Briefing Document for Gadobutrol Injection

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Applicant: Bayer HealthCare Pharmaceuticals

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List of abbreviations

ACR	American College of Radiology
ADR	adverse drug reaction
AE	adverse event
AUC	area under the curve
BBB	blood brain barrier
BW	body weight
CE	contrast-enhanced
CHMP	Committee for Medicinal Products for Human Use
CL	clearance
CLcr	creatinine clearance
C_{max}	maximum concentration
CNR	contrast-to-noise ratio
CNS	central nervous system
e.g.	Latin: *exempli gratia* (for example)
EMA	European Medicines Agency
ESRF	end-stage renal failure
ESUR	European Society of Urogenital Radiology
FDA	Food and Drug Administration
FLAIR	fluid attenuated inversion recovery
FoV	field of view
GBCA	gadolinium-based contrast agent
Gd	Gadolinium
GFR	glomerular filtration rate
GPV	Global Pharmacovigilance
GRIP	Safety of Gadovist in Renally Impaired Patients (study short title)
HCP	health care provider
i.e.	Latin: *id est* (that is)
i.v.	intravenous
MDRD	modification of diet-in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NDA	New Drug Application
NOAEL	no-adverse-effect-level
NSF	nephrogenic systemic fibrosis
OSE	Office of Surveillance and Epidemiology
PK	pharmacokinetics
QT	one specific ECG interval

QTc	QT corrected
SNR	signal-to-noise ratio
SOC	System Organ Class
SPA	special protocol assessment
$T_{1/2}$	half life
US	United States (of America)
V	volume
Vss	Volume of distribution at steady state

1. Executive summary

This document is prepared for members of the Food and Drug Administration (FDA) Peripheral and Central Nervous System Drugs Advisory Committee for the purpose of describing information pertinent to an assessment of the benefits and risks for Gadobutrol, a gadolinium-based contrast agent (GBCA) for magnetic resonance imaging (MRI) currently under FDA review as a diagnostic imaging agent of the central nervous system (CNS).

1.1. Development history

Gadobutrol is an extracellular GBCA for MRI, which consists of the paramagnetic gadolinium ion complexed with a macrocyclic ligand and has been first approved for CNS indications in Europe in 1998. Enabled by its physico-chemical properties, Gadobutrol is formulated as a 1.0 molar (1.0 M) aqueous solution, thus allowing for injection of a diagnostic dose with half the volume compared to other 0.5 M GBCAs.

Gadobutrol has high relaxivity (the highest relaxivity amongst all macrocyclic GBCAs), which, combined with the unique 1.0 M formulation, yields the highest T1-shortening effect per mL compared to other GBCAs. As a macrocyclic Gd chelate, Gadobutrol has a high complex stability with regard to release of gadolinium from the chelate.

The overall safety profile of Gadobutrol has been established in clinical programs in more than 4500 patients, and in the post-approval setting in more than 6.1 million exposures throughout 11 years of marketing. Gadobutrol is currently approved in 65 countries worldwide at doses up to 0.3 mmol/kg body weight (BW) for a variety of different imaging indications. The recommended dose of Gadobutrol for imaging of the CNS in the United States (US) is 0.1 mmol/kg BW (e.g. 0.1 mL/kg BW).

1.2. Non-clinical development

Based on the results of non-clinical studies, Gadobutrol is not expected to induce any severe or irreversible adverse effects after an i.v. bolus injection of the recommended human dose. The key findings/conclusions are as follows:

- Gadobutrol is quickly distributed throughout the plasma and extracellular fluid and is rapidly excreted in urine by glomerular filtration, without being metabolized.
- Gadobutrol did not cause adverse effects on the cardiovascular system, CNS, respiratory system, or on renal function, and did not produce histamine release in animals.

- After repeated daily administration for up to four weeks, no effects were observed in rats and dogs with daily doses exceeding the proposed human dose by 12 times and 10 times, respectively.

1.3. Clinical pharmacology

Based on results of clinical pharmacological studies, Gadobutrol was well tolerated. The key findings/conclusions are as follows:

- Gadobutrol is well tolerated at doses up to of 1.5 mmol/kg BW.
- After i.v. injection, Gadobutrol rapidly distributes into the extracellular space, followed by fast renal elimination.
- Gadobutrol is completely excreted within 24 hours by the kidney via glomerular filtration in patients with normal renal function. Excretion is prolonged in renally impaired patients.
- Gadobutrol is not metabolized.
- Gadobutrol is dialyzable.
- Safety and pharmacokinetics in pediatric patients (2 to 17 years of age) were similar to that in adults.
- No dose adjustment is needed for any patient population (including patients with renal impairment, geriatrics and pediatrics).

1.4. Efficacy

Bayer is currently seeking approval as a diagnostic imaging agent of the CNS indication in the US. The key efficacy findings are as follows:

- For CNS imaging, the dose of 0.1 mmol/kg BW is based on a dose selection study and is consistent with the standard dose for other marketed GBCAs for CNS imaging in the US.

- Two adequate and well-controlled Phase-3 clinical trials met all primary and secondary endpoints and demonstrated that combined Gadobutrol-enhanced plus unenhanced images compared to unenhanced images are:
    - Superior in diagnostic performance
    - Superior for the lesion visualization variables contrast enhancement, border delineation and internal morphology
    - Non-inferior for the number of lesions detected.

- One of the pivotal studies was a direct comparison between Gadobutrol and ProHance (Gadoteridol) in which:
  - Gadobutrol was shown to be non-inferior to ProHance with respect to the visualization variables contrast enhancement, border delineation and internal morphology, as well as number of lesions detected.
  - Gadobutrol showed higher sensitivity than ProHance for the determination of lesion malignancy
  - Gadobutrol-enhanced images were consistently favored over ProHance-enhanced images by all 3 blinded readers.

1.5. Safety

During a large clinical development program, the safety profile of Gadobutrol has been well characterized. This clinical development program included 34 studies (Phase 2-4) with 4549 patients (4411 adults and 138 children ages 2 to 17 years) dosed with Gadobutrol. Doses ranged from 0.03 to 0.51 mmol/kg BW, with the majority (2434 patients) receiving the recommended dose of 0.1 (±0.01) mmol/kg BW.

The safety profile that emerged during clinical development was confirmed over 11 years of post marketing experience outside the United States with an estimated total of 6.1 million applications.

The key safety findings are as follows:

- Overall, Gadobutrol was well tolerated. The most frequent adverse drug reactions were headache (1.5%) and nausea (1.2%)
- No clinically relevant differences in the incidence and type of AEs were seen between the dose groups given up to 0.51 mmol/kg BW and the different indications.
- During the entire clinical development program of Gadobutrol, no cases of Nephrogenic Systemic Fibrosis (NSF) or NSF-like symptoms were reported.
- The safety results from a Phase-1/3 pediatric study in children 2 – 17 years were consistent with the known safety profile of Gadobutrol in adult patients.
- The post-marketing safety data after more than 6.1 million administrations is consistent with the known safety profile of Gadobutrol as observed during clinical trials. Similar to other GBCAs with CNS indications,
  - Serious and even fatal anaphylactoid reactions have been reported rarely.
  - Local tolerance is similar to that of other GBCA
  - Reports of NSF or NSF-like symptoms have been received very rarely
  - There is no post-marketing evidence of dose misadministration impacting patient safety.

NSF is a rare, but serious, disease predominantly seen in patients with chronic, severe kidney disease (GFR < 30 mL/min/1.73 m^2) or Acute Kidney Injury. A potential association with GBCAs was first reported in 2006. While the exact cause is unknown and considered multifactorial, free gadolinium ions (Gd^{3+}) released from GBCAs are hypothesized to play a major role in the pathomechanism of NSF. For Gadobutrol, the following can be stated:

- Non-clinical studies suggest that GBCAs with a macrocyclic structure, such as Gadobutrol, exhibit the highest kinetic stability among all GBCAs and are thus expected to have a very low propensity to release free Gd^{3+}.
- After an estimated total of 6.1 million post-marketing administrations of Gadobutrol, 2 single agent reports of NSF or NSF-like symptoms have been received for Gadobutrol in which the available clinical and histological information is consistent with NSF according to the criteria of Cowper et al. One additional report fulfilling the same criteria is a multiple agent report. In addition, there were 7 reports involving Gadobutrol that do not fulfill these criteria or do not provide sufficient information.
- Taking all available information into account, the potential risk for NSF after receiving Gadobutrol appears to be similar to that of other macrocyclic GBCAs with a labeled lower risk for NSF, such as ProHance (the only macrocyclic GBCA currently approved in the US).
- Based on this lower potential risk, the labeling for Gadobutrol should include the same Boxed Warning, Warnings and Precautions, and Patient Counseling Information language as the other GBCAs which are labeled as having a lower risk for NSF.

1.6. Risk management

The safety profile of Gadobutrol is similar to other approved GBCAs considered to have a lower risk of NSF. Because of the 1.0 M concentration and lower dose volume than the currently approved agents, dose misadministration could occur post-approval. Bayer's position is that these risks can be minimized with an effective risk management plan. The key points are highlighted as follows:

- Labeling to include a Boxed Warning, Warnings and Precautions, and Patient Counseling Information language similar to the other GBCAs considered to have a lower risk of NSF.
- Expansion to the US of an on-going observational study in patients with moderate and severe renal impairment to further characterize the risk of NSF with Gadobutrol
- Ongoing pharmacovigilance
- Conspicuous packaging and labeling that prominently displays Gadobutrol's higher concentration and recommended lower dosing volume
- Dosing charts that clearly depict the correct dose per body weight
- Educational initiative to inform Health Care Providers (HCPs) of Gadobutrol's higher concentration to ensure proper dosing of Gadobutrol and to minimize the risk for dose administration errors.

1.7. Benefit-risk conclusion

Gadobutrol has demonstrated convincing efficacy, both with respect to superior diagnostic and visualization performance compared to unenhanced imaging in two adequate and well-controlled Phase-3 clinical studies. The efficacy and safety of Gadobutrol has been extensively characterized in more than 4500 patients in clinical studies, and the safety has been demonstrated in more than 6.1 million patients throughout 11 years of marketing outside the US.

Moreover, the safety profile of Gadobutrol is similar to that for other macrocyclic GBCAs with a labeled lower risk for NSF. With the proposed risk management plan, the potential for dose administration errors can be minimized with adherence to the proposed labeling. Gadobutrol has a favorable benefit-risk ratio and is an important diagnostic agent for all patients requiring contrast-enhanced MRI of the CNS, including patients with impaired renal function.

2. Introduction to contrast-enhanced magnetic resonance imaging (CE-MRI)

2.1. Clinical relevance of MRI

Since its introduction over 20 years ago, magnetic resonance imaging (MRI) has become the mainstay of central nervous system imaging. In comparison to conventional x-ray imaging modalities, MRI utilizes magnetic and radiofrequency fields to produce anatomic images. Superior soft tissue contrast resolution, ability to image anatomy in multiple planes, and lack of ionizing radiation are several reasons for widespread acceptance of MRI in medical imaging. It is estimated that there were 36 million MRI examinations performed in the US in 2009, with approximately 60% of these examinations performed to image the central nervous system (CNS), i.e. brain and spine. MRI of the CNS is the primary method of non-invasive diagnosis, and has been shown to be effective when searching for known or suspected primary or metastatic tumors, infection, inflammation, trauma, and demyelinating or degenerative diseases. In addition, MRI has a high negative predictive value which allows it to reliably rule out neoplasma.

Thus, MRI has contributed significantly to clinicians' ability to image the central nervous system by allowing better detection and characterization of pathology -- the requisites for diagnosis of disease. In the absence of contrast administration, this is accomplished by producing images which convey to clinicians basic disease information such as the total number of lesions, lesion location, border delineation, internal composition, and extent of disease involvement. Therefore, more accurate evaluation of these features can facilitate more accurate diagnosis.

2.2. MRI contrast

Non-contrast-enhanced MRI is a robust diagnostic tool, as evidenced by the fact that more than two-thirds of MRI exams performed in 2009 were performed without contrast. This is particularly relevant for patients for whom administration of a gadolinium-based contrast agent (GBCA) poses a greater risk and for whom a careful benefit risk assessment is needed before the administration of a GBCA, e.g. those with chronic, severe kidney disease or Acute Kidney Injury. On the other hand, contrast enhanced MR imaging is useful in providing additional diagnostic information beyond that obtained with unenhanced MRI exam and is a clinically relevant addition in the diagnostic workup for about one third of the patients referred for CNS imaging. A majority of medical errors occur as a result of misdiagnosis. Contrast enhancement provides another tool to increase diagnostic confidence and accuracy, and can impact the medical management of a significant number of patients. The benefit of contrast administration is widely accepted.

Contrast-enhanced MRI utilizes extracellular GBCAs as the clinical standard for detecting and delineating most intracranial and spinal lesions. Following administration of a GBCA, lesions are further characterized by their temporal and spatial patterns of

signal enhancement produced by the contrast material. The paramagnetic metal gadolinium (Gd^{3+}) is the rare earth element responsible for the enhancement effect of GBCAs.

Contrast-enhanced MRI of the CNS relies on the disruption of the blood brain barrier (BBB). The brain and spine (CNS) are surrounded by a BBB, which is both a physical barrier and a cellular transport system. Normally, it maintains homeostasis of the CNS by restricting the entrance of potentially harmful foreign substances from the blood, and by allowing the passage of essential nutrients. Water soluble molecules such as contrast agents, as well as electrolytes such as sodium and potassium ions, are unable to transverse the intact blood brain barrier. Pathology of the CNS, such as primary or metastatic brain tumors, stroke, and inflammation, causes local disruption of the blood-brain barrier (BBB). Contrast agents are able to diffuse through the disrupted BBB into lesions, resulting in increased signal intensity on contrast-enhanced magnetic resonance images.

2.3. Characteristics of GBCAs for MRI

All GBCAs are comprised of the same principle components: a gadolinium ion linked to a complexing agent (ligand). Beyond this similarity, GBCAs differ in a number of properties, such as chemical structure (linear [open-chain] versus macrocyclic), thermodynamic stability, kinetic stability (i.e. time course of dissociation of gadolinium), ionicity, concentration, osmolality, viscosity, pharmacokinetics, and relaxivity (a measure of their ability to enhance tissue during MRI exams). Several of these characteristics hold particular importance for safety and diagnostic performance:

Relaxivity:
Relaxivity is a measure of a GBCA's ability to create enhancement within tissue during an MRI examination. 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), and differences in the spin-spin or transverse relaxation time (T2).

When placed in a magnetic field, GBCAs shorten the T1 and T2 relaxation times. The extent of decrease of T1 and T2 relaxation times, and therefore the amount of signal enhancement obtained from a GBCA, is based upon several factors including the inherent relaxivity of the GBCA molecule (r1 relaxivity for T1 shortening and r2 relaxivity for T2 shortening), the concentration of the GBCA in the tissue, the quantity of the GBCA in the imaging field of view, the field strength of the MRI system, and the relative ratio of the longitudinal and transverse relaxation times. For signal enhancement in MR imaging, T1 shortening is the relevant parameter.

For reference, Text Table 1 demonstrates measured r1 and r2 relaxivities and resulting T1 shortening of Gadobutrol and GBCAs approved in the US for imaging of the CNS. Note that Gadobutrol has the second highest relaxivity measurements in this group.

Text Table 1 Relaxivity and T1 shortening of contrast media approved for CNS imaging in the U.S.

Gd chelate	Field strength Conc.	**Relaxivities** (L-mmol-1sec^{-1}) in plasma at 37°C 1.5 Tesla r_1	1.5 Tesla r_2	3.0 Tesla r_1	3.0 Tesla r_2	**T1 shortening** per unit volume (s) *
Gadobutrol	1.0 M	5.2	6.1	5.0	7.1	1.034
ProHance (gadoteridol)	0.5 M	4.1	5.0	3.7	5.7	0.886
Magnevist (gadopentetate dimeglumine)	0.5 M	4.1	4.6	3.7	5.2	0.853
MultiHance (gadobenate dimeglumine)	0.5 M	6.3	8.7	5.5	11.0	0.949
Omniscan (gadodiamide)	0.5 M	4.3	5.2	4.0	5.6	0.865
OptiMARK (gadoversetamide)	0.5 M	4.7	5.2	4.5	5.9	0.853

* Calculated from r_1 relaxivity in plasma (T_0 =1200 ms) at 37°C
Data taken from Rohrer et al. 2005

Ultimately, the T1 shortening effect of a paramagnetic contrast agent during a particular MRI examination is dependent on its r1 relaxivity and tissue concentration at the time of image acquisition. Mathematically, this can be represented by the equation below (from Rohrer et al. 2005), where r1 is the T1 relaxivity of the GBCA, C is its concentration, and $T_{1,0}$ is the baseline T1 of the tissue.

$$\frac{1}{T_1} = \frac{1}{T_{1,0}} + r_1 C$$

The concentration of a GBCA in tissue varies over time, with the maximum concentration in the target tissue likely occurring during the first pass of contrast agent after i.v. (bolus) injection. For a given r1 relaxivity, a higher concentration of GBCA provides greater T1 shortening (signal enhancement). This may be particularly relevant to MRI applications which utilize dynamic first-pass techniques such as CNS perfusion imaging.

