR} / kg	L/h/kg	0 *	0 – 0.00694	0*	0 – 0.00767
$A_{E,ur}$	(%ID)	106 ± 13.5 (12.7%)	93.6 - 137	102 ± 4.69 (4.62%)	91.5 - 105

Parameter	unit	Non-elderly women (N=8)		Elderly women (N=7)	
		Geo. mean (%CV)	Range	Geo. mean (%CV)	Range
C_{max}	mcmol/L	488 (24.4%)	316 – 677	481 (27.4%)	325 – 695
AUC(0–t_{last})	mcmol·h/L	849 (12.7%)	667 – 974	1306 (20.1%)	986 – 1589
MRT	h	2.38 (10.2%)	2.15 – 2.82	3.81 (26.2%)	2.64 – 6.20
V_{ss}	L	18.5 (13.4%)	15.0 – 22.0	18.5 (20.9%)	14.9 – 27.1
V_{ss} /kg	L/kg	0.280 (15.4%)	0.223 – 0.367	0.291 (17.9%)	0.233 – 0.390
V_z	L	20.3 (10.6%)	16.9 –23.0	20.0 (12.7%)	17.2 – 23.4
V_z / kg	L/kg	0.308 (11.9%)	0.257 – 0.363	0.316 (13.2%)	0.251 – 0.381
CL_R	L/h	7.81 (14.0%)	6.21 – 9.34	4.73 (17.0%)	3.94 – 6.34
CL_R / kg	L/h/kg	0.118 (12.7%)	0.0994 – 0.147	0.0747 (21.0%)	0.0607 – 0.106
CL_{NR}	L/h	0.00962*	0 – 0.517	0.0761*	0 – 0.604
CL_{NR} / kg	L/h/kg	0.000136*	0 – 0.00635	0.00110*	0 - 0.0108
$A_{E>ur}$	(%ID)	101 ± 5.15 (5.11%)	94.5 - 109	97.8 ±6.41 (6.56%)	89.3 - 105

C_{max} = maximum observed concentration
AUC(0–t_{last}) = area under the drug concentration vs. time curve from time 0 to the last data point >LLOQ
MRT = Mean residence time
V_{ss} = Apparent volume of distribution at steady state
V_{ss} /kg= Apparent volume of distribution at steady state, normalized to body weight
V_z = Apparent volume of distribution during terminal phase
V_z / kg= Apparent volume of distribution during terminal phase, normalized to body weight
CL_R = Renal body clearance of drug
CL_R /kg = Renal body clearance of drug, normalized to body weight
CL_{NR} = Non-renal body clearance of drug
CL_{NR} / kg = Non-renal body clearance of drug, normalized to body weight
$A_{E>ur}$ = Amount of drug excreted into urine from 0 to infinity
*the median is given

Table XXVII. Pharmacokinetic parameters of gadobutrol in plasma (model dependent 2 compartment)

Parameter	unit	Non-elderly men (N=8)		Elderly men (N=8)	
		Geo. mean (%CV)	Range	Geo. mean (%CV)	Range
AUC	mcmol·h/L	898 (20.4%)	705 – 1236	1184 (12.3%)	894 – 1289
$t_{1/2\ alpha}$	h	0.232 (180%)	0.0204 – 1.61	0.735 (65.6%)	0.280 – 1.60
$t_{1/2\ beta}$	h	2.13 (18.4%)	1.72 – 2.83	3.21 (11.8%)	2.85 – 3.94
CL	L/h	8.81 (21.8%)	6.43 – 12.9	6.68 (7.12%)	6.10 – 7.47
CL/kg	L/h/kg	0.111 (20.4%)	0.0809 – 0.142	0.0845 (12.3%)	0.0776 – 0.112
V_c	L	13.0 (77.0%)	3.02 – 35.2	16.1 (21.0%)	12.7 – 21.4
V_c /kg	L/kg	0.165 (73.8%)	0.0389 – 0.388	0.203 (21.0%)	0.156 – 0.267
V_{ss}	L	23.9 (21.6%)	18.3 – 37.7	23.9 (9.33%)	21.4 – 28.5
V_{ss} / kg	L/kg	0.302 (20.0%)	0.208 – 0.415	0.302 (6.91%)	0.272 – 0.342
MRT	h	2.71 (14.7%)	2.35 – 3.68	3.58 (8.08%)	3.05 – 3.90

Parameter	unit	Non-elderly women (N=8)		Elderly women (N=6)	
		Geo. mean (%CV)	Range	Geo. mean (%CV)	Range
AUC	mcmol·h/L	849 (12.1%)	673 – 958	1267 (20.2%)	987 – 1581
$t_{1/2\ alpha}$	h	0.209 (331%)	0.0191 – 1.65	0.724 (81.0%)	0.247 – 1.77
$t_{1/2\ beta}$	h	2.26 (55.6%)	1.43 – 5.88	3.03 (23.5%)	1.97 – 3.72
CL	L/h	7.76 (14.3%)	6.52 – 9.42	4.92 (15.0%)	4.33 – 6.04
CL/kg	L/h/kg	0.118 (12.1%)	0.104 – 0.149	0.0789 (20.2%)	0.0633 – 0.101
V_c	L	10.0 (81.7%)	2.03 – 19.5	12.7 (27.4%)	8.75 – 18.2
V_c /kg	L/kg	0.152 (77.3%)	0.0372 – 0.307	0.203 (27.3%)	0.145 – 0.305
V_{ss}	L	18.2 (18.7%)	13.1 – 24.5	17.5 (12.6%)	14.4 – 20.4
V_{ss} / kg	L/kg	0.276 (21.0%)	0.218 – 0.407	0.280 (12.5%)	0.243 – 0.342
MRT	h	2.34 (15.7%)	1.96 – 3.09	3.55 (18.3%)	2.54 – 4.33

AUC = area under the drug concentration vs. time curve from time 0 to the last data point >LLOQ
$t_{1/2\ alpha}$ = half-life associated with the first slope; $t_{1/2\ beta}$ = half-life associated with the second slope
CL = total body clearance of drug; CL / kg = total body clearance of drug, normalized to body weight
V_c = Apparent volume of the central compartment (volume)
V_c / kg = Apparent volume of the central compartment (volume), normalized to body weight
V_{ss} = Apparent volume of distribution at steady state
V_{ss} / kg= Apparent volume of distribution at steady state, normalized to body weight
MRT = Mean residence time

PK RESULTS:

After intravenous bolus injection of 0.1 mmol/kg Gadovist to non-elderly and elderly subjects, plasma concentrations of gadobutrol decreased rapidly due to instantaneous distribution into the extracellular space and subsequent renal elimination. Urinary excretion was largely complete within 12 hours in all subjects. There were no conspicuous differences between the groups.

For AUC and CL, a significant effect (on significance level α=0.05) was observed for volunteer's age ($p<0.0001$ for both parameters). Regarding sex, a significant effect of gender (on significance level α=0.05) could only be observed for CL ($p=0.0003$), but not for AUC ($p=0.6806$). No significant interaction effect between sex and age group was observed ($p=0.2304$ for AUC / $p=0.1014$ for CL) (Table XXV-XXVII).

In order to explore the effect of sex on CL more deeply, an ANOVA was performed on body weight normalized clearance (CL/kg) by gender, age group and their interaction. A significant effect (on significance level α=0.05) was observed only for age, but not for gender or the interaction between age and gender. These results indicate that the effect of gender on (unadjusted) clearance can be accounted for by the difference in body weight between genders and thus by the administered total dose. A dependency between the renal clearance of gadobutrol and creatinine clearance was observed.

Conclusions

Intravenous bolus injection of a 0.1 mmol/kg body weight Gadovist dose was safe and well tolerated in healthy, young and elderly, males and females. The plasma pharmacokinetics of gadobutrol in healthy, non-elderly and elderly, men and women were characterized by a rapid distribution into the extracellular space and subsequent fast renal excretion.

Gender had no significant effect on the pharmacokinetics of gadobutrol in the non-elderly volunteers and elderly subjects. There was however a gender effect seen in elderly volunteers, showing a slightly higher AUC and lower CL or CL/kg in elderly women. Age had a moderate effect on the pharmacokinetics of gadobutrol in plasma. In healthy elderly men and women plasma clearance was reduced by approximately 25% and 35%, respectively, as compared with non-elderly subjects paralleled by an increase in systemic exposure by 33% (men) and 54% (women) and in the terminal half-life by approximately 33% and 58%, respectively.

A complete recovery of the administered dose in urine could be shown in all subjects.

DOSE FINDING STUDY:

PROTOCOL 308200: This was a multi-center, double-blind, randomized, controlled, parallel group, dose comparison study with corresponding blinded image evaluation following a single intravenous injection of three different doses of gadobutrol 1.0 molar (Gadovist®) in patients with known or highly suspected focal blood brain barrier disturbances and/or abnormal vascularity of the central nervous system: Dose comparison using three different doses of gadobutrol 1.0 M for the determination of safety and efficacy in patients for central nervous system (CNS) imaging

The objective of this study was to determine a safe and effective dose of gadobutrol 1.0 molar based on evaluation of the following:
• Raw number of lesions detected in precontrast and combined precontrast and postcontrast magnetic resonance imaging (MRI), assessment of border delineation, degree of contrast enhancement, and internal morphology of lesions.
• The maximum Contrast to Noise ratio (CNR) between white and gray matter with gadobutrol perfusion MRI.

Additional objectives of this study were:
• To evaluate the proportion of all enhanced lesions detected and matched.
• To evaluate the proportion of all lesions detected and matched with gadobutrol MRI.
• To evaluate quantitative and qualitative parameters of perfusion MRI (uncorrected/corrected cerebral blood volume [CBV], cerebral blood flow [CBF], time to peak [TTP], mean transit time [MTT], permeability factor [PF]).
• To evaluate/describe the alteration of perfusion parameters in CNS lesions and in particular that this was associated with different tumor grades of malignancy and to determine the usefulness of these parameters for evaluation of tumor grades.
• To evaluate the CNR of lesion/gray matter and lesion/white matter with gadobutrol perfusion MRI.
• To evaluate diagnosis and confidence in diagnosis.
• To assess the safety profile of gadobutrol after intravenous administration.

Study design: Multi-center, double-blind, randomized, controlled, parallel group study.
Number of subjects per treatment group: Approximately 225 subjects 229 subjects for safety (69, 90, and 70 subjects in the 0.3, 0.1, and 0.03 mmol/kg dose groups, respectively); 206 subjects for efficacy, Full Analysis Set (FAS) (67, 69, and 70 subjects, respectively); 173 subjects for efficacy, Per Protocol Set (PPS) (56, 56, and 61 subjects, respectively)

Diagnosis and main criteria for inclusion:
Male and female subjects at least 18 years of age with either known or highly suspected focal areas of disruption in blood-brain barrier (BBB) (eg, primary and secondary tumors, focal inflammatory or demyelinating disorder) and/or abnormal vascularity in the central

nervous system (CNS) who were scheduled to undergo a routine contrast-enhanced MRI of the CNS.