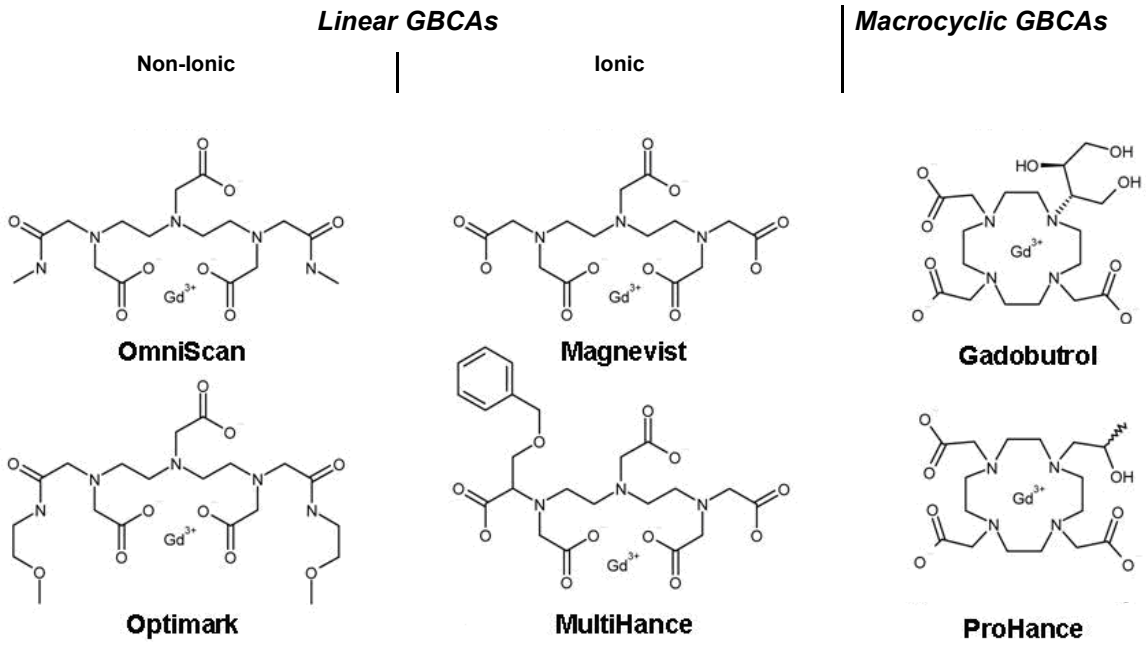
Gadobutrol has the highest T1 shortening per unit volume as shown in Text Table 1.

Concentration:

Another consequence of higher GBCA concentration is the reduction of its volume of administration for a given dose. When dosed by body weight, a 1.0 M concentration GBCA will have half the volume of administration of its corresponding 0.5 M concentration. Although this volume difference will be on the order of several milliliters, this may be of sufficient consideration in clinical management of patients requiring strict volume restriction, and in the pediatric population.

Chemical structure

Based on the structural association of the gadolinium atom with its chelate agent, currently approved GBCAs can be categorized as having either linear structure (Gd-complexes are based on the DTPA backbone) or macrocyclic structure (complexes are derived from DOTA) (Text Figure 1).



Text Figure 1 Chemical structure of Gadobutrol and gadolinium-based contrast agents (GBCAs) approved for CNS imaging in the US

Gadobutrol is a macrocyclic compound. Only one of the GBCAs approved for use in the US, ProHance (gadoteridol), is a macrocyclic compound. The other GBCAs available in the US have linear open-chain structures. Two of these have non-ionic (no net charge) linear structures and two of these have ionic (negatively charged) linear structures.

Stability:

Compared to the linear agents, macrocyclic GBCAs are kinetically inert under physiological conditions. With macrocyclic agents, a strong complex with the paramagnetic gadolinium ion is formed which results in high *in vivo* and *in vitro* kinetic stability, and thus low likelihood for release of free gadolinium under clinical conditions. The stability of macrocyclic compounds is determined mainly by their slow kinetics of decomplexation because significant activation energy is necessary to dissociate gadolinium from its macrocyclic complex.

According to the prevailing theory, stability of any GBCA molecule is of particular relevance in the context of nephrogenic systemic fibrosis (NSF). Therefore, details of pertinent physico-chemical characteristics of GBCAs are discussed in greater detail in a section dedicated to discussion of NSF (Section 9.3).

3. Overview of physico-chemical characteristics of Gadobutrol

Gadobutrol is characterized by the following physico-chemical features:

1. Macrocyclic structure (see Text Figure 1)

   The macrocyclic structure encloses gadolinium in a tight structure, resulting in a kinetically inert compound compared to linear chelates. Under clinical conditions, a macrocyclic compound has a low likelihood for release of free Gadolinium compared to linear chelates.

2. High stability

   The ligand of Gadobutrol with its macrocyclic structure forms a strong complex with the paramagnetic gadolinium ion resulting in high *in vivo* and *in vitro* kinetic stability.

   In vitro, the dissociation half-life of Gadobutrol at 37°C and pH 7 is calculated to be greater than 1000 years. This dissociation half-life is similar to the other macrocyclic GBCA marketed in the US (ProHance).

   This high stability minimizes the potential risk of free gadolinium ions being released *in vivo*, which is suggested to correlate to the risk of triggering NSF (see Section 9.3 for details).

3. High relaxivity

   The higher the relaxivity, the shorter the T1 relaxation time, which ultimately leads to better image quality as compared to GBCAs with a lower relaxivity. Relaxivity of Gadobutrol is greater than that of the other macrocyclic GBCA (ProHance) (Text Table 1).

4. High concentration

   Gadobutrol is formulated as a 1.0 M solution, which has twice the concentration of Gd per volume unit as the most commonly used GBCAs which are formulated as 0.5 M concentration. The 1.0 M concentration has the following potential advantages:

   – Low injection volume

   – Potential to apply a very tight bolus injection, favorable in particular for dynamic imaging applications

   – In conjunction with higher relaxivity, the T1 shortening per volume contrast agent administered is highest, which is important for dynamic MRI examinations.

5. Favorable pharmacokinetic profile

   Similar to other extracellular GBCAs, Gadobutrol is characterized by extracellular distribution (negligible protein binding, no intracellular uptake) and fast excretion from the blood and body by glomerular filtration without any metabolism.

6. Osmolality and viscosity

   The osmolality of Gadobutrol formulated at 1.0 M is less than the osmolality of the ionic linear GBCAs (MultiHance and Magnevist) formulated at 0.5 M (Text Table 2), and the viscosity of Gadobutrol is less than MultiHance or Magnevist formulated at 0.5 M.

Text Table 2 Osmolality and viscosity of GBCAs

Gd-chelate	Concentration (M)	Osmolality at 37°C (Osm/kg H_2O)	Viscosity at 37 °C (mPa•s)
Gadobutrol	1.0	1603	4.96
ProHance	0.5	630	1.3
MultiHance	0.5	1970	5.3
Magnevist	0.5	1960	2.9
Omniscan	0.5	789	1.4
OptiMARK	0.5	1110	2.0

Sources: Data on file, US Package Inserts

Taken together, the physico-chemical characteristics of Gadobutrol can be regarded as highly favorable for both safety and diagnostic performance.

4. Developmental history of Gadobutrol

Summary:

- Gadobutrol is a macrocyclic compound of high stability and high relaxivity.
- Gadobutrol is the only GBCA formulated at a 1.0 M concentration, and thus the injection volume is lower (half) compared to 0.5 M GBCAs. This may be advantageous for modern dynamic MRI applications requiring the GBCA to be administered as a tight bolus injection.
- Both formulations of Gadobutrol, 1.0 M and 0.5 M, were originally approved in Europe in the late 1990s, but the 0.5 M formulation has never been marketed.
- Gadobutrol was first approved in February 1998 (Switzerland). To date, approvals have been obtained in 65 countries worldwide, including Canada, Mexico, Australia, New Zealand, China, South Korea, Russia, Brazil and all European Union countries. It is currently marketed in 62 of these countries under the tradename "Gadovist" or "Gadovist 1.0".
- More than 6.1 million examinations have already been performed with Gadobutrol worldwide through 31 October 2010.
- Contrast-enhanced MR imaging of the CNS was the first approved indication and is the most widely used application for Gadobutrol.
- Efficacy and safety of Gadobutrol have been well characterized in a total of 34 Phase-2 to 4 clinical studies, involving more than 4500 patients exposed to Gadobutrol.
- All studies have consistently met their primary endpoints in demonstrating the efficacy and safety of Gadobutrol in a broad set of indications.

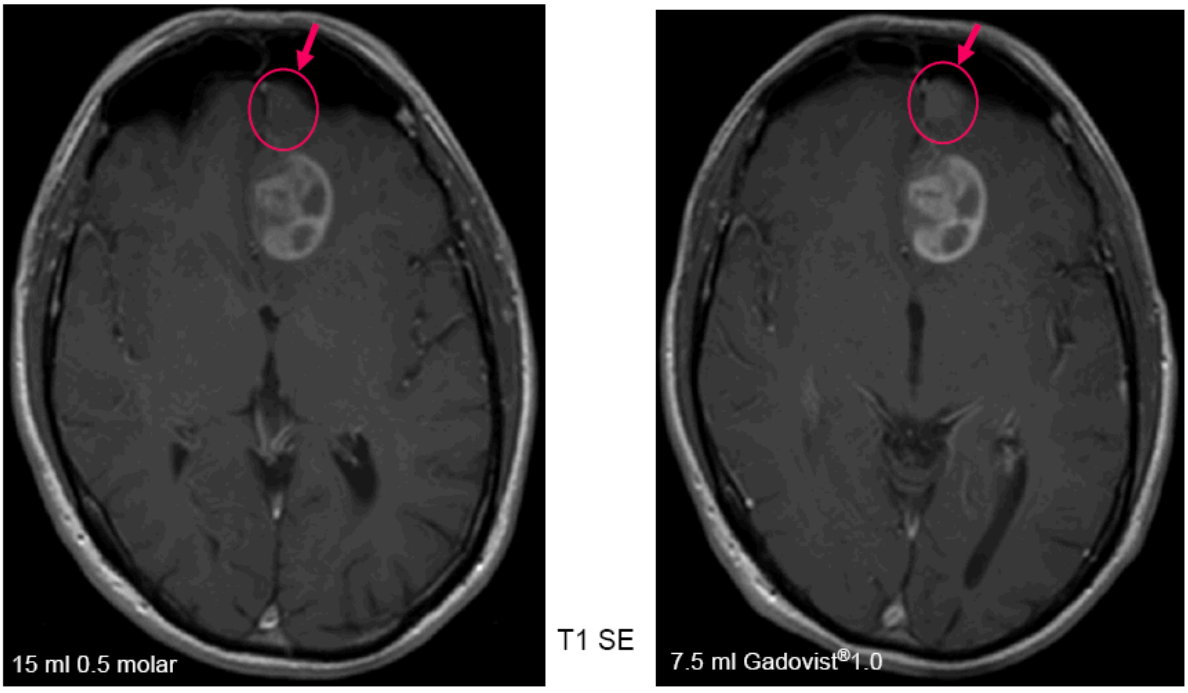
4.1. Choice of the concentration

Gadobutrol, due its physico-chemical properties (including solubility, hydrophilicity, and osmolarity), is the only GBCA formulated at a 1.0 M concentration, while maintaining an acceptable viscosity similar to other available extracellular GBCAs formulated at a 0.5 M concentration. Development of Gadobutrol originally began with both a 0.5 M concentration as well as its present 1.0 M formulation. The two formulations were studied in all phases of preclinical and clinical development prior to 1999 and both formulations were approved in many European countries. While both formulations were approved for CNS imaging in several countries, only the 1.0 M formulation has been marketed.

Due to the unique combination of the 1.0 M formulation and high relaxivity, Gadobutrol provides highest T1 shortening per mL compared to all other GBCAs. To apply the standard dose only half the volume (0.1 mL/kg BW) is needed, which may be preferred in certain clinical settings (where a lower contrast agent volume may be necessary) and in certain applications (such as dynamic contrast enhanced MRI). A standard dose (0.1 mmol/kg BW) yields high contrast-to-noise (CNR) and signal-to-noise (SNR) ratios and thus produces well delineated, sharp contrast enhancement, relevant for fast dynamic imaging such as brain perfusion as well as steady state imaging (Tombach et al. 1999).

The relevant parameter for signal and contrast enhancement is T1 shortening in the target tissue. This is influenced by tissue/lesion specifics (including water content and extracellular space), contrast media characteristics (relaxivity), injection characteristics, dose, individual cardio-vascular parameters, the target tissue and the local concentration of the GBCA.

Gadobutrol at a 0.5 M concentration achieved significantly lower CNR and SNR values at the same dose compared with 1.0 M Gadobutrol (Text Figure 2; Tombach et al. 1999; Herborn et al. 2003). Considering all possible clinical indications and applications for an all-purpose imaging agent, and the fact that the 1.0 M formulation did not alter the safety or local tolerability of Gadobutrol, further development focused on the 1.0 M formulation.



Text Figure 2 Images at different concentrations
Comparison of 0.5 M (left) and 1.0 M (right) contrast agent and effect of higher T1 shortening in CNS lesion imaging (courtesy of Prof. Schmieder/ Heuser, Bochum) [note: non-identical slices]

4.2. Current worldwide approval status of Gadobutrol

Worldwide approvals

Gadobutrol was first approved in February 1998 for the indication "Contrast enhancement in cranial and spinal MRI" in Switzerland. Subsequent to this initial approval, Gadobutrol has to date been approved in 65 countries worldwide, including all European Union countries, plus Canada, Mexico, Australia, New Zealand, China, South Korea, Russia, and Brazil. It is currently marketed in 62 of these countries, using the proprietary name "Gadovist®" or "Gadovist® 1.0", with the "1.0" added to the proprietary name in some countries to highlight the higher concentration.

Following the initial approvals of Gadobutrol for use in cranial and spinal MRIs, Gadobutrol has, to date, been approved for the following applications / populations in most of these countries:

- Contrast-enhanced magnetic resonance angiography (MRA)
- Contrast-enhanced MRI of the liver and kidneys
- Pediatrics

Approval processes for these indications / populations in additional countries are currently ongoing.

Approved dosages

For imaging of the CNS, the recommended standard dose is 0.1 mmol/kg BW (equivalent to 0.1 mL/kg BW of Gadobutrol). However, in many countries, a further injection of 0.2 mmol/kg BW (i.e. up to a total of 0.3 mmol/kg BW) is permitted (similar to the US label of ProHance) if strong clinical suspicion of a lesion persists following assessment of the contrast-enhanced MRI at 0.1 mmol/kg BW to increase the diagnostic yield of the examination.

The fixed-volume approach was chosen for contrast-enhanced MR Angiography to better standardize and optimize the bolus length and timing for this first-pass MRI technique. Corresponding doses range are between 0.1 and 0.15 mmol/kg BW for single field-of-view (FoV) imaging and 0.2 to 0.3 mmol/kg BW for multiple FoV imaging, depending on the actual body weight.

For contrast-enhanced MRI of the liver and kidneys, the recommended dose is 0.1 mmol/kg BW.

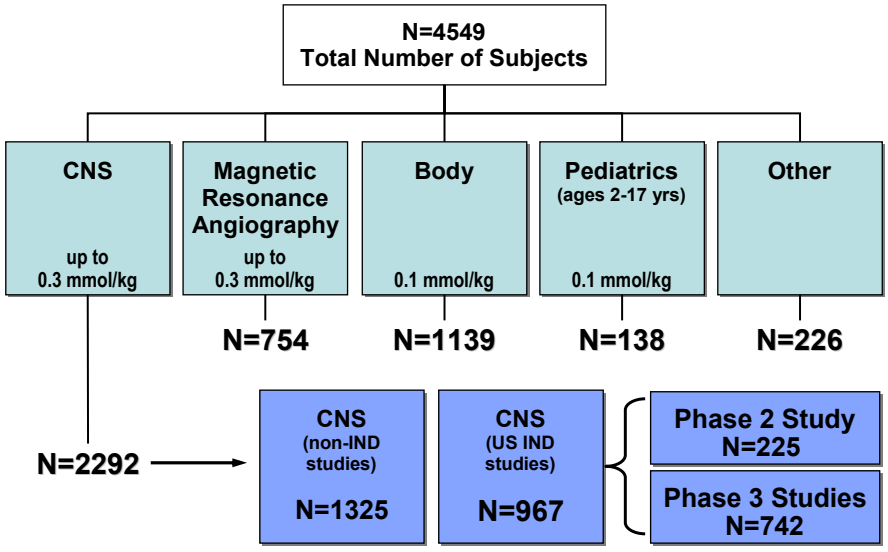
In children 2 years of age and older, the recommended dose is 0.1 mmol/kg BW.

4.3. Overview on clinical development program for Gadobutrol

A total of 43 clinical studies have been completed during the development of Gadobutrol, enrolling a combined total of 5858 patients. Many studies were conducted approximately 10 years ago to support the registration of Gadobutrol in Europe and Asia.

In 34 company-sponsored Phase-2 to 4 development trials, Gadobutrol has been administered to 4411 adult patients and to 138 pediatric patients (total number of patients exposed to Gadobutrol, n = 4549). The trials were performed in the EU (n = 2745 patients), Asia (n = 1223 patients), South/Central America (n = 308 patients), US/Canada (n = 264 patients), and Australia (n = 9 patients). All studies have consistently met their primary objectives in demonstrating the efficacy and safety of Gadobutrol in a broad set of indications.

The clinical development program for Gadobutrol, including indications, number of patients, and doses studied, is summarized in Text Figure 3. A table listing all clinical studies can be found in Appendix 13.1 and efficacy summaries of additional supportive studies in CNS imaging can be found in Appendix 13.2.



Text Figure 3 Clinical development program for Gadobutrol

The following additional adequate and well controlled studies were conducted to demonstrate the efficacy in CNS imaging in US:

Phase 2: - Study 308200: Dose selection study

Phase 3: - Study 310124: Non-comparator study (without active comparator)
- Study 310123: Comparator study (with active comparator ProHance)

4.4. Choice of the indication for the current application

Across the countries in which Gadobutrol is marketed, imaging of the CNS is the most widely used application of this product. Therefore, CNS imaging has been selected as the first indication proposed for marketing authorization in the US. The proposed indication is as follows:

> "Gadobutrol is a gadolinium-based contrast agent indicated 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"

Bayer intends to submit further applications for additional indications at a later point in time.

5. Non-clinical development

Summary:

Based on the results of the non-clinical studies, Gadobutrol is not expected to induce any severe or irreversible adverse effects after an intravenous bolus injection of the recommended human dose. In particular, in animal studies the following observations and conclusions were made:

- Gadobutrol is quickly distributed throughout the plasma and extracellular fluid and is rapidly excreted in urine by glomerular filtration, without being metabolized.
- Gadobutrol did not cause adverse effects on the cardiovascular system, CNS, respiratory system, or on renal function, and did not produce histamine release.
- The risk of severe intoxication after inadvertent overdosing is low.
- Results from animal studies indicate that local irritation may occur after inadvertent misadministration (e.g. paravenous injection).
- After repeated daily administration for up to four weeks, no effects were observed in rats and dogs with daily doses exceeding the proposed human dose by 12 times and 10 times, respectively. The most remarkable finding was partially reversible vacuolization of renal tubular epithelial cells, a well-known finding in non-clinical studies of other GBCAs and iodinated X-ray contrast agents which is considered to be without clinical relevance.
- Gadobutrol is not mutagenic.
- No teratogenicity or embryotoxicity was seen after repeated administration of multiples of the human diagnostic dose to either rats or rabbits.
- Non-clinical studies showed only limited transfer into milk and recovery from the stomach of suckling animals was less than 0.02% of the administered dose.
- Studies in neonatal rats showed prolonged exposure attributable to immature kidney function, however, tolerability of Gadobutrol was comparable to adult animals.

5.1. Pharmacologic class and mode of action

As already described in more detail in Section 3, Gadobutrol is an extracellular GBCA for MRI. As with other extracellular MR contrast agents, Gadobutrol contains the paramagnetic metal gadolinium (Gd^{3+}), a paramagnetic rare earth element responsible for the shortening of relaxation times of hydrogen protons.

5.2. Pharmacology and toxicology

5.2.1. Pharmacology

Before clinical development, favorable contrast-enhancing properties were observed in several animal models with experimentally-induced cerebral infarcts, brain tumors, liver tumors, or intramuscular tumors. These studies provided the basis for the subsequent clinical development of Gadobutrol.

5.2.2. Non-clinical studies

A non-clinical development program was performed for Gadobutrol to assess pharmacokinetics, safety pharmacology and toxicology of the compound. These studies are briefly summarized in the subsequent sections.

5.2.2.1. Pharmacokinetics

After intravenous (i.v.) administration to young adult animals, Gadobutrol is quickly distributed throughout the plasma and extracellular fluid and is rapidly excreted in urine by glomerular filtration, without being metabolized. Gadobutrol showed only negligible protein binding and was not transferred to blood cells. Distribution studies with radioactive ^{153}Gd-labeled Gadobutrol do not indicate a significant passage through the intact blood brain barrier.

5.2.2.2. Safety pharmacology

Gadobutrol was investigated for its potential effects on the CNS, the cardiovascular and respiratory system, on renal function, and on histamine release.

The only effect observed was a transient change in QT at 2.5 mmol/kg BW in dogs (i.e. 25 times the clinical dose) which was attributed to hysteresis and considered to be of no clinical relevance. A subsequent clinical "thorough QT study" did not show clinically relevant effects at clinically relevant doses (see Section 6.2).

5.2.2.3. Toxicology

Single-dose toxicity studies (i.v.)

Single administration of Gadobutrol to mice, rats, and weanling male rats resulted in a minimum lethal dose exceeding the proposed clinical dose by at least 200 times indicating a very wide safety margin.

Repeated dose toxicity studies (i.v.)

After repeated administration of Gadobutrol daily over four weeks to young adult rats and dogs, the most remarkable finding was partially reversible vacuolization of renal tubular epithelial cells. This has also been reported in toxicology studies of other GBCAs or iodinated X-ray contrast agents after administration of large volumes of hypertonic solutions and after administration of low-molecular weight dextrans and other exogenous solutes. This finding was not regarded as adverse. The No-Adverse-Effect Level (NOAEL) in rats (1.2 mmol/kg BW) and dogs (1.0 mmol/kg BW) exceeded the proposed human dose by 12 times and 10 times respectively. The results after repeated administration also suggest that prior exposure to gadolinium did not affect the overall tolerance and safety of subsequent injections of Gadobutrol. No macroscopic or microscopic skin findings were observed in any of the studies.

Genotoxicity

Gadobutrol was not mutagenic *in vitro* (Ames test, hypoxanthine guanine phosphoribosyl transferase test using cultured Chinese hamster V79 cells, chromosome aberration tests in human peripheral blood lymphocytes) or *in vivo* (micronucleus test in mice) after i.v. injection.

Developmental toxicity

Gadobutrol showed no effect on fertility and did not have serious adverse effects on the parental or F1 generations when administered intravenously during early development, organogenesis, late pregnancy, or early postnatal development, the latter also including behavioral and functional tests of the neonates. Specifically, no effects on embryonal development, embryolethality or teratogenicity occurred in pregnant rats and rabbits up to repeated doses of 15 times or in monkeys at repeated doses of 8 times the proposed human dose of 0.1 mmol/kg BW.

When radioactive ^{153}Gd-labeled Gadobutrol was administered intravenously to pregnant rats and rabbits, trace amounts of radioactivity were detected in their fetuses indicating minor placental passage of the compound. When administered to lactating rats, low levels of radioactivity were found in breast milk. The amount subsequently recovered from stomach milk of the neonates over 24 hours was less than 0.02% of the dose given to the dam.

Local tolerance and allergenicity

There were no significant findings in local tolerance studies, antigenicity or skin sensitization tests after i.v. administration. Local intolerance reactions, including moderate irritation associated with infiltration of inflammatory cells, were observed after paravenous administration to rabbits. This indicates a potential for irritation after misadministration in the clinical setting as also observed with other marketed GBCAs.

Studies in neonatal rats

After a single i.v. injection to male and female neonatal rats on postnatal Day 4, Gadobutrol was well tolerated without signs of delayed treatment effects up to a high dose of 6.0 mmol/kg BW. For the rats given 6.0 mmol/kg BW and kept for recovery, these changes were either greatly reduced (vacuoles in kidneys) or absent (microglia cells) by Day 28 and were therefore not considered adverse. The NOAEL in this study was 2.0 mmol/kg BW, or 20 times the recommended clinical dose. The estimated clearance values in the neonates were 1.9 to 2.5 times lower than in the adult rats, reflecting the known immaturity of renal function in neonates. However, the increased exposure in neonates did not decrease the tolerability of Gadobutrol as compared to the adult animals.

5.2.3. Non-clinical studies on the possible relationship between NSF and GBCAs

Bayer initiated a number of exploratory non-clinical studies to assess the possible association between the administration of GBCAs and NSF. All of these studies indicated that the potential for Gadobutrol to trigger NSF or NSF-like skin lesions is very low, even in animals with impaired renal function. These studies are described in detail in Section 9.4.

6. Clinical pharmacology (safety and pharmacokinetics)

Summary:

- In a Phase 1 study, Gadobutrol has been well tolerated at doses up to 1.5 mmol/kg BW
- After i.v. injection, Gadobutrol rapidly distributes into the extracellular space, followed by fast renal elimination.
- Gadobutrol is completely excreted within 24 hours by the kidney via glomerular filtration in patients with normal renal function.
- Gadobutrol is not metabolized.
- Gadobutrol is dialyzable.
- Safety and pharmacokinetics in pediatric patients aged 2 to 17 years were similar to that in adults.
- No dose adjustment is needed for any patient population (including patients with renal impairment, geriatric and pediatric patients).

Overall, 9 clinical pharmacology studies were conducted with Gadobutrol in humans. Objectives of the clinical pharmacology program included safety and pharmacokinetics after single (up to 1.5 mmol/kg BW) and repeated (up to 2 x 0.1 mmol/kg BW) i.v. administration.

6.1. Safety in clinical pharmacology studies

Single doses of up to 1.5 mmol/kg BW were studied in single-dose clinical pharmacology studies. Doses up to 1.5 mmol/kg BW were well tolerated, suggesting no acute toxicity related to the increased dose. Adverse events observed at the 1.5 mmol/kg BW dose level included dizziness, gastrointestinal disorder, headache, taste perversion, vasodilatation and paresthesia; similar adverse events were observed in the lower dose groups.

6.2. Thorough QT study

The cardiovascular safety of Gadobutrol was investigated in a "Thorough QT study" including PK analysis, according to ICH E14. For that purpose, a single-center, randomized, double-blind, placebo-controlled, 5-period crossover, dose-comparison study with moxifloxacin as positive control was performed. Overall, 64 subjects were enrolled, 54 with complete data. Gadobutrol doses of 0.1, 0.3 and 0.5 mmol/kg BW were investigated. The primary variable was the QTc mean change from baseline over measurements taken within 15 minutes post injection (15-minute average) and the maximum change from baseline up to 22 hours post injection for QTc with Fridericia correction.

Gadobutrol at any of the three doses had no significant QT/QTc prolonging effect in either primary variable.

The mean change in QTcFavg was not significantly prolonged and was less than 5 msec, with the upper bound of the 2-sided confidence interval for each treatment group not exceeding 10 msec.

No subject had a $\geq$ 30 msec increase in QTcFavg, or had a QTcFavg > 450msec.

6.3. Overview of pharmacokinetics

Relevant information on the pharmacokinetics of Gadobutrol is summarized in this section below. A discussion of the pharmacokinetics of Gadobutrol in the context of NSF is provided in Section 9.5.

Distribution

After single intravenous administration of Gadobutrol at doses ranging from 0.04 to 0.4 mmol/kg BW in healthy adult men, the plasma Gd concentrations decreased in a biphasic manner characterized by an early distribution phase during the first minutes followed by a second phase governed by elimination from plasma. The distribution volume at steady state (V_{ss}) of Gadobutrol is about 0.2 L/kg BW indicating that Gadobutrol distributes primarily into the extracellular space. Plasma protein binding in humans is negligible.

Metabolism

Gadobutrol is not metabolized.

Excretion

Gadobutrol is eliminated from plasma with a mean terminal half-life of 1.81 hours (range 1.33 to 2.13 hours) and excreted via urine. Renal clearance of Gadobutrol is 1.1 to 1.7 mL/min/kg BW in healthy subjects and, thus, similar to the renal clearance of inulin, indicating that Gadobutrol is eliminated by glomerular filtration. The urinary excretion of Gadobutrol is nearly complete 12 hours after administration.

Linearity / non-linearity

The maximum observed drug concentration (C_{max}) and area under the curve (AUC) increase in parallel to the dose after intravenous administration, whereas elimination half-life ($t_{1/2}$), total body clearance (CL), and apparent volume distribution during steady state (V_{ss}), are constant regardless of the dose, supporting linear PK of Gadobutrol in the dose range studied.

Effect of demographics on pharmacokinetics

The effects of intrinsic factors (age, body weight, race) on the PK of Gadobutrol were evaluated based on the pooled data consisting of all available Phase-1 clinical studies in healthy adults using the population analysis method. The population analysis showed that the renal clearance was reduced by 20.7% at the lower end of the adult body weight range (46.5 kg) and increased by 27.4% at the upper end (115 kg) as compared to the

typical renal clearance (BW of 75 kg). The observed changes of renal clearance with body weight were clinically not relevant.

6.3.1. Pharmacokinetics in special populations

6.3.1.1. Age and gender

The effect of age and gender on the PK of Gadobutrol was investigated during a study in non-elderly (18-45 years) and elderly (>65 years) healthy men and women following single intravenous administration of 0.1 mmol/kg BW. There was no clinically relevant effect on the PK in relation to gender. In contrast, a statistically significant effect was seen with age. The terminal half-life was increased to about 2.8 hours in elderly men compared to about 2.1 hours in non-elderly men and to about 2.9 hours in elderly women compared to 1.8 hours in non-elderly women. The age-dependent decrease in plasma clearance correlated well with the reduced glomerular filtration rate (GFR) in elderly subjects due to physiological changes in renal function with age.

6.3.1.2. Renal impairment

A further study was performed to investigate the safety, tolerability and PK in renally impaired subjects. Single-bolus intravenous injections of the dose levels 0.1 and 0.3 mmol/kg BW were investigated in moderately and severely impaired subjects and subjects dependent on dialysis. The results are described in detail in Tombach et al. (2000).

The pharmacokinetic parameters of Gadobutrol were calculated by a 2-compartment model analysis and summarized in Text Table 3.

In subjects with moderate renal impairment and severe renal impairment, V_{ss} was similar to that in healthy adults (0.194 to 0.201 L/kg BW). On the other hand, the CL was about 0.50 mL/min/kg BW in subjects with moderate renal impairment and about 0.155 mL/min/kg BW in subjects with severe renal impairment, respectively, compared to about 1.41 mL/min/kg BW in healthy adults. No differences in the total clearances were observed between the 0.1 and 0.3 mmol/kg BW dose. CL was highly correlated with the creatinine clearance (CL_{CR}) in accordance with the known renal excretion pathway via glomerular filtration. The $t_{1/2}$ was prolonged in the mean to 5.8 hours (0.1 mmol/kg BW) and 5.3 hours (0.3 mmol/kg BW) in subjects with moderate renal impairment as compared to about 1.81 hours in healthy adults. In subjects with severe renal impairment elimination half-life was further prolonged in the mean to 17.6 hours (0.1 mmol/kg BW) and 24.8 hours (0.3 mmol/kg BW). Gadobutrol was well tolerated at both dose levels with a similar safety profile as seen in healthy subjects.

Text Table 3 Pharmacokinetics of Gadobutrol under renal impairment

Pharmacokinetic parameters of Gadobutrol after single intravenous administration of Gadobutrol to patients with renal impairment not requiring dialysis at doses of 0.1 and 0.3 mmol/kg BW

Values represent mean ± SD

Creatinine clearance (mL/min)		**Moderate impairment** < 80 and > 30 (n=6)	**Severe impairment** < 30 (n=5)
0.1 mmol/kg BW	AUC (µmol·h/L)	4015 ± 1818	11531 ± 4255
	$t_{1/2\alpha}$ (h)	0.21 ± 0.47	0.079 ± 0.078
	$t_{1/2\beta}$ (h)	5.81 ± 2.41	17.60 ± 6.16
	V_{ss} (L/kg)	0.20 ± 0.042	0.22 ± 0.042
	CL (mL/min/kg)	0.49 ± 0.21	0.16 ± 0.058
	CL_R (mL/min/kg)	0.51 ± 0.22	0.12 ± 0.043
	$A_{E,ur}$ (%)	104.7 ± 13.7	77.3 ± 7.4
0.3 mmol/kg BW	AUC (µmol·h/L)	10339 ± 2466	45677 ± 34576 [a)]
	$t_{1/2\alpha}$ (h)	0.13 ± 0.15	0.29 ± 0.42[a)]
	$t_{1/2\beta}$ (h)	5.32 ± 1.43	24.79 ± 17.40[a)]
	V_{ss} (L/kg)	0.22 ± 0.046	0.24 ± 0.017[a)]
	CL (mL/min/kg)	0.51 ± 0.14	0.15 ± 0.091[a)]
	CL_R (mL/min/kg)	0.48 ± 0.12	0.13 ± 0.099[a)]
	$A_{E,ur}$ (%)	92.8 ± 9.1	76.5 ± 25.6[a)]

a: n = 3

$A_{E,ur}$: Amount of gadolinium excreted in urine from zero to 72 hours (moderate impairment) or 120 hours (severe renal impairment), expressed as % of dose.

6.3.1.3. Dialysis

The dialyzability of Gadobutrol was investigated in 11 patients with end-stage renal failure who required hemodialysis treatment. The first 3-hours hemodialysis eliminated 68.2 ± 12.7% of the administered Gadobutrol dose. After the 2nd and 3rd hemodialysis sessions, the total amount of eliminated Gadobutrol increased to 94.1% ± 4.3% and 98.0% ± 1.8%, respectively. After 30 min of the first hemodialysis session, the mean and SD of Gadobutrol clearances were 126.1 ± 17.8 mL/min, showing that dialysis is similarly effective as the renal elimination of Gadobutrol in healthy subjects.

6.3.2. Pharmacokinetics in pediatric patients

6.3.2.1. Overview of pediatric pharmacokinetic study

The pharmacokinetics and safety of Gadobutrol were investigated in pediatric patients aged 2 to 17 years. A population PK approach employing sparse sampling was selected for the PK evaluation to minimize the clinical burden to the children. Furthermore, age subgroups (2 to 6 years; 7 to 11 years; 12 to 17 years) were pre-defined to foster a homogeneous age distribution within the pediatric study population. The most important PK parameters were determined (i.e. CL, volume of distribution [V], AUC, and $t_{1/2}$). In addition, the population PK approach allowed further investigation of the effect of demographic parameters (covariates) such as age, sex, and body weight on the PK of Gadobutrol.

A total of 130 patients in the final PK analysis set with a total of 390 post-injection data points for measurement of Gd plasma concentrations were included in the population PK analysis.

Gadobutrol PK in children and adolescents aged 2 to 17 years could be adequately described by an open two-compartment model with elimination from the central compartment.

6.3.2.2. Comparison of adult and pediatric pharmacokinetics

A combined PK analysis of all PK data in adults was performed using a population pharmacokinetic approach. The final PK parameters obtained in adults were compared with respective parameters from the pediatric study.

In Text Table 4, post-hoc estimates and derived PK parameters in the overall pediatric population aged 2-17 years together with the parameters in adults are summarized.

The body-weight-normalized CL and V_{ss} (L/h/kg BW and L/kg BW) values were compared within the pediatric patients according to the predefined age subgroups and between pediatric patients and adults. Similar median clearance values of 0.1 L/h/kg BW (1.7 mL/min/kg) and 0.09 L/h/kg BW (1.5 mL/min/kg) were determined for the pediatric population and adults, respectively. The same holds true for the BW-normalized median V_{ss}: the median values were almost identical for pediatrics (0.20 L/kg BW) and adults (0.22 L/kg BW) and the respective 2.5-97.5 percentile ranges were largely overlapping. The subgroup analysis within the pediatric patients showed also very similar results for CL and V_{ss}.

Text Table 4: Pharmacokinetic parameters in the pediatric population and adults

Summary of individual post-hoc estimates and derived pharmacokinetic parameters in the overall pediatric population aged 2 to 17 years and adults

Parameter	Population	Median estimate	Parameter distribution	
			2.5th percentile	97.5th percentile
CL/kg [L/h/kg]	2-17 years	0.10	0.05	0.17
	Adults	0.09	0.05	0.13
V_{ss}/kg [L/kg]	2-17 years	0.20	0.12	0.28
	Adults	0.22	0.15	0.33
AUC [µmol*h/L]	2-17 years	999	590	1808
	Adults [a]	1110	724	1956
MRT [h]	2-17 years	1.94	1.24	2.99
	Adults	2.43	1.87	4.08

a Adult AUC estimated for patients receiving 0.1 mmol/kg BW dose

In addition to body-weight-normalized CL and V_{ss}, the median systemic exposure (AUC) was similar between adults and pediatric patients as well as between the different age groups. Across all pediatric patients, a median AUC of 999 µmol*h/L at a dose of 0.1 mmol/kg BW was estimated which was about 11% less than the median AUC in adults (1110 µmol*h/L) suggesting a slight trend to lower systemic exposures in pediatric patients as compared to adults. The distribution of AUC values was greatly overlapping between pediatric patients and adults as shown by the 2.5th and 97.5th percentile distribution of 590 to 1808 µmol*h/L and 724 to 1956 µmol*h/L in children/adolescents and adults, respectively.