COMPARATOR: OPTIMARK 0.1 mmol/kg

EFFICACY EVALUATIONS: Three MRIs were obtained on each subject: unenhanced MRI, gadobutrol-enhanced MRI consisting of perfusion and steady-state MRI; and comparator-enhanced MRI consisting of steady-state MRI only. The CNR in white and gray matter, uncorrected and corrected CBV, CBF, TTP, MTT, and PF were evaluated by blinded readers and compared to histopathology, where applicable. The unenhanced MRI, combined unenhanced and gadobutrol-enhanced MRI, and combined unenhanced and comparator-enhanced MRI were evaluated by clinical study investigators and 3 independent blinded readers. To allow exact matching of lesions throughout the different imaging sequences, an independent radiologist (lesion tracker) performed 'lesion tracking' based only on the available CNS diagrams, separate from the investigator image and blinded image evaluations.

STATISTICAL METHODS: The primary efficacy analyses of the first 4 primary efficacy variables were done using a composite score (Categorical Visualization Score [CVS]). As there were 3 doses of gadobutrol, the 2 pairs of consecutive lower-higher doses were analyzed. The difference in mean scores of the higher and lower doses (DCVS) were calculated, and a 95% confidence interval (using t-distribution) was constructed for the DCVS. The secondary efficacy analysis of these variables and the analyses of the secondary efficacy variables were based on the data from the 3 blinded readers individually and the investigators. The analysis of the fifth primary efficacy variable (CNR in perfusion imaging) was conducted on the data of the independent radiologist. Descriptive statistics for the white and gray matter CNR was calculated by dose group, as well as confidence intervals for the difference of 2 mean CNRs. Analyses of lesion detection and tumor grading were performed using the unenhanced and/or combined image sets. Analysis of safety data was performed using all available data from all subjects administered gadobutrol. The most appropriate dose was selected based on both the safety profiles and efficacy analyses.

Study Population:
The study population consisted of subjects aged 18 and over, with known or highly suspected focal areas of disrupted BBB or abnormal vascularity of the CNS who were willing to undergo a routine contrast-enhanced MRI examination. Most subjects in the SAS were Caucasian (45.4%) or other race (South American, Latino- American, Native American, or Aborigine American; 40.6%). More than one-half (56.3%) of the subjects were female. Most of the subjects were <65 years of age (86.5%), with a mean age of 46.4 years. The mean height was 165.85 cm and the mean weight was 71.55 kg. Approximately one-third of all subjects were enrolled at US study centers (31.9%) and one-third at Colombian study centers (32.3%); the remaining subjects were divided between centers in Argentina and Brazil. The tumor type was malignant in 31.0% of subjects overall. In subjects with primary brain tumor, the main referral types were meningioma (16.2% of subjects); glial tumor, high grade (9.6% of subjects); glial tumor, low grade (7.0% of subjects); and glial tumor (4.4% of subjects).

A total of 242 subjects were screened for enrollment in the study at 13 sites in the US, 4 sites in Columbia, 2 sites in Argentina, and 1 site in Brazil. Thirteen screened subjects were withdrawn from the study prior to receiving study drug: 5 withdrew consent, 4 did not meet inclusion/exclusion criteria, IV access could not be obtained in 2, an administrative problem occurred in 1, and 1 subject was unable to remain still for the scans. The remaining 229 subjects were randomized to 1 of the 3 gadobutrol dose groups, including 69 subjects in the 0.3 mmol/kg group, 90 subjects in the 0.1 mmol/kg group, and 70 subjects in the 0.03 mmol/kg group. Twelve (5.2%) of the 229 subjects were withdrawn prematurely from the study. Two (0.9%) subjects, both in the 0.1 mmol/kg dose group, were withdrawn from the study after receiving gadobutrol and before receiving comparator—1 subject (Subject 19010) due to an AE (endocranial hypertension and brain edema) and 1 subject due to other reasons. Four (1.7%) subjects were withdrawn after receiving comparator and before receiving gadobutrol—1 subject due to a protocol deviation, 1 subject due to loss to follow-up, and 2 subjects due to other reasons. The other 6 subjects who received study drug and were withdrawn from the study prematurely were withdrawn after receiving both gadobutrol and comparator, including 2 subjects who withdrew consent, 1 who was lost to follow-up, and 3 for other reasons. The efficacy analysis sets included the full analysis set (FAS) and the per protocol set (PPS). A total of 206 subjects comprised the FAS, which included data from all subjects for whom case report form (CRF) entries and images were available for unenhanced MRI, combined unenhanced and gadobutrol-enhanced MRI, and combined unenhanced and comparator-enhanced MRI. A total of 173 subjects were included in the PPS, which included all subjects in the FAS with valid images who received ±10% of the intended dose of study drug and had no major protocol or MRI procedure deviations. The PPS was used for the primary efficacy analyses. Subjects who received any amount of study drug were included in the safety analysis set (SAS), which comprised 229 subjects overall (225 subjects received gadobutrol and 227 subjects received OptiMARK).

Efficacy Results:
The four primary visualization efficacy variables were condensed to a composite score, the CVS. The higher the CVS, the more effective the respective treatment. For the average reader, the lowest CVS value (1.43) was obtained for the 0.03 mmol/kg dose group and the highest CVS value (2.02) was obtained for the 0.1 mmol/kg (standard) dose group. The difference in CVS between these 2 dose groups was statistically significant ($p = 0.003$) in favor of the 0.1 mmol/kg dose. CVS values appeared to plateau with the 0.1 mmol/kg dose; ie, the highest dose group 0.3 mmol/kg showed no further increase in CVS (1.98) compared with 0.1 mmol/kg. The difference in CVS between the standard
and the highest dose was not statistically significant ($p = 0.844$). Scores for 2 of the 3 the individual blinded readers were similar to those of the average reader scores. Increasing the dose of gadobutrol did not significantly increase the number of lesions detected between the unenhanced and the enhanced MRI, as was expected.