As the AUC is a parameter describing the total exposure of the patient to Gadobutrol following an intravenous injection and thus may be related to the overall safety profile, the trend to lower AUC values in children and adolescents as compared to adults is favorable.

In the pediatric population, Gadobutrol was cleared from plasma with an estimated median terminal half-life of 1.69 hours which is well in accordance with the half-lives determined and known in adults with normal renal function in the individual PK studies (mean 1.81 hours). The median mean residence time (MRT) of Gadobutrol in pediatrics was slightly reduced when compared to adults. Furthermore, comparable plasma concentrations at C_{20min} and C_{30min} post injection as a parameter that is associated to efficacy were simulated in pediatric patients and adults.

These comparative results show that the administration of the body-weight normalized adult standard dose of 0.1 mmol/kg BW to pediatric subjects aged 2 to 17 years results in similar gadolinium exposure and adequate plasma concentrations needed for efficacy. Thus, no dose adjustment in pediatric subjects is needed.

6.4. Drug-drug interaction potential

A metabolic drug interaction or an interaction involving an active transport process with a co-administered drug is unlikely for the following reasons:

- Gadobutrol is not metabolized
- Gadobutrol has negligible protein binding
- Gadobutrol is not actively excreted, but only passively via glomerular filtration. Thus, there should be no competition or interaction, and no saturation effect expected.

Therefore, no specific studies have been performed.

7. Efficacy (US development program)

Summary:

- The dose of 0.1 mmol/kg BW is well supported by a dose selection study and consistent with the standard dose for other marketed GBCAs for CNS imaging.
- Two adequate and well-controlled Phase-3 clinical trials met all primary and secondary endpoints and showed that Gadobutrol-enhanced images compared to unenhanced images are:
  - Superior in diagnostic performance
  - Superior for the lesion visualization variables contrast enhancement, border delineation and internal morphology
  - Non-inferior for the number of lesions detected
- In a Phase-3 study where ProHance (Gadoteridol) was the active comparator,
  - Gadobutrol was shown to be non-inferior to ProHance with respect to the lesion visualization variables contrast enhancement, border delineation and internal morphology, as well as number of lesions detected.
  - Gadobutrol was found to have higher sensitivity than ProHance for the detection of malignancies
  - Gadobutrol-enhanced images were consistently favored over ProHance-enhanced images by all 3 blinded readers.

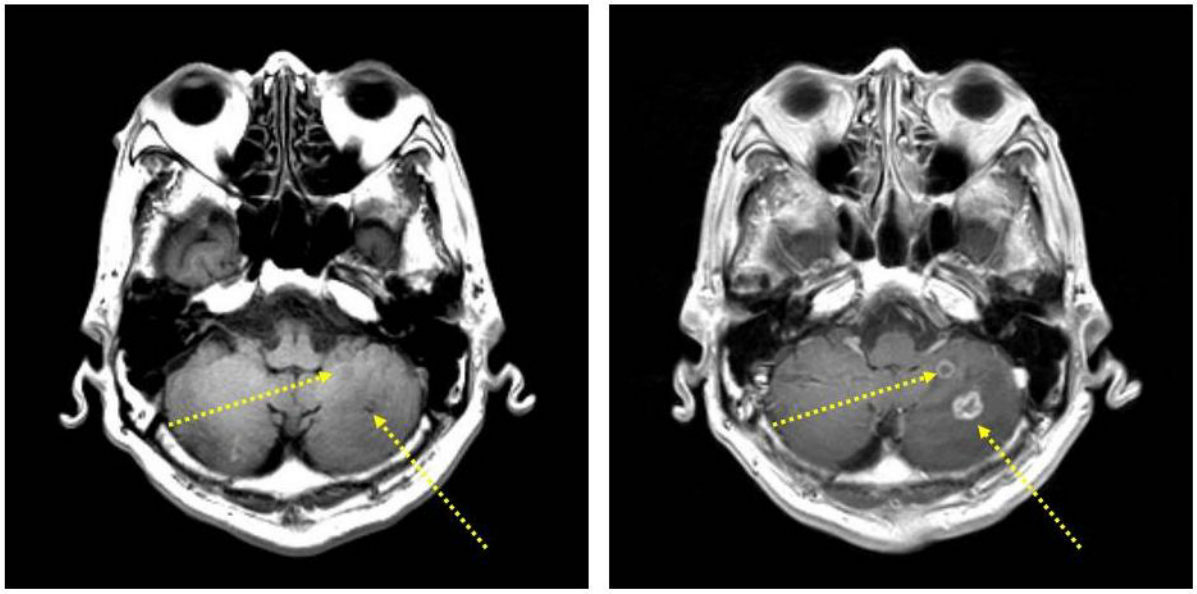
7.1. General aspects of CNS imaging

7.1.1. Diagnosing CNS lesions

Text Figure 4 shows a representative sample of a pair of images taken from the same patient: Examination of the unenhanced image notes the presence of two suspicious areas of decreased signal intensity in the left cerebellum. Without contrast enhancement, these lesions have the potential of being missed entirely, and establishing a diagnosis of a metastatic disease is far less certain.

In comparison, the contrast-enhanced image clearly shows two brightly enhancing lesions. The ring-like positive enhancement pattern observed in these lesions indicates that the lesions have vascular borders, and the lack of enhancement in the center of the lesions is indicative of central necrosis. These enhancement patterns are consistent with the pathophysiology of metastatic lesions.

The enhancement patterns seen in lesions following the administration of contrast is key to making a correct diagnosis and is why contrast-enhanced MR is the standard of practice for assessing CNS lesions.



Unenhanced **Gadobutrol-enhanced**

Text Figure 4 Sample image set of a patient with CNS lesions

Note: Non-identical slices. While the slice level in the cerebellum is very similar in both images, different angulation leads to more pronounced slice difference in the frontal aspects. Slices at different levels show similar patterns.

7.1.2. Image comparisons in clinical development

The clinical development of Gadobutrol for CNS imaging is consistent with the published guidance from the Food and Drug Administration (FDA): *Developing Medical Imaging Drug and Biological Products, Part 2: Clinical Indications, June 2004*.

At doses used in clinical practice, the extracellular contrast-agent Gadobutrol, like other approved gadolinium extracellular agents, has its largest effect on the T1 relaxation time. Therefore, this effect is best seen as high signal enhancement on T1-weighted MR pulse sequences. Unenhanced MRI provides useful diagnostic information using various imaging techniques including T1-weighting, T2-weighting, and fluid attenuated inversion recovery (FLAIR). Therefore, the impact of Gadobutrol-enhanced imaging is based on the comparison of the

- Unenhanced images [T1-weighted, T2-weighted, and FLAIR]
- Enhanced images [includes all of the unenhanced sequences as well as the contrast-enhanced T1-weighted sequence]

7.1.3. Prospective blinded image reading

To avoid potential investigator bias (i.e. knowledge of patient history or previous imaging results), the primary assessment of diagnostic efficacy for the Phase 2 and 3 CNS studies was based on the prospective evaluation of study images by independent blinded readers in a centralized manner.

For each study, the unenhanced and enhanced images were evaluated by three or more blinded readers. All blinded readers were independent, board-certified radiologists who were not involved in the conduct of the respective clinical study. They were blinded to all patient history and clinical information and did not have any information about the study center, the application of the contrast agent, or the study protocol. Images were shown randomly.

For each variable, the three readers' results were combined as follows:

- Average read
  (done for the numerical visualization variables defined in Section 7.3.3.3)
  Arithmetic mean of all three individual results
- Majority read
  (done for the categorical diagnostic variables defined in Section 7.3.2.3)
  Choice made by at least two of the three readers. If for an image set no majority read could be determined because all three readers disagreed with each other regarding their assessment, the image set was excluded from the respective analysis. This led to corresponding reductions of the sample size.

7.2. Dose selection (Study 308200, Phase 2)

Design of dose-selection study

The dose selection Study 308200 was conducted in 229 patients between 2005 and 2007 to evaluate three doses of Gadobutrol (0.03, 0.1 and 0.3 mmol/kg BW).

The study was designed as a multi-center, double-blind, randomized, controlled, parallel-group study with corresponding blinded image evaluations in male and female patients ≥ 18 years of age who were scheduled to undergo routine contrast-enhanced MRI of the CNS (due to e.g. known or highly suspected CNS disease).

Each patient underwent two contrast-enhanced MR imaging sessions: one imaging session with one of three randomized doses of Gadobutrol (0.03, 0.1 or 0.3 mmol/kg BW), and the other imaging session using OptiMARK as an active comparator approved for the indication.

The primary efficacy variables were the same for the whole Phase-2/3 program as specified in Section 7.3.2.2 below (i.e. contrast enhancement; border delineation; internal morphology; number of lesions).

Efficacy results

Regarding the comparison between the 0.1 mmol/kg BW (standard dose) and the 0.03 mmol/kg BW (low dose), a statistically significant difference in favor of the 0.1 mmol/kg dose was found for three of the four primary efficacy variables. No statistically significant difference was seen for the number of lesions detected. When comparing the 0.1 mmol/kg BW dose to the 0.3 mmol/kg BW (high dose), no statistically significant difference was found for any of the four primary efficacy variables.

Conclusions from dose-selection study

A dose of 0.1 mmol/kg BW was found to be well supported by this dose-selection study. This dose was chosen for the subsequent Phase-3 program.

7.3. Phase-3 program

The Phase-3 clinical development program comprised two adequate and well-controlled studies:

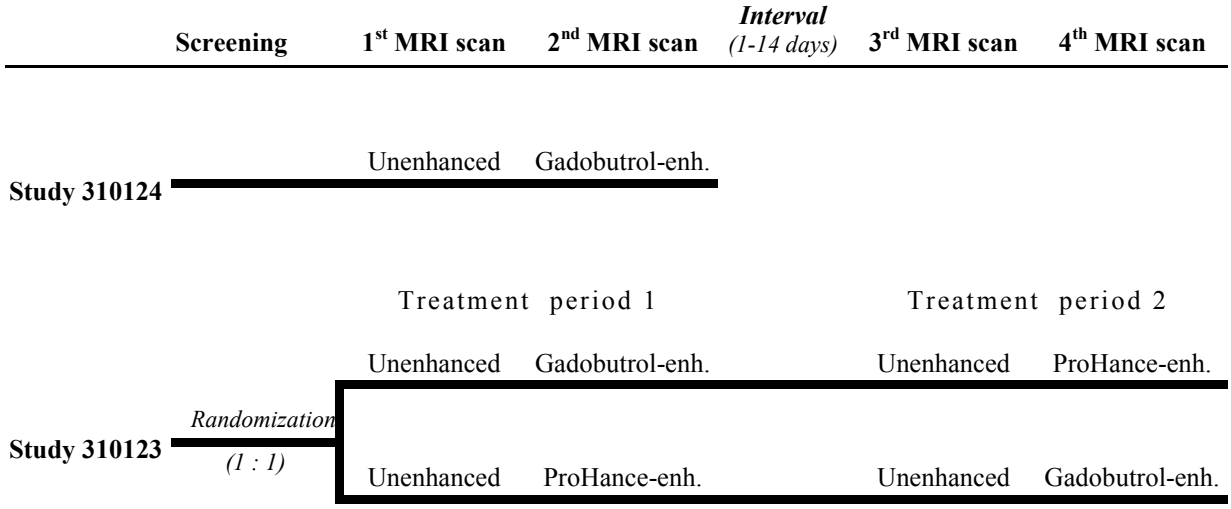
- Non-comparator study (Study 310124)
  This study addressed FDA guidelines requiring the demonstration of improvement of the diagnostic information obtained with the combined unenhanced and contrast-enhanced images over images obtained using the MRI device alone.
- Comparator study (Study 310123)
  This study, which also required the demonstration of improvement of the diagnostic information obtained with combined unenhanced and contrast-enhanced images over images obtained using the device alone, was also designed to demonstrate non-inferiority to an approved GBCA indicated for CNS imaging.

7.3.1. Special protocol assessment (SPA)

The protocol for Study 310123 was submitted to the US FDA for an SPA; through this process, a letter of concurrence was received prior to initiation of the study. This letter of concurrence confirms FDA's agreement that the design and statistical analysis plan of clinical study 310123 supports a CNS imaging indication for Gadobutrol. The efficacy analyses for the comparison of enhanced to unenhanced images that were agreed to as part of the SPA for Study 310123 were duplicated in the non-comparator Phase-3 Study 310124.

7.3.2. Design of the Phase-3 studies

The design of the two Phase-3 studies is depicted in Text Figure 5:



Text Figure 5 Phase-3 studies: Design overview
enh. = enhanced

7.3.2.1. Selection of the study population for the Phase-3 studies

For both Phase-3 studies, the inclusion and exclusion criteria were designed to best mirror the population of patients that would be likely to undergo a contrast-enhanced MRI of the CNS in routine clinical practice.

Patients were eligible for inclusion if they were referred for contrast-enhanced MRI of the CNS (brain or spine) based on symptomatology or previously completed diagnostic testing, i.e. patients in the Phase-3 program were not required to have known or highly suspected CNS disease.

7.3.2.2. Lesion visualization endpoints (primary efficacy variables)

For the clinical development program of Gadobutrol, four primary efficacy variables were chosen which are scored based on the unenhanced and enhanced image sets (see Section 7.1.2):

1. Lesion border delineation
2. Lesion contrast enhancement
3. Lesion internal morphology
4. Number of lesions detected

As prospectively agreed with the FDA, each primary efficacy variable was selected based on its relevance for diagnostic performance.

For each of the first three visualization variables, superiority was to be demonstrated for the enhanced image set compared with unenhanced imaging. The scoring code for these variables is provided in Text Table 5.

The fourth visualization variable (the number of lesions detected) was also prospectively defined. Since many CNS pathologies have few lesions which are often detectable on one or more of the unenhanced imaging sequences, non-inferiority was to be demonstrated for the enhanced image set compared with the unenhanced image set. In this instance, non-inferiority also helps to confirm the quality of the unenhanced image sets.

Non-inferiority of the number of lesions detected was assessed using confidence intervals based on the t-distribution, using a non-inferiority margin of 0.35 which had been agreed with the FDA. This means that a 95% 2-sided confidence interval for the mean difference Gadobutrol-enhanced score minus unenhanced score must have excluded the value -0.35 for non-inferiority to be achieved (that is, the lower limit of the confidence interval must be greater than -0.35). If the lower limit of the confidence interval was greater than 0, superiority was achieved. A one-sided test conducted at the 0.025 level of significance would be a statistically equivalent procedure.

Because patients in the Phase-3 program were not required to have known or highly suspected CNS disease, there was a greater likelihood to enroll patients with no CNS lesions. Because primary efficacy was based on lesion visualization scores, patients with no lesions would be left out of the primary efficacy analysis. For this reason, normal structures within the brain which enhance following the administration of gadolinium contrast (pineal gland, pituitary gland, choroid plexus, sagittal venous sinus) were also scored by the readers. Therefore, even if a patient had no pathologic lesions, they were included in the primary efficacy analysis on the basis of the scoring of the normal brain structures. The assessment of normal structures is described in Section 7.3.2.4.

7.3.2.3. Diagnostic performance endpoints (secondary efficacy variables)

In discussions with the FDA, which occurred at the end-of-Phase-2 meeting, improvement in diagnostic accuracy for the enhanced images compared to the unenhanced images was considered to be an important secondary efficacy requirement in the Phase-3 studies.

7.3.2.3.1. Standard of truth for diagnostic accuracy

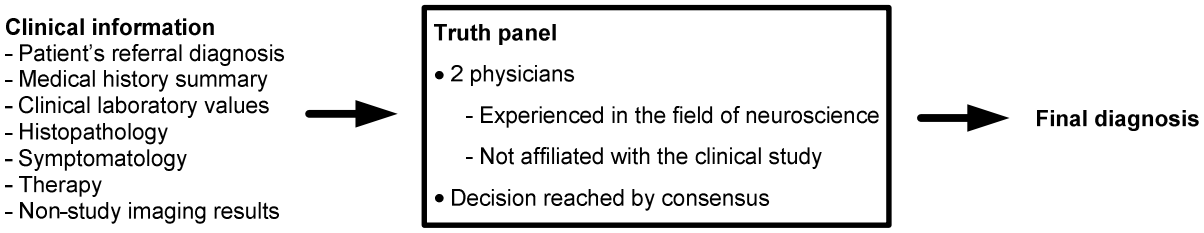
In order to calculate diagnostic variables such as sensitivity, specificity, and accuracy, a final clinical diagnosis, based on a defined standard of truth, is required.

Contrast-enhanced MR imaging is the non-invasive 'gold standard' for establishing a CNS diagnosis. Since contrast-enhanced MR imaging was the test whose performance was being assessed, it could not be utilized as both a comparator and a truth standard. Therefore, the study MR images could not contribute to the diagnostic information used to reach a final clinical diagnosis. This restriction has varied impact on the diagnostic accuracy. For example, a patient with a history of multiple sclerosis will likely have had previous MR imaging results which can be used as part of the diagnostic assessment because those MR results were not part of the study protocol. Patients with primary brain malignancy will often have histology results which confirm the diagnosis. For patients with new symptoms or who are being screened for metastatic brain disease, independent or alternative confirmation of the study MR findings might not be possible.

Despite these challenges, it was specified in the protocols that the final clinical diagnosis for each patient would be determined by one or more region/country-specific independent truth panels consisting of 2 experienced physicians in the neuroscience field not affiliated with the study, who reached a final diagnosis by consensus. All available patient-related information from their referral for contrast MRI to 3 months after the last study-related MRI procedure was collected. This may have included, but was not limited to:

- Pertinent information regarding the patient's referral for diagnosis
- Medical history summary (e.g. discharge summary)
- Clinical laboratory values
- Histopathology
- Symptomatology (better, worse, same, or new)
- Therapy (e.g. radiation, surgery, and medication)
- Imaging results from 3 months before study enrollment to 3 months after study enrollment.

As noted previously, the protocol required MR images could not be used by the truth panels for their assessment of a final clinical diagnosis. The process of establishing a final clinical diagnosis is shown below:



7.3.2.3.2. Determination of lesion malignancy (sensitivity, specificity)

The study protocols prospectively defined malignancy. The following diagnoses were defined as malignant:

- Anaplastic/malignant meningioma
- Glial tumor, low grade (II)
- Glial tumor, high grade (III/IV)
- Glial tumor, tumor grade cannot be determined
- Metastases
- Oligodendrogliomas grade III (anaplastic/malignant)
- Meningeal carcinomatosis
- Chordomas
- Primary lymphoma
- Other malignant lesions, specify

A majority reader diagnosis was determined for the enhanced and unenhanced image sets. The final clinical diagnosis as assessed by the independent truth panels was used as a comparative standard of truth.

7.3.2.3.3. Exact match diagnostic accuracy

The study protocols prospectively specified the following diagnoses of CNS lesions:

- Meningioma
- Anaplastic/malignant meningioma
- Glial tumor, low grade (I/II)
- Glial tumor, high grade (III/IV)
- Glial tumor, tumor grade cannot be determined
- Metastases
- Multiple sclerosis (acute and chronic)
- Optic neuritis
- Meningeal disease (focal enhancement)
- Pituitary adenomas (macro and micro)
- Craniopharyngiomas
- Tumors of the chroidal plexus
- Tumors of the pineal gland
- Meningeal carcinomatosis
- Oligodendrogliomas grade II
- Oligodendrogliomas grade III (anaplastic/malignant)
- Chordomas
- Primary lymphoma
- Dermoid/Epidermoid tumors
- Infectious disease (e.g. brain abscess, cisticercosis)
- Venous angiomas
- Meningeal spread of meningiomas (dural involvement)
- Cerebelopontine angle tumors
- Von Hippel Lindau syndrome
- Hypertensive leukoencephalopathy
- Subacute/chronic ischemia
- Encephalitis
- No lesion
- Others, specify
- Not assessable

Each of the three blinded readers provided a diagnosis for both the enhanced image set and the unenhanced image set. A majority-reader diagnosis was determined for the enhanced and unenhanced image sets. The majority-reader diagnosis was established if 2 or 3 of the blinded readers' diagnoses matched. Cases were excluded from analysis if no majority reader diagnosis could be determined.

The final clinical diagnosis as assessed by the independent truth panels (see Section 7.3.2.3.1) was used as a comparative standard of truth.

Readings assessed by the truth panel as "other" or "not assessable" were excluded from the exact-match diagnosis, which resulted in reduced sample sizes for this analysis.

For each of these analyses, a combined total of 104 patients (310124: 60; 310123: 44) were excluded due to standard of truth diagnoses of "not assessable" or "other."

7.3.2.3.4. Normal / abnormal brain tissue

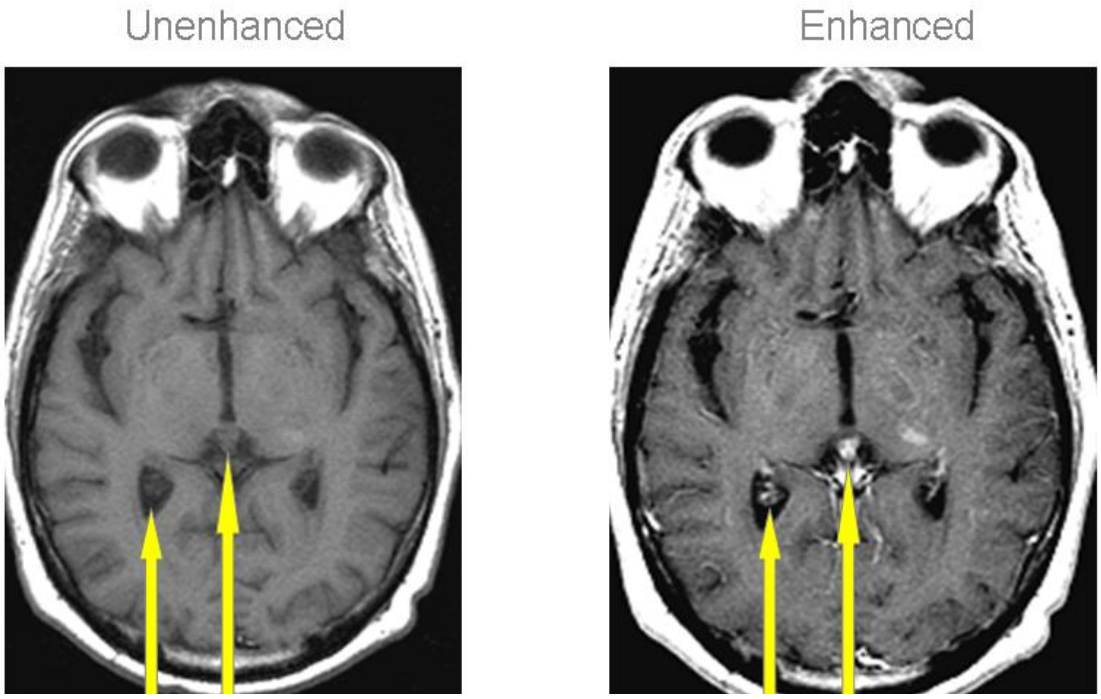
The blinded readers provided their assessments of whether the brain tissue was normal or abnormal based on T1-weighting pre-contrast and post-contrast images. These assessments were compared to the standard-of-truth diagnoses, and sensitivity, specificity, and accuracy measurements were calculated for each individual blinded reader and the majority read. For this measure, a truth panel diagnosis of 'no lesion' was considered normal, and any other diagnosis was considered abnormal.

7.3.2.4. Assessment of normal structures

The inclusion criteria for the pivotal Phase-3 studies permitted the enrollment of any patient referred for contrast-enhanced MRI. This differed from the Phase-2 study which required patients to have known or highly suspected CNS pathology. The primary efficacy analysis focused on lesion detection and improvement in lesion visualization. With the broadening of the inclusion criteria, it was expected that many patients without focal CNS pathology would be enrolled. Since these patients would not have pathologic lesions, they would not be included in the primary efficacy analysis. Clearly, contrast-enhanced MRI is an important non-invasive test in this population to rule out the presence of CNS pathology.

In order to include all patients in the primary efficacy analysis, areas of the normal brain that are not shielded by the BBB (i.e. they enhance following the administration of MR contrast), were scored as well. Four normal brain structures which fit this criterion were selected: (i) pineal gland, (ii) pituitary gland, (iii) choroidal plexus, (iv) sagittal venous sinus. Since the number of normal structures is the same on unenhanced and enhanced images, only the visualization variables (delineation, enhancement, and internal morphology) were scored (see Section 7.3.2.2 for details of the visualization variables).

A set of representative images highlighting two normal structures in an unenhanced and in a contrast-enhanced image is shown in Text Figure 6. The scoring system used for normal structures and lesions is shown in Text Table 5.



Text Figure 6 **Sample MRI images: Unenhanced versus enhanced**
Images from normal brain structures – Choroidal plexus and pineal gland
Note: Non-identical slices

Text Table 5 Scoring of primary visualization variables

Contrast enhancement

1 = No (lesion/normal structure is not enhanced)
2 = Moderate (lesion/normal structure is weakly enhanced)
3 = Good (lesion/normal structure is clearly enhanced)
4 = Excellent (lesion/normal structure is clearly and brightly enhanced)

Border delineation

1 = None (no or unclear delineation of the lesion/normal structure boundaries)
2 = Moderate (some border delineation of the lesion/normal structure)
3 = Good (almost clear but not complete delineation of the lesion/normal structure)
4 = Excellent (sharp and complete delineation of the lesion/normal structure)

Internal morphology

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

7.3.2.5. Choice of active comparator

During discussions of the Phase-3 study designs, FDA also agreed that one of the two Phase-3 studies (310123) would require the demonstration of non-inferiority for the 4 visualization parameters versus an active comparator approved by the FDA for CNS imaging. Knowing that the stability of the gadolinium chelate may play a role in an agent's relative risk for producing NSF, ProHance was selected because both Gadobutrol and ProHance are chemically similar macrocyclic gadolinium chelates (see Section 3).

7.3.3. Results of Phase-3 studies

7.3.3.1. Study population

Patient disposition

The patient disposition for both Phase-3 studies is summarized in Text Table 6. A combined total of 742 patients received Gadobutrol.

Text Table 6 Patient disposition Phase 3

	Comparator study **310123**	Non-comparator study **310124**	**Total**
Screened	419	347	766
Treated with Gadobutrol	399	343	742
Completed	380	336	716
Full analysis set (for efficacy analysis)	336	321	657

Among the 742 patients treated with Gadobutrol in the two pivotal Phase-3 studies, a combined total of 657 of were eligible for efficacy evaluation.

The first patient enrolled at each study site was considered a 'sample' patient. The images of these patients were evaluated by an independent consultant to insure image quality and compliance with the protocol imaging guidelines. Once a site was confirmed to be in compliance with the imaging guidelines, they were notified that they could begin enrolling additional patients. The 73 'sample' patients (310124: 22; 310123: 51) were included in the safety analysis but not included in the efficacy analysis. The number of 'sample' patients mostly accounts for the difference in the number of Gadobutrol-treated patients in the safety analysis population compared to the efficacy analysis population. In Study 310123, patients who did not receive both treatments (Gadobutrol and ProHance) were also excluded from the efficacy analysis population.

Demographics

Despite some inter-study differences with regard to racial and geographical origin of the patients as described below, adequate comparability of the studies can be concluded with regard to their patients' demography (Text Table 7).

In both Phase-3 studies, more females than males were enrolled.

No patient was younger than 18 years. Most patients were between the age of 18 and 64 years.

Between the individual studies, some differences were seen with regard to the ethnical composition of their populations. This can be seen as a reflection of the geographical origin of the patients.

No relevant differences between the individual studies were seen with regard to the weight categories.

Text Table 7 Phase-3 studies: Demographics

Figures denote number (percentage) of patients - Full analysis set

		Comparator Study 310123	Non-comparator Study 310124
		336 (100.0%)	321 (100.0%)
Sex	Male	144 (42.9%)	135 (42.1%)
	Female	192 (57.1%)	186 (57.9%)
Age	18 to < 45 years	122 (36.3%)	139 (43.3%)
	45 to < 65 years	139 (41.4%)	136 (42.4%)
	65 to < 80 years	70 (20.8%)	44 (13.7%)
	≥ 80 years	5 (1.5%)	2 (0.6%)
Weight	< 60 kg	106 (31.5%)	99 (30.8%)
	60 kg to < 90 kg	163 (48.5%)	192 (59.8%)
	≥ 90 kg	67 (19.9%)	30 (9.3%)
Race	Caucasian	192 (57.1%)	61 (19.0%)
	Black	21 (6.3%)	8 (2.5%)
	Hispanic	25 (7.4%)	82 (25.5%)
	Asian	97 (28.9%)	152 (47.4%)
	Other*	1 (0.3%)	18 (5.6%)
Region	Europe	101 (30.1%)	0
	USA/Canada	107 (31.8%)	52 (16.2%)
	South/Central America	27 (8.0%)	119 (37.1%)
	Asia	94 (28.0%)	150 (46.7%)
	Australia	7 (2.1%)	0

* "Other" includes South American, Latino-American, Native American and Aborigine American

7.3.3.2. Diagnostic performance endpoints

Because all primary endpoints for lesion visualization were met (see Section 7.3.3.3), the presentation of the efficacy results starts with the most clinically important endpoints of diagnostic performance. The diagnostic performance endpoints are based on a majority reader diagnosis. The majority reader diagnosis is based on the agreement of 2 or 3 of the blinded readers.

7.3.3.2.1. Exact match diagnosis

As described in Section 7.3.2.3.3, an exact match analysis was performed for the enhanced and unenhanced image set using the majority reader diagnoses compared to the truth panel diagnosis.

The most frequent truth panel diagnoses (≥ 3% in either study) determined for each of the Phase-3 studies are listed in Text Table 8:

Text Table 8 Phase-3 studies: Diagnosis

Figures denote number of patients for truth panel diagnoses - Full analysis set

	Study 310124 (n=321)	**Study 310123** (n=336)
Metastasis	21	54
Meningioma	48	36
Glial tumor, high grade	18	21
Glial tumor (any grade)	31	29
Multiple sclerosis	32	45
Pituitary adenoma	20	11
Subacute/chronic ischemia	5	13
No lesion	51	78

Unenhanced versus Gadobutrol-enhanced (both Phase-3 studies)

The results were very consistent across both Phase-3 studies. The accuracy for the Gadobutrol-enhanced image was significantly improved relative to the unenhanced set. Considering that there were more than 30 possible diagnoses available for matching and that the truth panel diagnosis did not always have MR image results available (see Section 7.3.2.3.1) for establishing a diagnosis, this is a clinically meaningful improvement.

Text Table 9: Accuracy of diagnosis: Unenhanced versus Gadobutrol-enhanced

Blinded readers' Full Analysis Set for non-comparator Study 310124 and comparator Study 310123

		N	Unenhanced	Gadobutrol-Enhanced	Difference	95% CI limits Lower	95% CI limits Upper	P-value
310124 (non- comparator)	Reader 1	261	48.3%	54.0%	5.7%	0.5%	11.0%	0.0321
	Reader 2	261	44.1%	52.1%	8.0%	2.6%	13.5%	0.0046
	Reader 3	261	47.1%	54.0%	6.9%	1.8%	12.0%	0.0094
	Majority	**224**	**51.8%**	**61.2%**	**9.4%**	**4.7%**	**14.1%**	**0.0002**
310123 (comparator)	Reader 1	292	51.7%	56.2%	4.5%	-0.5%	9.4%	0.0796
	Reader 2	292	43.5%	49.0%	5.5%	0.2%	10.7%	0.0422
	Reader 3	292	45.9%	54.5%	8.6%	3.8%	13.3%	0.0006
	Majority	**225**	**58.2%**	**64.4%**	**6.2%**	**1.7%**	**10.8%**	**0.0082**

See Section 7.1.3 and 7.3.2.3.3 for explanation of reduced sample sizes.
CI = confidence interval

Gadobutrol-enhanced versus ProHance-enhanced (comparator Study 310123)

All 3 blinded readers demonstrated very similar accuracy of diagnosis for both contrast agents (Text Table 10). Using the pre-specified and FDA-agreed non-inferiority margin of -10%, non-inferiority of Gadobutrol to ProHance was demonstrated for all three readers and the majority reader.

Text Table 10: Accuracy of diagnosis: Gadobutrol-enhanced versus ProHance-enhanced

Blinded readers' Full Analysis Set for comparator Study 310123

	N	Gadobutrol-enhanced	ProHance-enhanced	Difference	95% CI limits Lower	95% CI limits Limit
Reader 1	292	56.2%	58.6%	-2.4%	-6.7%	1.9%
Reader 2	292	49.0%	47.3%	1.7%	-3.4%	6.8%
Reader 3	292	54.5%	53.1%	1.4%	-2.4%	5.2%
Majority	**229**	**65.1%**	**65.5%**	**-0.4%**	**-3.8%**	**2.9%**

See Section 7.1.3 and 7.3.2.3.3 for explanation of reduced sample sizes.
CI = confidence interval

7.3.3.2.2. Determination of malignancy

As described in Section 7.3.2.3.1, the CNS diagnoses were prospectively grouped as malignant or not malignant. Malignancy was considered disease positive for calculating sensitivity. As a pre-specified secondary variable, the diagnostic statistics sensitivity, specificity, and accuracy were calculated for the Gadobutrol-enhanced (plus unenhanced) image set and the unenhanced image set only using the majority reader diagnoses compared to the truth panel diagnosis.

Unenhanced versus Gadobutrol-enhanced (both Phase-3 studies)

The results were very consistent across both Phase-3 studies. Accuracy and sensitivity for the Gadobutrol-enhanced image set was significantly improved compared to the unenhanced image set (Text Table 10). Specificity was high (> 90%) for both image sets. Therefore, the significant and clinically meaningful improvement in sensitivity and accuracy was not accompanied by any reduction in specificity.

Text Table 11: **Determination of malignancy: Unenhanced versus Gadobutrol-enhanced**

Blinded readers' Full Analysis Set for non-comparator Study 310124 and comparator Study 310123

			N	Unenhanced	Gadobutrol-Enhanced	Difference	95% CI limits Lower	Upper	P-value
Sensitivity	**310124** (non-comparator)	Reader 1	63	57.1%	73.0%	15.9%	5.8%	25.9%	0.0039
		Reader 2	63	65.1%	81.0%	15.9%	3.3%	28.5%	0.0184
		Reader 3	63	65.1%	81.0%	15.9%	6.8%	24.9%	0.0016
		Majority	**63**	**57.1%**	**77.8%**	**20.6%**	**10.6%**	**30.6%**	**0.0003**
	310123 (comparator)	Reader 1	93	51.6%	63.4%	11.8%	1.1%	22.5%	0.0343
		Reader 2	93	50.5%	67.7%	17.2%	7.0%	27.4%	0.0017
		Reader 3	93	48.4%	65.6%	17.2%	7.5%	26.9%	0.0011
		Majority	**93**	**47.3%**	**66.7%**	**19.4%**	**9.4%**	**29.4%**	**0.0004**
Specificity	**310124** (non-comparator)	Reader 1	198	92.9%	91.9%	-1.0%	-4.7%	2.7%	0.5930
		Reader 2	198	86.9%	86.4%	-0.5%	-5.0%	4.0%	0.8273
		Reader 3	198	89.9%	88.9%	-1.0%	-5.0%	2.9%	0.6171
		Majority	**198**	**90.4%**	**90.4%**	**0.0%**	**-3.4%**	**3.4%**	**1.0000**
	310123 (comparator)	Reader 1	199	97.5%	98.0%	0.5%	-1.7%	2.7%	0.6547
		Reader 2	199	91.0%	94.5%	3.5%	-1.0%	8.0%	0.1266
		Reader 3	199	96.5%	96.5%	0.0%	-2.0%	2.0%	1.0000
		Majority	**199**	**97.0%**	**97.5%**	**0.5%**	**-1.7%**	**2.7%**	**0.6547**
Accuracy	**310124** (non-comparator)	Reader 1	261	84.3%	87.4%	3.1%	-0.7%	6.9%	0.1167
		Reader 2	261	81.6%	85.1%	3.4%	-1.2%	8.1%	0.1495
		Reader 3	261	83.9%	87.0%	3.1%	-0.7%	6.9%	0.1167
		Majority	**261**	**82.4%**	**87.4%**	**5.0%**	**1.3%**	**8.7%**	**0.0093**
	310123 (comparator)	Reader 1	292	82.9%	87.0%	4.1%	0.3%	7.9%	0.0339
		Reader 2	292	78.1%	86.0%	7.9%	3.4%	12.4%	0.0008
		Reader 3	292	81.2%	86.6%	5.5%	2.0%	9.0%	0.0025
		Majority	**292**	**81.2%**	**87.7%**	**6.5%**	**2.8%**	**10.2%**	**0.0006**

See Section 7.1.3 and 7.3.2.3.3 for explanation of reduced sample sizes.