Statistically significant differences between the 0.03 and 0.1 mmol/kg dose groups were

observed for every reader for contrast enhancement and for 2 of 3 readers for border delineation and internal morphology. Mean CNR values were higher for the 0.1 (27.0) and 0.3 (22.2) mmol/kg dose groups compared with the 0.03 mmol/kg dose group (9.42). There was no statistically significant difference between the 0.03 and 0.1 mmol/kg dose groups or between the 0.1 and 0.3 mmol/kg dose groups. Secondary efficacy variables included lesion detection (all matched lesions and contrast enhanced matched lesions), diagnosis and confidence in diagnosis, perfusion parameters (maps and artifacts), evaluation of tumor grade, and CNR of lesion/gray matter and lesion/white matter.
The results of the analyses of secondary efficacy variables provided variable support of the results of the primary efficacy analysis. For one of the blinded readers, there was a statistically significant difference between the low and standard doses ($p = 0.03$) and between the standard and high doses ($p = 0.02$) in favor of the 0.1 mmol/kg dose with respect to the accuracy comparison of low-standard gadobutrol doses (0.03 and 0.1 mmol/kg) and the accuracy comparison of the standard-high gadobutrol doses (0.1 and 0.3 mmol/kg) using detection of all matched lesions. For the other 2 blinded readers, there was no significant difference between the 0.03 and 0.1 mmol/kg doses or between the 0.1 and 0.3 mmol/kg doses. For 2 of 3 readers, there was a statistically significant difference between the low and standard doses ($p = 0.02$) and between the standard and high doses ($p = 0.02$ and $p = 0.04$) in favor of the standard (0.1 mmol/kg) dose with respect to the accuracy comparison of low-standard gadobutrol doses (0.03 and 0.1 mmol/kg) and standard-high gadobutrol doses (0.1 and 0.3 mmol/kg) using detection of enhanced matched lesions. For the remaining 2 blinded readers (one for low-standard comparison and the other for standard-high comparison), there was no significant difference between the 0.03 and 0.1 mmol/kg doses or between the 0.1 and 0.3 mmol/kg doses.

Conclusions:
The 0.1 mmol/kg dose of gadobutrol is supported by the CVS and AE profile and therefore meets the criteria outlined in the protocol for the determination of the minimally effective and safe dose for steady state CNS imaging. The CNR, a variable used to assess tumor perfusion imaging, showed no statistically significant differences among the 3 dose groups. Consistent with the CVS parameter, the highest CNR value was also obtained for the 0.1 mmol/kg dose. The 0.1 mmol/kg dose is consistent with the standard dose of other marketed extracellular gadolinium contrast agents approved for CNS imaging and will be further studied in phase 3 CNS studies. Additional efficacy studies for tumor perfusion imaging at the 0.1 mmol/kg dose are justified.

CNR Between White and Gray Matter in Perfusion Maps
CNR is a variable derived from the signal intensity (SI) measurement, which was performed using a centralized procedure by an independent radiologist.
CNR between white and gray matter in the perfusion imaging is defined as the SI difference between white and gray matter divided by the standard deviation of the SI of white matter and was calculated according to the following formula:

CNR= (SIwhite-SIgray)/SDwhite

where,
SI_{white} = the SI in the Region of Interest (ROI) in the white matter of the hemisphere contralateral to a lesion

SI_{gray} = the SI in the ROI in the gray matter of the hemisphere contralateral to a lesion
SD_{white} = standard deviation of the SI of the white matter

ANALYSIS: The primary efficacy analyses of the first 4 primary efficacy variables were done using a composite score (the Categorical Visualization Score [CVS]). The secondary efficacy analysis of these variables and the analyses of the secondary efficacy variables were based on the data from the 3 blinded readers individually and the investigators. The analysis of the fifth primary efficacy variable (CNR in perfusion imaging) was conducted on the data of the independent radiologist.

For all ordinal efficacy variables, the average (arithmetic mean) for the 3 readers was calculated and analyzed in the same way that the individual data were analyzed. Analyses of lesion detection and tumor grading were performed using the unenhanced and/or combined image sets previously described.
All statistical tests were 2-tailed and at the 0.05 level of significance. All confidence intervals produced were 2-sided, 95% intervals

Visualization parameters
The primary efficacy analysis for steady-state imaging was based on the following 4 visualization parameters:
• the number of lesions detected;
• the border delineation (measured on an ordinal 4-point scale);
• the contrast enhancement (measured on an ordinal 4-point scale); and
• the internal morphology of lesions (measured on an ordinal 3-point scale)

and were evaluated in precontrast and combined precontrast and postcontrast MRI, except for contrast enhancement, which was obtained from only the combined precontrast and postcontrast image sets. These 4 primary visualization efficacy variables were condensed to a composite score, the CVS, based on the assessment of each of the 3 blinded readers. Considering each of the 4 variables as a category, the CVS for each subject was calculated as:

CVS = (number of categories with increase over precontrast) – (number of categories with decrease over precontrast).

For the category "contrast enhancement", the precontrast value was set to "1 = No = lesion is not enhanced" to evaluate the CVS.
The possible outcomes of the CVS for a single subject and each reader were in the range of -3 to +4. Then the CVS was averaged across the 3 blinded readers, producing 1 mean CVS per subject.

To compare each pair of different doses of gadobutrol, the difference of the 2 mean values of CVS for the higher and lower dose (DCVS) was calculated along with a 95% confidence interval (using t-distribution) to assess the statistical significance of the difference.