CI = confidence interval

Gadobutrol-enhanced versus ProHance-enhanced (comparator Study 310123)

For the majority reader, Gadobutrol demonstrated higher sensitivity (nominal p-value = 0.014) and accuracy (nominal p value = 0.034) versus ProHance without a decrease in specificity (Text Table 12). In addition, non-inferiority of Gadobutrol to ProHance was demonstrated for all three measures for all three readers and the majority reader.

Text Table 12 Determination of malignancy: Gadobutrol-enhanced versus ProHance-enhanced

Blinded readers' Full Analysis Set for comparator Study 310123

		N	Gadobutrol-enhanced	ProHance-enhanced	Difference	95% CI limits Lower	Upper
Sensitivity	Reader 1	93	63.4%	61.3%	2.2%	-5.1%	9.4%
	Reader 2	93	67.7%	59.1%	8.6%	0.4%	16.8%
	Reader 3	93	65.6%	64.5%	1.1%	-5.2%	7.4%
	Majority	**93**	**66.7%**	**60.2%**	**6.5%**	**1.5%**	**11.4%**
Specificity	Reader 1	199	98.0%	97.5%	0.5%	-1.2%	2.2%
	Reader 2	199	94.5%	95.0%	-0.5%	-3.8%	2.8%
	Reader 3	199	96.5%	96.5%	0.0%	-2.4%	2.4%
	Majority	**199**	**97.5%**	**97.5%**	**0.0%**	**-1.4%**	**1.4%**
Accuracy	Reader 1	292	87.0%	86.0%	1.0%	-1.6%	3.6%
	Reader 2	292	86.0%	83.6%	2.4%	-1.1%	5.9%
	Reader 3	292	86.6%	86.3%	0.3%	-2.3%	2.9%
	Majority	**292**	**87.7%**	**85.6%**	**2.1%**	**0.2%**	**3.9%**

See Section 7.1.3 and 7.3.2.3.3 for explanation of reduced sample sizes.
CI = confidence interval

7.3.3.2.3. Normal / abnormal brain tissue

As provided in Section 7.3.2.3.4, the blinded readers provided their assessments of whether the brain tissue was normal or abnormal.

For accuracy and sensitivity, statistically significant increases from unenhanced to enhanced were found for the majority read of both studies (accuracy: $p = 0.0002$ [310123], $p = 0.0285$ [310124]; sensitivity: $p < 0.0001$ [310123], $p = 0.0004$ [310124]).

For specificity, no statistically significant changes were seen.

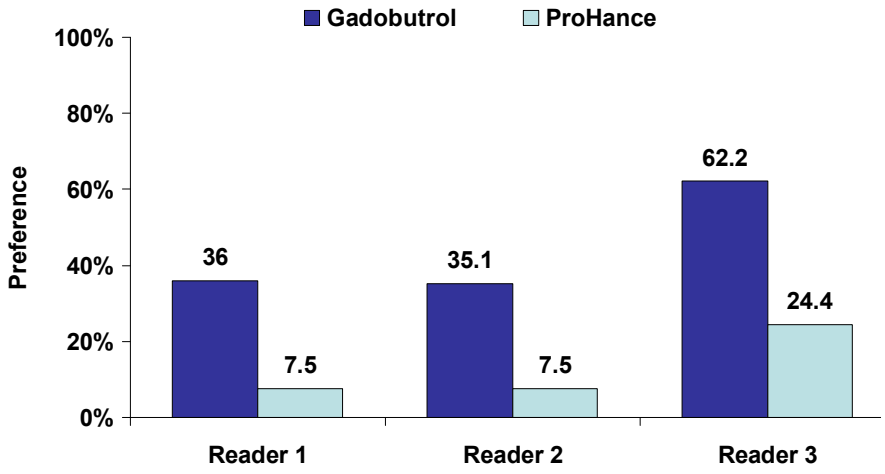
7.3.3.2.4. "Image quality": Gadobutrol-enhanced compared to ProHance-enhanced (Study 310123)

In an additional blinded reading session, 3 blinded readers viewed, in a randomized fashion, images for the same patient after enhancement with Gadobutrol, and after enhancement with ProHance, and provided their assessments of the relative quality of the images. This was done using a 5-point scale ranging from -2 (Gadobutrol image was worse), to 2 (Gadobutrol image was better). A score of 0 indicated the 2 images were of equal quality.

The mean scores for this scale ranged from 0.33 to 0.53 for the 3 readers, and in each case these values were statistically significantly different from 0 ($P<0.0001$ for each

reader). This finding indicates that these readers found the Gadobutrol images to be of significantly higher quality than the ProHance images.

Text Figure 7 compares the readers' preferences for either of the two agents.



Text Figure 7 Image quality: Gadobutrol versus ProHance

The comparison of Gadobutrol's performance to that of ProHance demonstrated statistically meaningful increases in both diagnostic accuracy and image preference. These differences are most likely attributable to Gadobutrol's higher relaxivity.

7.3.3.3. Lesion visualization variables (primary endpoints)

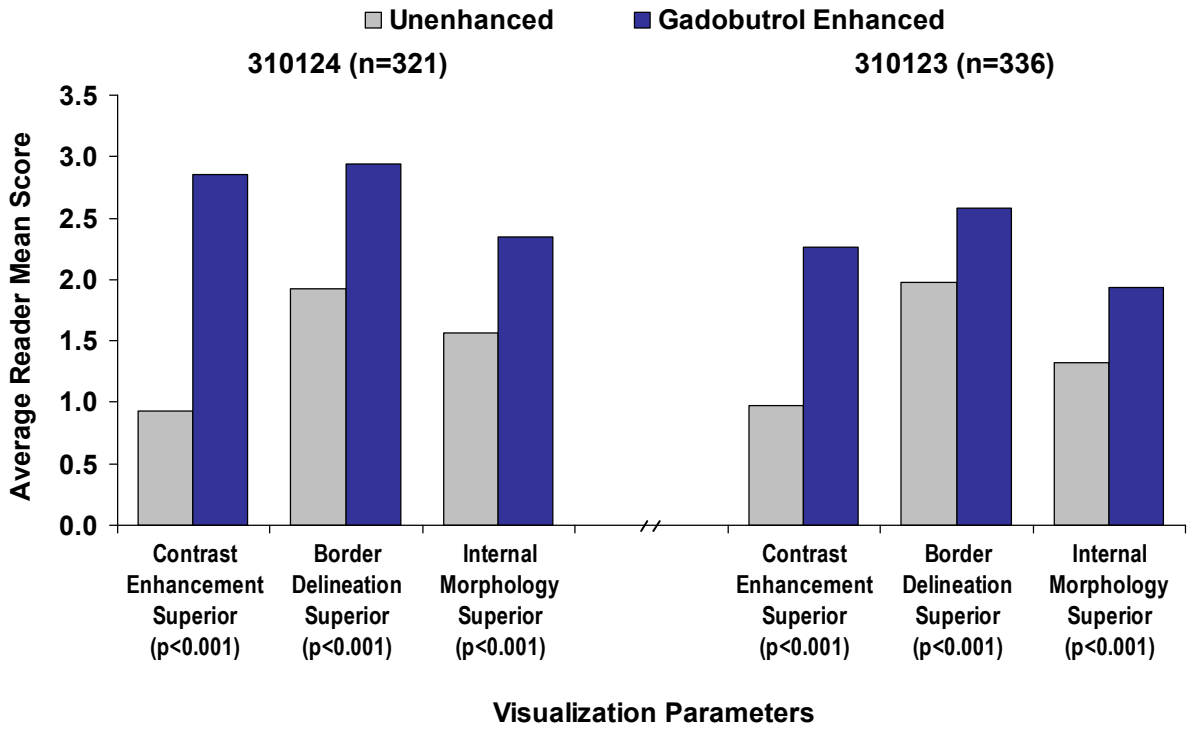
Summary:

- Consistently across both Phase-3 studies, all four primary efficacy objectives for the comparison unenhanced images compared to Gadobutrol-enhanced images were met:
  - Superiority for enhanced images over unenhanced images was demonstrated for
    - Lesion contrast enhancement
    - Lesion border delineation
    - Lesion internal morphology
  - This superiority was achieved without compromising lesion detectability as demonstrated by the non-inferiority of enhanced images compared to unenhanced with regard to number of lesions.

7.3.3.3.1. Lesion visualization variables: Unenhanced compared to Gadobutrol-enhanced (both Phase-3 studies)

Superiority for contrast enhancement, border delineation and internal morphology

Text Figure 8 summarizes the results for the primary efficacy objectives of lesion contrast enhancement, lesion border delineation and lesion internal morphology. For both Phase-3 studies, Gadobutrol-enhanced images were shown to be superior over unenhanced images. This superiority was statistically significant (all $p < 0.001$).



Text Figure 8: Visualization parameters from pivotal Phase-3 studies (unenhanced versus enhanced)

Average reader results (= mean of the 3 individual blinded readers) for non-comparator study 310124 (left panel) and comparator study 310123 (right panel).

Non-inferiority for number of lesions

Text Table 13 summarizes the results for number of lesions.

In both studies, there was a very high level of variability across the 3 readers for this endpoint.

Despite this high variability, non-inferiority for Study 310124 could be statistically demonstrated, based on the average reader mean results using the pre-specified parametric methods.

For Study 310123, this variability was higher than anticipated. As a result, based on parametric methods, the pre-defined non-inferiority margin of 0.35 was just missed. However, the protocol and statistical analysis plan specified that, if the planned parametric tests were not considered appropriate based on the observed data, non-parametric tests would be provided as well. In the non-parametric analysis, the lesion counts were replaced by a categorical variable. This variable contained the value of which modality had a higher number of lesions – "equal" (no difference between modalities), "unenhanced", or "Gadobutrol-enhanced". Using the non-inferiority margin of -10%, which was pre-specified as the non-inferiority margin for the categorical variables, non-inferiority of Gadobutrol was demonstrated for all three blinded readers.

Consequently, for both Phase-3 studies, Gadobutrol-enhanced images were shown to be non-inferior relative to unenhanced images.

Text Table 13: Number of lesion from pivotal Phase-3 studies (unenhanced versus enhanced)

Average reader results (= mean of the 3 individual blinded readers) Full Analysis Set

	Number of lesions	
	Unenhanced	**Gadobutrol-enhanced**
Non-comparator study (310124) n = 321 patients	2.65	2.97
Comparator study (310123) n = 336 patients	8.08	8.24

7.3.3.3.2. Results for active comparator ProHance (Study 310123)

Lesion visualization results for ProHance (Study 310123)

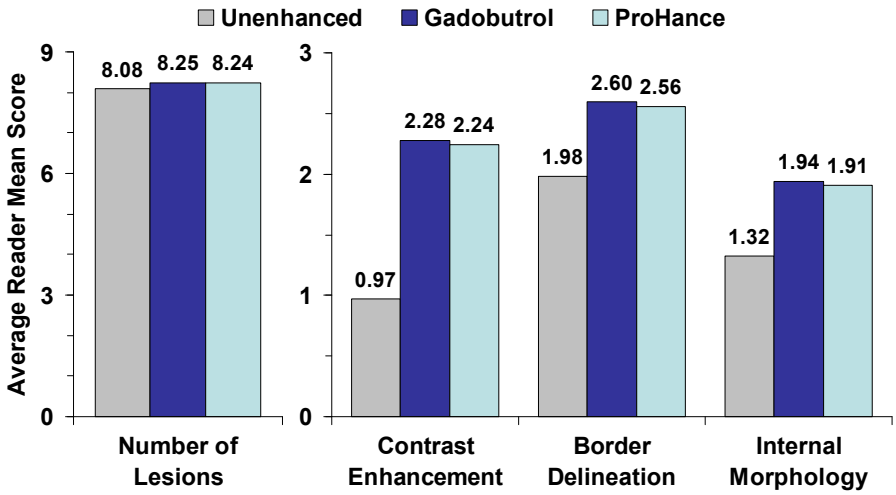
As presented in Section 7.3.2.3, the comparator study included the marketed extracellular MR contrast agent ProHance. The same primary efficacy analysis used for Gadobutrol was also performed for ProHance. For the average blinded reader, non-inferiority was demonstrated for the number of lesions as well as superiority for the other three visualization endpoints. Therefore, ProHance met the primary efficacy criteria for success.

Since the demonstration of non-inferiority of Gadobutrol relative to ProHance was a requirement for the comparator study, it is important to note that both agents achieved the prospective primary efficacy criteria.

This shows that the study design was suitable to demonstrate the visualization advantages of contrast agents. Thus, the non-inferiority results for the comparison Gadobutrol versus ProHance as presented in Section 7.3.3.3.1 are meaningful.

Lesion visualization variables: Gadobutrol-enhanced compared to ProHance-enhanced (Study 310123)

As depicted in Text Figure 9, both drugs revealed similar results on the primary endpoints. Non-inferiority of Gadobutrol-enhanced images relative to ProHance-enhanced images was statistically demonstrated for all lesion visualization variables.



Text Figure 9: Lesion visualization variables: Gadobutrol-enhanced compared to ProHance-enhanced (Study 310123)

For all lesion visualization endpoints, Gadobutrol had numerically higher mean values. The lesion visualization endpoints of contrast enhancement, border delineation, and internal morphology were a combination of the scores for lesions and normal structures.

The relaxivity difference is also the most plausible reason for the improvement in sensitivity and accuracy for the determination of malignancy of Gadobutrol versus ProHance. As had been noted previously, the lesion visualization scores (contrast enhancement, border delineation, and internal morphology) are a composite of scores for (i) lesions and (ii) normal brain structures. When the scores for lesions are examined separately, Gadobutrol scores are higher for all three variables with a nominal p-value of

0.045 for the improvement for the lesion's internal morphology (Text Table 14). As these visualization endpoints impact the correct characterization of pathology, the improvement in sensitivity and accuracy is consistent with this finding.

Text Table 14 Visualization endpoints for lesions only: Gadobutrol-enhanced versus ProHance-enhanced

Average blinded readers' Full Analysis Set for comparator Study 310123

	N	Gadobutrol enhanced	ProHance enhanced	Difference	95% CI limits Lower	Upper	Nominal p-value	Non-inferiority achieved
Contrast enhancement	289	1.65	1.58	0.07	-0.009	0.151	0.0828	yes
Border delineation	289	2.29	2.22	0.07	-0.030	0.177	0.1639	yes
Internal morphology	289	1.68	1.59	0.08	0.002	0.163	0.0450	yes

CI = confidence interval

7.3.3.4. Subgroup analyses

In order to demonstrate that the efficacy of Gadobutrol for CNS imaging was not adversely effected by demographic or disease groups, several subgroup analyses were performed on the primary efficacy variables. The demographic subgroup analyses utilized pooled results from the two Phase-3 studies as well as the 0.1 mmol/kg BW dose group of the Phase-2 dose selection study.

7.3.3.4.1. Demographic subgroups

For the demographic subgroups (age, gender, and race), there were no clinically relevant differences in efficacy based on age, gender, or race.

7.3.3.4.2. Disease subgroups

Two disease-based criteria were used for subgroup analyses:

- Malignancy (absent – present)
- Primary brain tumor (absent – present)

As was seen with the demographic subgroups, no clinically relevant differences in efficacy were noted based on disease subgroups.

7.4. Efficacy conclusions

The efficacy of Gadobutrol in MRI of the CNS has been demonstrated in two adequate and well-controlled Phase-3 studies. All prospectively defined primary and important secondary efficacy analyses were positive and support the effectiveness of Gadobutrol at a standard dose of 0.1 mmol/kg BW.

In the comparison of Gadobutrol to the approved GBCA ProHance, non-inferiority was demonstrated for all endpoints. The higher relaxivity of Gadobutrol compared to ProHance contributed to advantages in both overall image quality and diagnostic performance in Study 310123.

8. Safety

Summary:

- During a large Phase-2 to 4 clinical development program (total of 4549 patients), the safety profile of Gadobutrol has been well characterized.
- No clinically relevant differences in the type, intensity or incidence of adverse events (AEs) were seen between the dose groups (which included doses as high as 0.51 mmol/kg BW).
- The most frequently reported adverse drug reactions were headache (1.5% of the patients) and nausea (1.2%).
- Serious AEs (including fatal) were observed in 17 (0.4%) of 4549 patients in the Gadobutrol group, which was a similar proportion as seen in the other treatment groups. Only one of the 17 serious AEs reported in the Gadobutrol group was considered drug-related by the investigator (crystals in urine 1 day after injection).
- During the entire clinical development program of Gadobutrol, no cases of NSF or NSF-like symptoms have been reported.
- The results of a pediatric study in children 2 to 17 years were consistent with the known safety profile of Gadobutrol as obtained in adult patients.
- The post-marketing safety data in 6.1 million administrations are consistent with the known safety profile of Gadobutrol as obtained during clinical trials. Rare reports of serious anaphylactoid reactions, including fatalities, are also in line with the safety experience gained from similar contrast agents. Reports of NSF or NSF-like symptoms have been received by Bayer very rarely and are discussed in Section 9.6.2.

8.1. Clinical trials

The evaluation of the clinical safety of Gadobutrol is based on a total of 43 clinical studies:

Phase 1: 9 studies which dosed 313 healthy volunteers with Gadobutrol

Phase 2 to 4: 34 studies which dosed 4549 patients with Gadobutrol

The evaluation of the clinical safety of Gadobutrol in this document is based on data from the 4549 patients (4411 adults and 138 children aged 2 to 17 years) who received at least one dose of Gadobutrol in 34 Phase-2 to 4 controlled clinical trials.

The present application for CNS imaging is based on 2 Phase-3 trials using a dose of 0.1 mmol/kg BW with an intravenous administration rate of about 2 mL/sec via a power injector.

The safety data summarized includes adverse events (AEs), clinical laboratory assays, vital signs, physical examinations, and electrocardiography evaluations. Consistent with common practice for the safety assessments of single-administration contrast agents, the post-administration follow-up period for the Phase-3 studies extended to 72 hours post GBCA administration.

8.1.1. Methods for safety analyses

8.1.1.1. Data pool used for the integrated analyses of safety

In support of a safety profile for the use of Gadobutrol in contrast-enhanced MRI, all clinical Phase-2 to 4 studies were pooled into one integrated analysis pools (Text Table 15).

This pool included 34 Phase-2 to 4 studies with 5545 patients referred (by a physician) for a CE-MRI based on clinical symptoms or based on a previous imaging procedure. Of the 5545 patients enrolled, 4549 patients were treated with Gadobutrol. Due to the cross-over design, patients from Studies 308200, 309762, 310123, and 310864 were analyzed by period and counted twice when they continued in the second period with another study drug. Patients from cross-over study 94383 were counted only once because different Gadobutrol doses were administered. Therefore, the total number of patient treatments analyzed was higher (6393) than the total number of patients enrolled (5545). The data pool includes:

- Twenty studies with a single Gadobutrol treatment arm,
- Nine parallel-group design studies either with different Gadobutrol doses or Gadobutrol and a comparator contrast agent, and
- Five crossover studies with either different Gadobutrol doses or Gadobutrol and a comparator contrast agent.

Text Table 15: Integrated data pool for safety analysis

Study phase		Studies	Patients treated	Patient treatments[1]
Gadobutrol	Phase 2	13	1326	1326
	Phase 3	20	3174	3174
	Phase 4	1	49	49
	Total	**34**	**4549**	**4549**
Gadobutrol **or comparators**	Phase 2	13	1333	1715
	Phase 3	20	4163	4629
	Phase 4	1	49	49
	Total	**34**	**5545**	**6393**

[1] Patients from crossover studies (studies 308200, 309762, 310123, 310864) were analyzed by period. Therefore, the number of analyzed patients (based on patient treatments) is higher than the number of enrolled patients.

8.1.1.2. Statistical methods for the integrated analyses of safety

All presented adverse events are treatment-emergent adverse events. Events were considered to be treatment emergent if they started between start of the injection and 72 hours after the injection or beginning of the next period, whichever occurred first.

The analysis is not stratified by indication because the use of Gadobutrol as a diagnostic contrast agent in any study (irrespective of its indication) will contribute to the safety data.

8.1.2. Exposure

The number of patient treatments with Gadobutrol by study, phase, and actual dose is presented in Text Table 16.

Among the 4549 patients, the majority (4122) received Gadobutrol at a dose between 0.09 and 0.31 mmol/kg BW. Most of them (2434 treatments; 53.5%) received the standard dose of 0.1 mmol/kg BW (± 0.01 mmol/kg BW), while 1735 (38.1%) patients received a higher dose.

In the 2 pivotal Phase-3 studies, the majority of patients received > 0.09 to 0.11 mmol/kg BW Gadobutrol.

Text Table 16: Patient treatments by phase and Gadobutrol dose

mmol / kg BW	≤0.09	>0.09-0.11	>0.11-0.21	>0.21-0.31	>0.31-0.51	Any dose
All phases	380 (100%)	2434 (100%)	679 (100%)	1009 (100%)	47 (100%)	4549 (100%)
Phase 2, n (%)	286 (75.3%)	259 (10.6%)	369 (54.3%)	373 (37.0%)	39 (83.0%)	1326 (29.1%)
Phase 3, n (%)	93 (24.5%)	2175 (89.4%)	269 (39.6%)	629 (62.3%)	8 (17.0%)	3174 (69.8%)
Phase 4, n (%)	1 (0.3%)	0	41 (6.0%)	7 (0.7%)	0	49 (1.1%)

During the course of its clinical development program, Gadobutrol has been dosed in clinical trials in formulations of 0.5 M and 1.0 M concentrations (see Section 4.1). Most patients had received Gadobutrol at the marketed concentration of 1.0 M (Text Table 17).

Text Table 17: Number of treated patients by Gadobutrol concentration

Molarity group	≤0.09	>0.09-0.11	>0.11-0.21	>0.21-0.31	>0.31-0.51	Total
Total	380	2434	679	1009	47	4549
0.5 M	24	634	42	300	2	1002
1.0 M	356	1800	637	709	45	3547

8.1.3. Drug-related adverse events

8.1.3.1. Analysis by concentration

No clinically relevant differences were seen between both concentration groups (0.5 M versus 1.0 M) with regard to the overall frequencies of drug-related adverse events (Text Table 18).

Text Table 18: Drug-related adverse events by Gadobutrol concentration and dose

Figures denote number (percentage) of patients

Dose group (mmol/kg BW)		≤0.09		>0.09-0.11		>0.11-0.21		>0.21-0.31		>0.31-0.51		Total	
0.5 M	No. of subjects	24	100.0%	634	100.0%	42	100.0%	300	100.0%	2	100.0%	1002	100.0%
	Drug-related AE	1	4.2%	15	2.4%	9	21.4%	14	4.7%	0		39	3.9%
1.0 M	No. of subjects	356	100.0%	1800	100.0%	637	100.0%	709	100.0%	45	100.0%	3547	100.0%
	Drug-related AE	16	4.5%	78	4.3%	18	2.8%	28	3.9%	3	6.7%	143	4.0%

AE = Adverse event

8.1.3.2. Analysis by dose

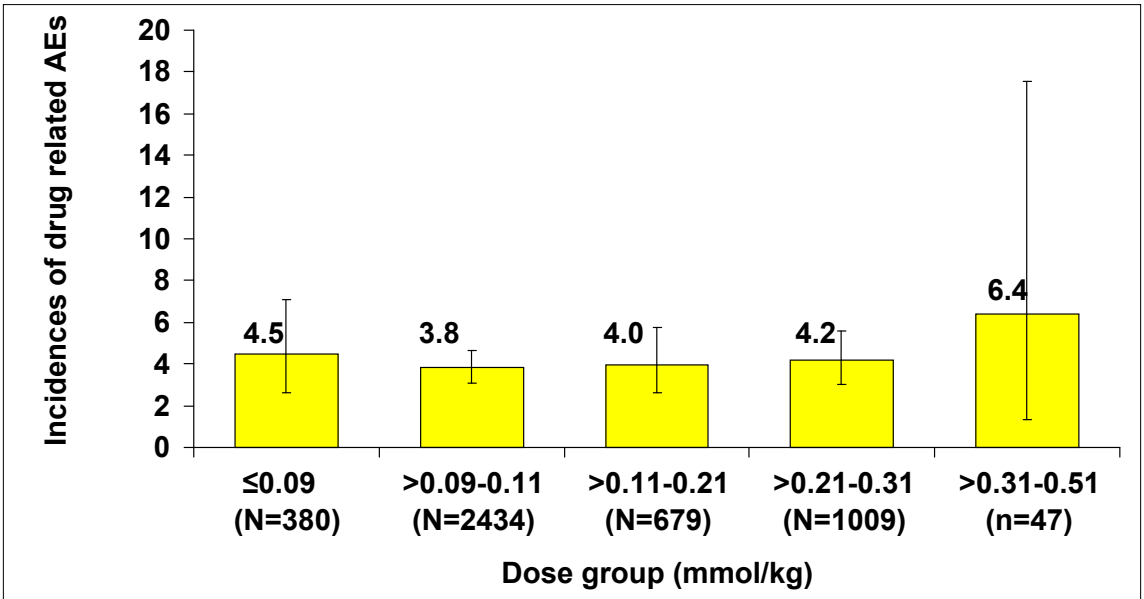
Text Table 19 provides an overview on the most frequent AEs (≥ 0.5% incidence) experienced in any Gadobutrol dose group. The most frequently recorded AEs were headache and nausea.

Text Table 19: Drug related adverse events with ≥ 0.5% incidence by Gadobutrol dose

		Gadobutrol				
	mmol/kg BW	**≤0.09**	**>0.09-0.11**	**>0.11-0.21**	**>0.21-0.31**	**>0.31-0.51**
Number of subjects		**380 (100%)**	**2434 (100%)**	**679 (100%)**	**1009 (100%)**	**47 (100%)**
Number of subjects with any drug related event		17 (4.5%)	93 (3.8%)	27 (4.0%)	42 (4.2%)	3 (6.4%)
Total number of events		72 (100.0%)	414 (100.0%)	111 (100.0%)	111 (100.0%)	8 (100.0%)
Number of drug related events		22 (30.6%)	125 (30.2%)	31 (27.9%)	58 (52.3%)	4 (50.0%)
	Gastrointestinal disorders					
	Dry mouth	0	2 (<0.1%)	0	0	1 (2.1%)
	Nausea	2 (0.5%)	24 (1.0%)	5 (0.7%)	3 (0.3%)	1 (2.1%)
General disorders and administration site conditions						
	Feeling hot	2 (0.5%)	4 (0.2%)	2 (0.3%)	12 (1.2%)	2 (4.3%)
Nervous system disorders						
	Dizziness	2 (0.5%)	3 (0.1%)	1 (0.1%)	1 (<0.1%)	0
	Dysgeusia	0	10 (0.4%)	5 (0.7%)	7 (0.7%)	0
	Headache	4 (1.1%)	8 (0.3%)	0	4 (0.4%)	0

AEs coded by Medical Dictionary for Regulatory Activities (MedDRA), Version 12.1

There was no evidence of a dose relationship which impacted patient safety at doses up to 0.51 mmol/kg BW evaluated in the Phase-2 to 4 clinical trials (Text Figure 10).



Text Figure 10: Frequencies of drug-related adverse events across different dose groups

8.1.3.3. Drug misadministration

The marketed GBCAs indicated for CNS imaging are all formulated at a 0.5 M concentration. As these agents have been marketed for many years, end users of GBCAs are quite familiar with a dosing volume of 0.2 mL/kg. Gadobutrol is formulated at a 1.0 M concentration and thus has a dosing volume of 0.1 mL/kg BW, or half the volume of the 0.5 M agents. In the two Phase-3 pivotal clinical trials, 7 of 742 (0.9%) patients were incorrectly administered a double dose (0.2 mL/kg) of Gadobutrol.

The double dosing was noticed in routine monitoring, and investigative sites were sent a reminder in two study newsletters noting the proper dosing for Gadobutrol. No other re-training or communication by the sponsor to the site was conducted and further dosing errors were not observed. The dosing of Gadobutrol at 0.2 mmol/kg in these 7 patients would not be expected, in general, to be a significant safety issue as Gadobutrol is approved in many countries at doses up to 0.3 mmol/kg. Indeed, none of these 7 patients experienced an adverse event associated with misadministration of study drug. However, the potential for an unintended administration of a double dose of Gadobutrol exists and a post-approval risk mitigation strategy is outlined Section 10.

8.1.3.4. Analysis by age / gender / race

Patients ranged in age from 2 to 93 years with a mean of 54.2 years. There were 1377 (30.3%) patients 65 years of age or older. Analyses of AEs based on age revealed no significant differences in incidence rates or severity.

Pediatric safety is discussed in Section 8.2.

Of the 4549 patients, 2663 (58.5%) were male. Analyses of AEs based on gender revealed no significant differences in incidence rates or severity.

The majority of patients were Caucasian (64.8%) followed by Asian (27.3%), other (3.6%), Hispanic (3.0%), and Black (1.3%). Analyses of AEs based on race revealed no significant differences in incidence rates or severity.

8.1.4. Deaths during clinical development

No death was reported in any of the 9 Phase-1 studies evaluated for this analysis.

Overall, there were 2 deaths in the Phase-2 to 4 studies, one each in the Gadobutrol and the ProHance treatment groups; neither was regarded as related to study medication. One additional patient died after the follow-up period of the study and is included for transparency.

- Patient 1211 / Study 95363, who received 0.3 mmol/kg Gadobutrol, died during the follow-up period; death was considered not related to Gadobutrol. The patient developed dyspnea and pleural effusion 5 days post injection and died 11 days after the injection. The investigator considered that the death was caused by the deterioration of primary disease (lung cancer).
- Patient 1506 / Study 310864, who received 0.1 + 0.1 mmol/kg ProHance, died during the follow-up period. The patient developed general physical health deterioration (MedDRA preferred term) 1 day after ProHance injection and died 4 days after the injection. The investigator considered that the patient died due to worsening of primary disease (breast cancer) and the death was not related to the study drug.
- Patient 100080002 / Study 310123 (with history of glioblastoma) in the ProHance:Gadobutrol treatment sequence died after the follow-up period of the study. The patient experienced mild nausea about 20 minutes after receiving ProHance, which resolved within an hour. This event was considered related to both study drug and study conduct. Approximately 26 hours after ProHance injection, the patient experienced a worsening of his condition and somnolence, considered not related. He received Gadobutrol, prematurely discontinued the study due to the persistence of the pre-existing events, and died 8 days after Gadobutrol injection. The death was attributed to progression of the underlying disease.

8.1.5. Serious adverse events

8.1.5.1. All serious adverse events

During the entire clinical development program of Gadobutrol, only isolated reports of serious adverse events were recorded. Overall, serious AEs (including fatal) were observed in 17 (0.4%) of 4549 patients treated with Gadobutrol group during Phase 2 or 3 (Text Table 20); no dose dependency could be seen. Only one of the 17 serious AEs reported in the Gadobutrol group was considered drug-related by the investigator (crystals in urine 1 day after injection).

One additional SAE was reported during Phase 1 (drug-related anaphylactoid reaction of moderate intensity recorded after administration of > 0.11 to 0.21 mmol/kg BW of 1.0 M Gadobutrol).

Text Table 20: Serious adverse events by dose (Phase 2 to 3)

Figures denote number/percentage of patients

Primary System Organ Class (SOC) / Preferred term	Gadobutrol dose (mmol/kg body weight)									
	<=0.09		>0.09-0.11		>0.11-0.21		>0.21-0.31		>0.31-0.51	
	N=380 100%		N=2434 100%		N=679 100%		N=1009 100%		N=47 100%	
Any event	2	0.5%	7	0.3%	5	0.7%	3	0.3%	0	
General disorders and administration site conditions	0		1	<0.1%	1	0.1%	0		0	
Pyrexia	0		1	<0.1%	1	0.1%	0		0	
Infections and infestations	1	0.3%	1	<0.1%	0		0		0	
Meningitis	0		1	<0.1%	0		0		0	
Pneumonia	1	0.3%	0		0		0		0	
Injury, poisoning and procedural complications	0		0		0		1	<0.1%	0	
Cerebral haemorrhage traumatic	0		0		0		1	<0.1%	0	
Injury	0		0		0		1	<0.1%	0	
Investigations	1	0.3%	0		0		0		0	
Crystal urine	1	0.3%	0		0		0		0	
Neoplasms benign, malignant and unspecified	0		1	<0.1%	0		0		0	
Metastases to central nervous system	0		1	<0.1%	0		0		0	
Nervous system disorders	1	0.3%	4	0.2%	5	0.7%	0		0	
Aphasia	0		0		1	0.1%	0		0	
Brain oedema	0		1	<0.1%	1	0.1%	0		0	
Cerebral infarction	0		0		1	0.1%	0		0	
Cerebrovascular accident	0		0		1	0.1%	0		0	
Haemorrhage intracranial	1	0.3%	0		1	0.1%	0		0	
Haemorrhagic transformation stroke	0		0		1	0.1%	0		0	
Hemiplegia	0		0		1	0.1%	0		0	
Hydrocephalus	0		1	<0.1%	0		0		0	
Intracranial pressure increased	0		1	<0.1%	0		0		0	
Neurological symptom	0		1	<0.1%	0		0		0	
Somnolence	0		0		1	0.1%	0		0	
Transient global amnesia	0		1	<0.1%	0		0		0	
Transient ischaemic attack	0		1	<0.1%	1	0.1%	0		0	
Respiratory, thoracic and mediastinal disorders	0		0		0		2	0.2%	0	
Dyspnoea	0		0		0		1	<0.1%	0	
Pleural effusion	0		0		0		1	<0.1%	0	
Respiratory arrest	0		0		0		1	<0.1%	0	
Vascular disorders	0		0		0		1	<0.1%	0	
Hypotension	0		0		0		1	<0.1%	0	

1 additional SAE was reported during Phase 1 (see text above).

8.1.5.2. Nephrogenic systemic fibrosis (NSF)

During the entire clinical development program of Gadobutrol, no cases of NSF or NSF-like symptoms have been reported.

Post-marketing information on NSF reports is provided in Section 9.6.2.

8.1.6. Adverse drug reactions

Overall, 4.0% of the 4549 patients reported one or more adverse drug reactions (ADRs) following Gadobutrol administration in the Phase-2 to 4 clinical trials. Among all of these studies, the patient follow-up time post Gadobutrol administration ranged from 24 hours up to 7 days.

The most frequent (≥ 0.5%) adverse reactions were headache, nausea, injection site reactions, dysgeusia, and feeling hot. Adverse reactions following Gadobutrol administration were usually mild to moderate in severity and transient in nature. ADRs occurring in ≥ 0.1% of patients following Gadobutrol administration are summarized in Text Table 21.

Text Table 21: Most frequent adverse drug reactions in Phase-2 to 4 trials

Reaction	Rate (%) n = 4549
Headache	1.5
Nausea	1.2
Injection site reaction (various kinds)	0.6
Dysgeusia	0.5
Feeling hot	0.5
Dizziness	0.4
Vomiting	0.4
Rash (includes generalized, macular, papular, pruritic)	0.3
Pruritis (includes generalized)	0.2
Erythema	0.2
Dyspnea	0.2
Parasthesia	0.1

Adverse drug reactions that occurred with a frequency of < 0.1 % in patients treated with Gadobutrol injection include: hypersensitivity/anaphylactoid reaction, loss of consciousness, convulsion, parosmia, tachycardia, palpitation, dry mouth, malaise and feeling cold.

8.1.7. Clinical laboratory and vital signs

In controlled clinical trials with Gadobutrol, laboratory analyses have been performed on a large percentage of the enrolled population. These investigations included assessments of hematology, serum chemistry, and urinalysis parameters. No remarkable changes from baseline were observed for these parameters. Therefore, laboratory evaluations are not necessary following Gadobutrol administration.