Categorical Visual Scores:
The 4 primary visualization efficacy variables were condensed to a composite score, the CVS. The higher the CVS score, the more effective the respective treatment was considered. The average of the findings for the 3 blinded readers is summarized in Table XXVIII. For the average reader, the lowest CVS value (1.43) was obtained for the 0.03 mmol/kg dose group and the highest CVS value (2.02) was obtained for the 0.1 mmol/kg dose group. The difference in CVS between these 2 dose groups was statistically significant ($p = 0.003$) in favor of the 0.1 mmol/kg dose. CVS values appeared to plateau with the 0.1 mmol/kg dose; ie, the highest dose group 0.3 mmol/kg showed no increase in CVS over the 0.1 mmol/kg dose and the actual difference was not statistically significant ($p = 0.844$). Scores for 2 of the 3 the individual blinded readers were similar to those of the average reader scores (Table 14). The difference in CVS between the 0.1 mmol/kg and 0.03 mmol/kg dose groups was statistically significant ($p = 0.004$ and 0.013 for Readers 1 and 2, respectively) in favor of the 0.1 mmol/kg dose. The trend observed for Reader 3 was consistent with that for Readers 1 and 2, and the average reader, although the difference in CVS between the low and standard dose did not achieve statistical significance ($p = 0.112$).

Table XXVIII. Summary of average readers –Contrast Visual Scores (CVS)

Dose (mmol/kg)	Rate	Total Lesions	Lesions Detected	Border Delineation	Internal Morphology	Contrast Enhancement	CVS	CVS StD	T-test P-value
0.3 (N=56)	Precontrast	261	4.66	2.42	1.62	1.00	1.98	1.20	
0.3	Pre + Post	271	4.85	3.07	2.40	2.77	1.98	1.20	
									0.844
0.1 (N=55)	Precontrast	273	4.96	2.41	1.60	1.00	2.02	1.04	
0.1	Pre + Post	270	4.92	3.09	2.50	2.78	2.02	1.04	
									0.003
0.03 (N=61)	Precontrast	347	5.69	2.50	1.73	1.00	1.43	1.07	
0.03	Pre + Post	346	5.67	2.78	2.23	2.01	1.43	1.07	

CVS = Contrast Visualization Score; N = number of subjects in dose group; Pre = precontrast; Post = postcontrast; StD = standard deviation

Number of Lesions Detected:

The average of the findings for the 3 blinded readers is summarized in Table XXIX. There was no statistically significant difference between the 0.03 and 0.1 mmol/kg doses, nor was there a significant difference between the 0.1 and 0.3 mmol/kg doses with regard to the number of lesions detected between the unenhanced and the enhanced MRI.

Table XXIX. Summary of average readers – Total number of lesions

Dose (mmol/kg)	Rate	Total Lesions	No. of Subjects	Mean	Median	StD	Min, Max	Dose Difference (Lower, Upper)
0.3	Precontrast	264	56	4.71	1	7.68	0, 30	
0.3	Pre + Post	269	56	4.80	1	7.83	0, 30	
0.3	Difference	5	56	0.09	0	2.22	-9, 9	
								-0.053 (-0.9, 0.7942)
0.1	Precontrast	271	55	4.93	1	8.41	1, 30	
0.1	Pre + Post	273	55	4.96	1	8.56	1, 30	
0.1	Difference	2	55	0.04	0	2.28	-13, 5	
								-0.069 (-0.825, 0.6866)
0.03	Precontrast	349	61	5.72	1	9.91	0, 30	
0.03	Pre + Post	347	61	5.69	1	10.0	0, 30	
0.03	Difference	-2	61	-0.03	0	1.82	-10, 5	

Max = maximum; Min = minimum; Pre = precontrast; Post = postcontrast; StD = standard deviation

Lesion Contrast Enhancement:

The average of the findings for the 3 blinded readers is summarized in Table XXX. There was a statistically significant difference (95% CI: -1.171, -0.424) between the 0.03 and 0.1 mmol/kg doses in favor of the 0.1 mmol/kg dose according to the average reader with regard to lesion contrast enhancement. In addition, although clinical significance between doses was not specifically defined for this study, lesion contrast enhancement based on the average reader was 82% better for the 0.1 mmol/kg dose than for the 0.03 mmol/kg dose, which was a clinically meaningful improvement. There was no significant difference between the 0.1 and 0.3 mmol/kg doses.

Table XXX Summary of average readers – Contrast Enhancement

Dose (mmol/kg)	Rate	No. of Subjects	Mean	Median	StD	Min, Max	Dose Difference (Lower, Upper)
0.3	Precontrast	53	1.00	1.00	0.00	1, 1	
0.3	Pre + Post	53	2.79	3.20	1.15	1, 4	
0.3	Difference	53	1.79	2.20	1.15	0, 3	
							-0.011 (-0.436, 0.414)
0.1	Precontrast	55	1.00	1.00	0.03	1, 1	
0.1	Pre + Post	55	2.78	3.11	1.08	1, 4	
0.1	Difference	55	1.78	2.11	1.07	0, 3	
							-0.797 (-1.171, -0.424)
0.03	Precontrast	58	1.00	1.00	0.00	1, 1	
0.03	Pre + Post	58	1.98	1.86	0.93	1, 4	
0.03	Difference	58	0.98	0.86	0.93	0, 3	

Max = maximum; Min = minimum; Pre = precontrast; Post = postcontrast; StD = standard deviation
Scale: 1=None 2=Moderate 3=Good 4=Excellent
Confidence intervals are asymptotic confidence intervals adjusted for clustering.

Border Delineation:

The average of the findings for the 3 blinded readers is summarized in Table XXXI. According to the average reader, there was statistically significant improvement (95% CI: -0.619, -0.17) in borderline delineation between the unenhanced and enhanced MRI for the 0.1 mmol/kg dose as compared with the 0.03 mmol/kg dose. This difference also was clinically significant, representing a 143% improvement with the 0.1 mmol/kg dose compared with the 0.03 mmol/kg dose. There was no statistically significant difference between the 0.1 and 0.3 mmol/kg doses. The same trend was observed for 2 of the 3 individual readers.

Table XXXI Summary of average reader- Border delineation

Dose (mmol/kg)	Rate	No. of Subjects	Mean	Median	StD	Min, Max	Dose Difference (Lower, Upper)
0.3	Precontrast	53	2.42	2.33	0.45	2, 4	
0.3	Pre + Post	53	3.12	3.33	0.72	2, 4	
0.3	Difference	53	0.70	0.67	0.60	0, 2	
							-0.016 (-0.247, 0.2148)
0.1	Precontrast	55	2.41	2.33	0.52	2, 4	
0.1	Pre + Post	55	3.09	3.17	0.63	2, 4	
0.1	Difference	55	0.68	0.67	0.61	-1, 2	
							-0.395 (-0.619, -0.17)
0.03	Precontrast	58	2.50	2.33	0.49	2, 4	
0.03	Pre + Post	58	2.79	2.67	0.71	2, 4	
0.03	Difference	58	0.28	0.17	0.60	-1, 2	

Max = maximum; Min = minimum; Pre = precontrast; Post = postcontrast; StD = standard deviation
Scale: 1=None 2=Moderate 3=Good 4=Excellent

PERFUSION IMAGING: CONTRAST TO NOISE RATIO:

The derived variable CNR is summarized by gadobutrol dose group in Table XXXII. CNR values were higher for the 0.1 and 0.3 mmol/kg dose groups compared with the lowest dose group (0.03 mmol/kg). There was no statistically significantly difference between the 0.03 and 0.1 mmol/kg dose groups or between the 0.1 and 0.3 mmol/kg dose groups.

Table XXXII CNR for different dose groups

Dose (mmol/kg)	No. of Subjects	Mean	Median	StD	Min, Max	Dose Difference (Lower, Upper)
0.3	55	22.2	17	15.2	3, 70	
						4.7421 (-15.86, 25.347)
0.1	56	27.0	14	75.6	4, 573	
						17.54 (-37.11, 2.022)
0.03	60	9.42	7	11.4	-21, 77	

Max = maximum; Min = minimum; StD = standard deviation
For each subject, mean of the CNRs for the 6 maps is used.

EFFICACY OF GADOBUTROL:

TITLE OF STUDY: A multicenter, randomized, double-blind, crossover, phase 3 study to determine the safety and efficacy of gadobutrol 1.0 molar (Gadovist®) in patients referred for contrast-enhanced MRI of the central nervous system (CNS).

STUDY CENTERS: 13 sites in the United States, 15 sites in Germany, 12 sites in Japan, 2 sites in Australia, 2 sites in Austria, 3 sites in Colombia, and 4 sites in Switzerland enrolled subjects.

OBJECTIVES: The primary objectives of this study were to demonstrate:
The superiority of combined unenhanced and gadobutrol-enhanced magnetic resonance imaging (MRI) compared to unenhanced MRI based on the evaluation of the following:

- Degree of contrast enhancement
- Assessment of border delineation
- Internal morphology of lesions

And noninferiority of combined unenhanced and gadobutrol-enhanced magnetic resonance imaging (MRI) compared to unenhanced MRI based on the evaluation of the following:

- Total number of lesions detected

The secondary objectives of this study were to:
Demonstrate noninferiority of gadobutrol compared to gadoteridol at a dose of 0.1 mmol/kg for:

- Degree of contrast enhancement
- Assessment of border delineation
- Internal morphology of lesions
- Total number of lesions detected

Demonstrate improvement of gadobutrol-enhanced MRI to unenhanced MRI and noninferiority to gadoteridol-enhanced MRI for:

- Exact match of the MR diagnoses with the final clinical diagnosis
- Sensitivity and specificity for normal/abnormal brain tissue based on the comparison of the T1-weighted (T1w) contrast-enhanced and T1w unenhanced MR images
- Sensitivity and specificity for the detection of malignant CNS lesions
- Confidence in diagnosis

Compare gadobutrol to gadoteridol for:

- T1w MRI image quality in a paired comparison
- The number of contrast-enhanced lesions

(Confirm, using adjudication, differences in the number of contrastenhanced lesions on T1w images.)

- Quantitative parameters based on signal intensity (SI) measurements

Assess the safety profile of gadobutrol compared to gadoteridol after intravenous (i.v.) administration

STUDY POPULATION:

A total of 419 subjects were screened for inclusion into the study; 17 subjects prematurely discontinued from the study prior to receiving any study drug. A total of 402 subjects received study drug; 228 subjects were in the gadobutrol:gadoteridol treatment sequence and 174 subjects were in the gadoteridol:gadobutrol treatment sequence. (Note: With the exception of the 54 sample subjects [gadobutrol:gadoteridol treatment sequence], randomization was 1:1. Images from sample subjects were not included in the efficacy evaluation; their safety data were included in the safety analyses.)

Of the 402 treated subjects, 399 subjects received gadobutrol, 393 subjects received gadoteridol, and 390 subjects received both gadobutrol and gadoteridol. A total of 380 completed the study; 211 subjects in the gadobutrol:gadoteridol treatment sequence and 169 subjects in the gadoteridol:gadobutrol treatment sequence. Twenty-two subjects prematurely discontinued the study.

Primary efficacy variables

Combined unenhanced/gadobutrol-enhanced vs. unenhanced

The 4 primary efficacy variables were contrast enhancement, border delineation, internal morphology, and number of lesions, as assessed by the blinded readers. For contrast enhancement, border delineation, and internal morphology, the improvement in scores from unenhanced to combined unenhanced/gadobutrol-enhanced was statistically significant for the average reader, as well as for the 3 individual readers ($P<0.0001$ in all cases). The mean contrast enhancement average reader score increased from 0.97 unenhanced to 2.26 combined unenhanced/enhanced (using a scale of 1 = no enhancement to 4 = excellent enhancement) (Table XXXIII). The mean differences were very consistent across the 3 readers, with all 3 readers demonstrating increases of between 1.06 and 1.59 units on the 4-unit scale. The mean border delineation average reader score increased from 1.98 unenhanced to 2.58 combined unenhanced/enhanced (using a scale of 1 = no or unclear delineation to 4 = excellent delineation). The mean differences were consistent across the 3 readers, with all 3 readers demonstrating increases of between 0.43 and 0.72 units on the 4-unit scale.

The mean internal morphology average reader score increased from 1.32 unenhanced to 1.93 combined unenhanced/enhanced (using a scale of 1 = poor visibility to 3 = good visibility). The mean differences for the 3 blinded readers, while all showing statistically significant increases, had some variability across the readers, with mean changes of 0.62, 0.82, and 0.41 for readers 1, 2, and 3, respectively.

For the number of lesions, there was a high level of variability across the 3 readers. In particular, reader 2 had a higher mean number of lesions for both the unenhanced and combined unenhanced/enhanced modalities. Reader 2 also had much more variability within his assessments than there was for readers 1 and 3. As a result, the variability in the average reader change from unenhanced to combined unenhanced/enhanced was higher than anticipated in the protocol. There was a mean increase of 0.17 lesions, with a 95% confidence interval of (-0.439, 0.780).

The lower limit of this confidence interval, -0.439, was slightly lower than the prespecified noninferiority margin of -0.35. However, this was mainly driven by the high standard deviation from reader 2. For readers 1 and 3, the lower limits of the confidence intervals were above the prespecified value of -0.35.

Based upon the observed data, a nonparametric analysis was performed where the lesion counts were replaced by a categorical variable. For the average reader, the number of lesions detected was equal for the 2 modalities for 20.8% of the subjects, higher for combined unenhanced/gadobutrol-enhanced in 44.0% of subjects, and higher for unenhanced in 35.1% of the subjects. The difference between combined unenhanced/gadobutrol-enhanced and,unenhanced was 8.9%, and the 95% confidence interval was (-0.5%, 18.4%). Using the noninferiority margin of -10%, which was prespecified as the noninferiority margin for the categorical variables, noninferiority was demonstrated for gadobutrol. Noninferiority was demonstrated for all 3 blinded readers as well.

Combined unenhanced/gadobutrol-enhanced vs. combined unenhanced/gadoteridol enhanced

For the average reader, as well as for all 3 individual readers, the contrast enhancement, border delineation, and internal morphology scores were extremely similar for the 2 agents. The noninferiority of gadobutrol to gadoteridol was proven for each parameter. For the average reader, as well as for all 3 individual readers, the numbers of lesions seen were very similar for the 2 agents. However, as mentioned previously, the variability for reader 2 was much higher than for the other 2 readers, which resulted in higher than expected variability for the average reader. The 95% confidence interval for the difference between gadobutrol and gadoteridol was (-0.601, 0.622). The lower limit of this interval was lower than the prespecified noninferiority margin of -0.35.
The results of the nonparametric analysis for the number of lesions show for the average reader, the difference between gadobutrol and gadoteridol was 8.3%, and the 95% confidence interval was (-0.9%, 17.6%). Using the prespecified noninferiority margin of -10%, noninferiority of gadobutrol to gadoteridol was demonstrated. Noninferiority was demonstrated for all 3 blinded readers as well.

Table XXXIII Summary of Contrast Enhancement; Blinded readers, Combined Gadobutrol enhanced vs unenhanced Full Set Analysis

Reader	Image Set	No. of Subjects	Mean	Median	SD	Min	Max	95% CI Lower Limit	95% CI Upper Limit	P-Value
1	Unenhanced	314	0.94	1.0	0.14	0.5	1.3			
	Combined	314	2.21	2.1	0.57	0.0	3.6			
	Difference	314	1.26	1.1	0.61	-1.0	2.9	1.197	1.332	<.0001
2	Unenhanced	314	1.01	1.0	0.28	0.0	2.5			
	Combined	314	2.60	2.5	0.70	0.0	4.0			
	Difference	314	1.59	1.4	0.77	-1.0	3.4	1.503	1.673	<.0001
3	Unenhanced	312	0.96	1.0	0.16	0.5	1.5			
	Combined	312	2.02	1.9	0.46	1.0	3.3			
	Difference	312	1.06	1.0	0.51	-0.4	2.8	1.002	1.117	<.0001
Average	Unenhanced	316	0.97	1.0	0.15	0.0	1.5			
	Combined	316	2.26	2.2	0.52	0.0	3.5			
	Difference	316	1.29	1.2	0.56	-1.0	2.8	1.228	1.351	<.0001

Scale: 1 = no, 2 = moderate, 3 = good, 4 = excellent. Zero scores are due to the zero-filled averaging used when different numbers of lesions were detected by different modalities in order for the averages to be based on the same number of scores.

CI = confidence interval; Combined = combined unenhanced and enhanced; Max = maximum; Min = minimum; SD = standard deviation.

Contrast Enhancement:

Results for the blinded reader analysis of contrast enhancement are shown in Table XXXIII. For the average reader, as well as for all 3 individual readers, the change in scores from unenhanced to combined unenhanced/enhanced was statistically significant (P<0.0001 in all cases). The mean contrast enhancement average reader score increased from 0.97 unenhanced to 2.26 combined unenhanced/enhanced. The mean differences were very consistent across the 3 readers, with all 3 readers demonstrating increases of between 1.06and 1.59 units on the 4-unit scale. These results demonstrate that contrast enhancement was statistically significantly superior after administration of gadobutrol as compared to the unenhanced values.

Border Delineation:

Results for the blinded reader analysis of border delineation are shown in Table XXXIV. For the average reader, as well as for all 3 individual readers, the change in scores from unenhanced to combined unenhanced/enhanced was again statistically significant (P<0.0001 in all cases). The mean border delineation average reader score increased from 1.98 unenhanced to 2.58 combined unenhanced/enhanced. The mean differences were consistent across the 3 readers, with all 3 readers demonstrating increases of between 0.43 and 0.72units on the 4-unit scale. These results demonstrate that border delineation was statistically significantly superior after administration of gadobutrol as compared to the unenhanced values.

Table XXXIV Summary of Border Delineation; Blinded readers, Combined Gadobutrol enhanced vs unenhanced Full Set Analysis

Reader	Image Set	No. of Subjects	Mean	Median	SD	Min	Max	95% CI Lower Limit	95% CI Upper Limit	P-Value
1	Unenhanced	314	2.03	2.1	0.37	0.9	3.3			
	Combined	314	2.70	2.7	0.53	0.0	3.9			
	Difference	314	0.67	0.6	0.66	-2.0	2.6	0.599	0.745	<.0001
2	Unenhanced	314	2.19	2.3	0.49	0.0	3.2			
	Combined	314	2.91	3.0	0.60	0.0	4.0			
	Difference	314	0.72	0.7	0.78	-2.0	3.0	0.632	0.805	<.0001
3	Unenhanced	312	1.73	1.8	0.32	0.6	2.6			
	Combined	312	2.16	2.2	0.35	1.0	3.3			
	Difference	312	0.43	0.4	0.50	-1.0	2.3	0.373	0.485	<.0001
Average	Unenhanced	316	1.98	2.0	0.30	0.0	2.5			
	Combined	316	2.58	2.6	0.43	0.0	3.5			
	Difference	316	0.60	0.6	0.53	-2.0	3.0	0.537	0.654	<.0001

Scale: 1 = none, 2 = moderate, 3 = good, 4 = excellent. Zero scores are due to the zero-filled averaging used when different numbers of lesions were detected by different modalities in order for the averages to be based on the same number of scores.

CI = confidence interval; Combined = Combined unenhanced and enhanced; Max = maximum; Min = minimum; SD = standard deviation.

Similarly, the mean internal morphology average reader score increased from 1.32 unenhanced to 1.93 combined unenhanced/enhanced (using a scale of 1 = poor visibility to 3 = good visibility). The mean differences for the 3 blinded readers, while all showing statistically significant increases, had some variability across the readers, with mean changes of 0.62, 0.82, and 0.41 for readers 1, 2, and 3, respectively.

For the number of lesions, there was a high level of variability across the 3 readers. In particular, reader 2 had a higher mean number of lesions for both the unenhanced and combined unenhanced/enhanced modalities. Reader 2 also had much more variability within his assessments than there was for readers 1 and 3. As a result, the variability in the average reader change from unenhanced to combined unenhanced/enhanced was higher than anticipated in the protocol. There was a mean increase of 0.17 lesions, with a 95% confidence interval of (-0.439, 0.780).

4.3. Consult review (Including pharmacometric review)
Not applicable. There was no consult review.

4.4. Coversheet and OCP filing review form
Please refer to the OCP filing form in DARRTS signed off on 7/2/2010 under NDA 201-277.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTY S JOHN
02/25/2011

YOUNG M CHOI
02/25/2011
I concur.

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**2012277**	**Brand Name**	**Gadovist**
OCPB Division (I, II, III, IV, V)	**DCP V**	**Generic Name**	**Gadobutrol**
Medical Division	**Division of Medical Imaging Products**	**Drug Class**	**Imaging**
OCPB Reviewer	**Christy S. John, Ph.D.**	**Indication(s)**	**Gadovist injection (gadobutrol) is a gadolinium-based contrast agent indicated for intravenous use in diagnostic MRI in adults and children (2 years of age and older) to detect and visualize areas with disrupted blood brain barrier and/or abnormal vascularity of the central nervous system (CNS).**
OCPB Team Leader	**Young Moon Choi, Ph.D.**	**Dosage Form**	**One mL Gadovist solution for injection contains 604.72 mg (1.0 mmol) gadobutrol. This 1.0 M solution has an osmolality of 1603 mos mol/kg (at 37°C.**
		Dosing Regimen	**0.1 mmol/kg**
Date of Submission	**May 14, 2010**	**Route of Administration**	**IV**
Estimated Due Date of OCPB Review	**January 15, 2011**	**Sponsor**	**Bayer HealthCare Pharmaceuticals, Inc**
PDUFA Due Date	**March 15, 2011**	**Priority Classification**	**1 S**
Division Due Date	**February 23, 2011**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE		**11**		
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**5**		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	**X**	**1**		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	7		
multiple dose:				
Patients-				
single dose:	X			

multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X	3		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -		**3**		
ethnicity:	X			
gender:	X			
pediatrics:	X	1		
geriatrics:	X			
renal impairment:	X	1		
hepatic impairment:				
PD:				
Phase 2:	**X**	**4**		
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	X	2		
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:	**N/A**			
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan	**X**			**Deferal 0-2 years old**
Literature References				
Total Number of Studies				

Filability and QBR comments				
	"X" if yes	**Comments**		
Application filable ?		**The application is filable from Clinical Pharmacology perspective.**		
Comments sent to firm ?		**The sponsor has been requested to submit the data set, NONMEM control streams (base, covariate and final models) and the output listings for the population PK analysis (Module 5.3.3.5) by June 30th, 2010. We encourage the sponsor to refer to the following pharmacometric data and models submission guidelines (http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm180482.htm):** **All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).**		
QBR questions (key issues to be considered)	**To focus on the incidence of NSF reported in post-marketing reports and see if NSF is related to the dose administered.** **Did the sponsor use the optimal dose?**			
Other comments or information not included above				
Primary reviewer Signature and Date	**Christy S. John, Ph.D**			
Secondary reviewer Signature and Date	**Young Moon Choi, Ph.D.**			

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201277	ORIG-1	BAYER HEALTHCARE PHARMACEUTICALS INC	GADOBUTROL INJECTION

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTY S JOHN
06/30/2010

YOUNG M CHOI
07/02/2010
I concur.