For vital sign parameters, no clinically significant trends or dose dependency were observed post-Gadobutrol injection. The mean values showed minimal fluctuations from pre-procedure at each time point post-injection. The changes observed in vital sign parameters can be attributed to underlying conditions (e.g. hypertension, anxiety).

8.1.8. Safety in Thorough QT Study

A thorough QTc study was performed with Gadobutrol against moxifloxacin as positive control and physiological saline solution as negative control (Study 307362; see Section 6.2). Gadobutrol had no clinically relevant effect on QT interval up to a dose of 0.5 mmol/kg BW administered as a bolus injection (2 mL/sec) using a power injector. There were no unusual or unexpected AEs with either Gadobutrol or moxifloxacin. In particular, there were no clinically relevant cardiovascular side effects with either drug.

8.2. Pediatrics

The safety of Gadobutrol in pediatric patients was investigated in a clinical pharmacology study involving 138 patients aged 2 to 17 years (see Section 6.3.2), and the safety results in pediatric patients were pooled with the adult population described in Section 8.1 above.

Overall, and consistent with the known safety profile of Gadobutrol as obtained in adult patients, Gadobutrol was well tolerated by the patients in this study. The safety population encompassed 138 patients, who had received a single injection of Gadobutrol at a dosage of 0.1 mmol/kg BW. Regarding the safety in children, the safety profile of Gadobutrol obtained in this study gave no indications for a different profile than known for adult patients.

A total of 74 AEs were recorded for 49 (35.5%) of the 138 patients. At least one drug-related AE occurred in 8 patients (5.7%). As assessed by the investigators, 10 of the 74 AEs were related to administration of Gadobutrol. Related AEs (preferred term) were dysgeusia (2 AEs), feeling hot (2 AEs), crystal urine, headache, nausea, rash, rash pruritic, and pruritus (1 AE each).

There were 3 SAEs (included in Text Table 20 above) recorded in 2 patients (1.4%), all with an outcome of recovered/resolved:

- 2 SAEs were reported for a 9-year old patient:
  - Crystal urine (serious and considered by the investigator to be drug-related), an alternative etiology for this event could have been the patient's concomitant medications (augmentin); and
  - Pneumonia, reported as mild but requiring hospitalization. The pneumonia was assessed as not related to study drug and the patient recovered completely.
- 1 SAE was reported for a 3-year old patient. This SAE was meningitis of moderate intensity requiring hospitalization, assessed to be unrelated to the study drug. The patient recovered completely.

No clinically relevant changes in laboratory or vital sign assessments were noted post Gadobutrol injection.

8.3. Post-marketing safety data

Based on global sales and marketing data (as of 31 October 2010), it is estimated that 6.1 million administrations of Gadobutrol have been given since it was first launched in Switzerland in 1999. Gadobutrol is currently authorized to be marketed in 65 countries and is marketed in 62 countries.

For routine post-marketing safety analysis, 5.9 million administrations were given through 30 September 2010. The adverse events received from spontaneous sources between launch and 30 September 2010 are consistent with the adverse events observed in clinical trials (see Section 8), and the known safety profile of Gadobutrol. A total of 1175 spontaneous case reports were received, the majority (858/1175) were non serious, and consisted of nausea, vomiting, urticaria, pruritus, erythema, rash, feeling hot, or malaise, in general well recognized reactions to occur with all GBCAs.

In worldwide post-marketing experience, isolated reports of inadvertent overdoses have been received. The Bayer Global Pharmacovigilance safety database contains 3 reports coded as "overdose". In these reports, the reported administered volumes were 35, 47 and 65 mL.

- In one report, a patient with concomitant peripheral arterial occlusive disease experienced renal pain, pallor, creatinine increased and suspicion of toxic pulmonary edema on the day of Gadobutrol administration. Baseline creatinine values and renal function were not reported. With the scarce data provided, this report was classified as not assessable.
- In the other 2 reports, "vagal faintness"; nausea/"feeling hot" were reported

Hypersensitivity/anaphylactoid reactions, consisting primarily of cutaneous, respiratory, and cardiovascular symptoms, have been infrequently reported with Gadobutrol and are recognized to occur in association with all GBCAs, including rare instances of life-threatening or fatal shock.

Fourteen cases have been reported with a fatal outcome, with the age ranging between 31 and 91 years; 9/14 were males, and 5/14 females. Patients had multiple confounding factors: diabetes and cardiovascular disease, with/without renal disease (N=4), cancer with/without metastasis (N=4), cardiovascular risk factors (N=3), chronic renal failure (N=1), severe condition due to coma (N=1), and not specified (N=1). Death was reported to occur ranging from on the same day up to 22 months after Gadobutrol administration. The causes of death were reported as anaphylaxis/anaphylactic shock (N=3), cardiac arrest (N=3), unknown (N=3), multiorgan failure (N=2), Staphylococcus aureus sepsis (N=1), liver failure as a complication of infection in blood (N=1), and pulmonary embolism (N=1).

Overall, the reporting rate of fatal events is similar to the safety experience observed with another GBCA, e.g. Magnevist, which is the GBCA with the largest safety experience. After the first 10 million applications of Magnevist, there were 23 fatal reports and after 20 million applications, 52 reports with fatal outcome were recorded in the spontaneous reporting data (Knopp et al. 2006).

Isolated reports of NSF or NSF-like symptoms have been reported for Gadobutrol. They are presented and discussed in Section 9.6.2.

Post-marketing observational studies

The positive benefit /risk profile of Gadobutrol has also been confirmed in a report of six prospective post-marketing observational studies including more than 14,000 patients (Forsting et al. 2010). The patient population mostly comprised elderly and adult patients. The body regions most frequently examined were head/neck/brain (54.3%), followed by spine (7.2%), pelvis/joints/limbs (6.7%) and multiple body regions (6.4%). Gadobutrol-enhanced magnetic resonance angiography (MRA) was performed in 14.7% of patients. Seventy-eight of the 14,299 patients (0.55%) reported at least one ADR. The most frequently reported ADR was nausea, which occurred in 36 patients (0.25%).

Two (0.01%) serious ADRs were reported: One patient had a severe anaphylactoid reaction and the other one presented with itching and swelling in the throat. This rate is again similar to the rate of acute allergic-like reactions found for another GBCA, e.g. Magnevist, which reported 10 moderate and 4 severe allergic reactions in an observational study of 78,000 patients (Dillmann et al. 2007).

In conclusion, Gadobutrol was shown to have a good safety and tolerability profile. The incidence of ADRs in observational studies was low (0.55%), and consistent with the low rates reported for other GBCAs, including Magnevist, Dotarem (gadoterate meglumine, a macrocyclic GBCA not marketed in the US), and MultiHance (as cited by Forsting et al. 2010) (Text Table 22).

Text Table 22: Adverse drug reactions reported from different GBCAs

	Gadobutrol n = 14,299	Magnevist n = 15,496	Dotarem n = 24,308	MultiHance n = 23,533
Mean dose (mmol/kg BW)	0.16	0.1	0.11	Not available
ADR[a]	Gadobutrol (*N* = 14,299) Rate (%)	Gadopentetate dimeglumine (*N* = 15,496) [16] Rate (%)	Gadoterate meglumine (*N* = 24,308) [18] Rate (%)	Gadobenate dimeglumine (*N* = 23,533) [19] Rate (%)
Overall rate	0.55	2.4	0.4	0.76
Nausea/vomiting	0.31	0.61	0.23	0.56
Heat/warmth	0.04		0.02	–
Headache	0.01	0.44	–	
Paraesthesia	0.01	0.17	0.02	0.004
Dizziness	0.02	0.19	–	
Focal convulsions	–	–	–	
Urticaria	0.08	0.07	0.02	0.15
Other allergic-like skin reactions	0.07	0.09	–	
Allergic-like mucosal reactions	0.07	–	–	
Flush/vasodilation	0.01	0.07	–	
Cardiovascular reactions	0.05	–	–	
Tachycardia, arrhythmia	0.04	–	–	
Other symptoms[b,c,d]	0.2	–	0.11	0.05

BW, body weight; ADR, adverse drug reaction.
[a] ADRs classified as possible.
[b] Other symptoms include not specified, oedema eyelid, agitation, unconsciousness (case not assessed as serious), chills, malaise, pricking skin sensation and stomach pain.
[c] Include injection site pain, pruritus, taste alterations, retching, coughing.
[d] Include gagging, chest pain, dyspnoea, perioral/periorbital angioneurotic oedema, olfactory hallucinations, itchiness without hives, hypertensive crisis, sneezing and loss of bowel control.

Source: Forsting et al 2010, Table 8

8.4. Safety conclusions

During a large clinical development program (total of 4549 patients), the safety profile of Gadobutrol has been well characterized. No clinically relevant differences in the incidence of adverse events were seen between the dose groups (which included doses as high as 0.51 mmol/kg BW). Outside the US, Gadobutrol is approved in doses up to 0.3 mmol/kg BW.

The safety in pediatric patients is consistent with the known safety profile of Gadobutrol as obtained in adult patients.

Post-marketing safety data are consistent with the known safety profile of Gadobutrol as obtained during clinical trials. In rare instances, serious anaphylactoid reactions, including fatalities, have been reported, also in line with the safety experience gained from similar contrast agents. Isolated reports of NSF or NSF-like symptoms have been rarely reported to Bayer and are discussed in Section 9.6.2.

9. Nephrogenic systemic fibrosis (NSF)

Summary

Nephrogenic Systemic Fibrosis (NSF) is a rare, but serious, disease characterized by fibrosis of the skin and subcutaneous tissues (muscles and internal organs may also be affected in some patients).

- NSF is predominantly seen in patients with chronic, severe kidney disease (GFR < 30 mL/min/1.73 m^2) or Acute Kidney Injury.
- The etiology of NSF is still unknown but is thought to be multifactorial. The prevailing theory regarding GBCAs and NSF is that gadolinium ions (Gd^{3+}) are released from the Gd-chelate (GBCA) and accumulate in tissue (predominantly skin), thereby initiating a "toxic" reaction for which the precise pathomechanism is not yet known.
- The likelihood of a particular GBCA to release Gd^{3+} ions depends in large part on that particular chelate's physicochemical properties, in particular its stability.
- Gadobutrol belongs to the group of macrocyclic GBCAs.
- Non-clinical studies suggest that GBCAs with a macrocyclic structure exhibit the highest stability among all GBCAs and thus are expected to have a very low propensity to release free Gd^{3+}.
- After an estimated total of 6.1 million post-marketing administrations of Gadobutrol, 2 single agent reports of NSF or NSF-like symptoms have been received for Gadobutrol in which the available clinical and histological information is consistent with NSF according to the criteria of Cowper et al. One additional report fulfilling the same criteria is a multiple agent report. In addition, there were 7 reports involving Gadobutrol that do not fulfill these criteria or do not provide sufficient information.
- Taking all available information into account, the potential risk for NSF after receiving Gadobutrol appears to be similar to that for other GBCAs with a labeled lower risk for NSF, such as ProHance.
- Based on this lower potential risk, the labeling for Gadobutrol should include the same Boxed Warning, Warnings and Precautions, and Patient Counseling Information language as the other GBCAs which are labeled as having a lower risk for NSF.

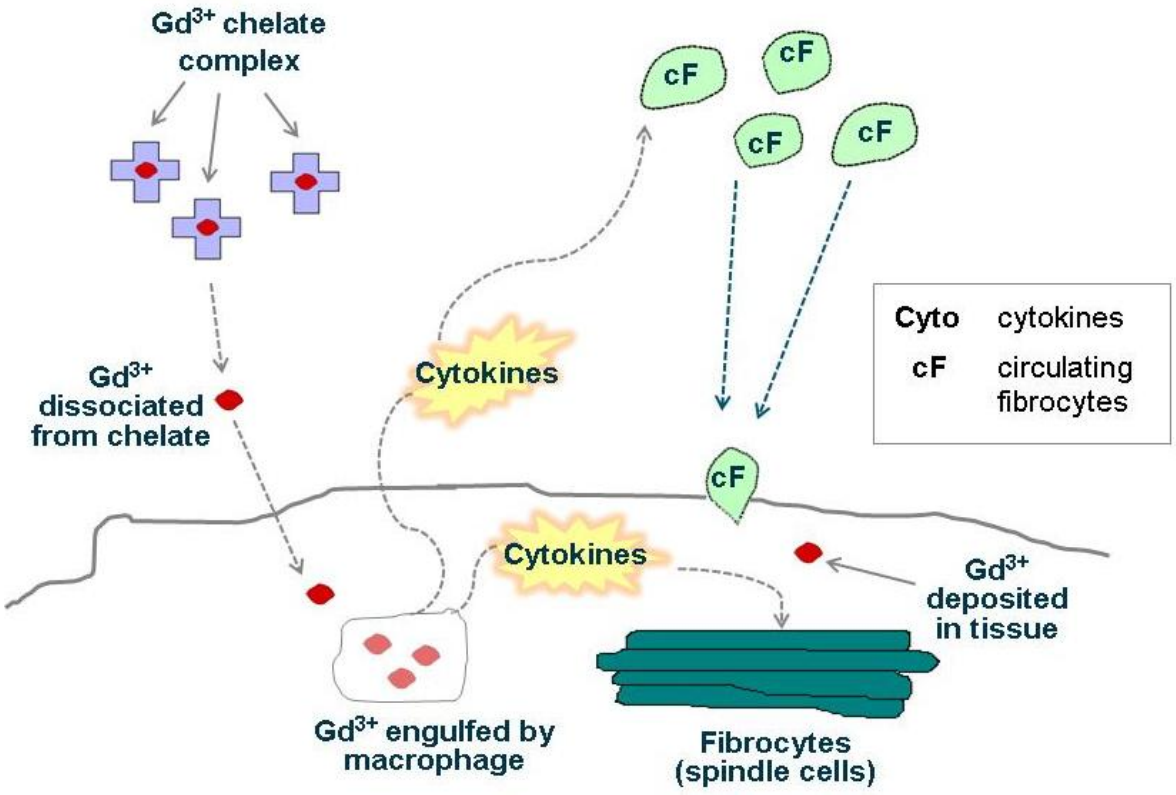
9.1. Description of NSF and population at risk

Nephrogenic Systemic Fibrosis (NSF), previously known as nephrogenic fibrosing dermopathy (NFD), is a rare systemic disease typically characterized by fibrosis of the skin and other connective tissues throughout the body (muscles and internal organs may also be affected in some patients). It was first described in the medical literature in 2000 with the first reported case dating back to 1997 (Cowper 2006). NSF is predominantly seen in patients with severe or end-stage renal insufficiency or acute kidney injury. A possible association between the administration of GBCAs in patients with severe kidney impairment and development of NSF was first reported in 2006 (Grobner 2006, Grobner 2006 erratum).

Symptoms of NSF may include hardening and thickening of the skin, swelling of the lower extremities, joint contractures, redness, pruritus, and burning sensations. The disease may develop over a period of a few days to several weeks and months. It has been reported that in approximately 5% of patients, the course of the disease is rapidly progressive and may potentially lead to a fatal outcome (Cowper www.icnfdr.org). Definitive diagnosis of NSF is difficult; it requires deep skin biopsy and histopathology. Males and females are affected in approximately equal numbers, and there is no predilection for one race over another. Although the majority of cases seem to occur in middle age, NSF has been reported in patients of all ages including geriatric patients and, very rarely, children as young as eight years (Jan et al. 2003).

The etiology of NSF is still unknown but may be multifactorial. The particular combination and severity of co-factors necessary to trigger the development of NSF has not, as yet, been elucidated. Specific triggers under scientific evaluation have included surgery and/or the occurrence of thrombosis or other vascular injury (Cowper 2003), proinflammatory state (Sandowski et al. 2007), the administration of high doses of erythropoietin (Swaminathan et al. 2004) disorders of iron metabolism, dialysis equipment, unidentified microorganisms/pathogens, and since 2006 the use of GBCAs.

The prevailing theory regarding gadolinium and NSF is, that gadolinium (Gd^{3+}) ions are released from the Gd-chelate complex and accumulate in tissue (predominantly skin), thereby initiating a “toxic” reaction for which the precise pathomechanism is not yet known (Text Figure 11).



Text Figure 11 Speculative mechanism by which gadolinium (Gd^{3+}) might trigger nephrogenic systemic fibrosis

In the setting of kidney disease, impaired renal excretion of the Gd-chelate prolongs the half-life and enhances the chance for dissociation of Gd^{3+} from its chelate, allowing increased tissue exposure. Vascular trauma and endothelial dysfunction allow free (Gd^{3+}) to enter tissues more easily, where macrophages phagocytose the metal and produce local profibrotic cytokines as well as signals that attract circulating fibrocytes to the tissues. Once in tissues, circulating fibrocytes induce a fibrosing process that is indistinguishable from normal scar formation. Adapted from: Perazella (2007)

The likelihood of a particular Gd-chelate to release Gd^{3+} ions depends strongly on that particular chelate's physicochemical properties, in particular its stability.

Currently, there is no known cure for NSF. Improving renal function seems to slow or arrest NSF and may even result in a gradual reversal. In a patient on hemodialysis, hemodialysis following the administration of a GBCA may enhance the contrast agent's elimination. The usefulness of hemodialysis in the prevention of NSF is unknown.

Many factors should be considered when determining the potential risk of a GBCA to trigger NSF-like symptoms in the population at risk. These factors include the available clinical evidence such as the number of reports, range of approved indications, range of dosages approved for use in CE-MRI, the number of administrations, and the length of

time since initial approval. In addition to the clinical evidence, based on the prevailing theory on the possible role of GBCAs in the development of NSF, the following factors should also be considered:

- Stability
- Pharmacokinetics
- Non-clinical exploratory studies

9.2. Activities from regulatory authorities and professional societies regarding NSF

Since the initial description of NSF, and the first report of a possible association with gadolinium in 2006 (Grobner 2006, Grobner 2006 erratum), Health Authorities, GBCA manufacturers, and radiological societies worldwide have initiated actions and recommendations to minimize the potential risk of NSF.

9.2.1. Regulatory activities

United States

In June 2006, FDA issued a Public Health Advisory on GBCAs for MRI. This was followed by an additional FDA notice in December 2006. In May 2007, the FDA requested a class labeling for all GBCAs approved in the US (Omniscan, OptiMARK, Magnevist, ProHance and MultiHance). Class labeling included a Boxed Warning on the possible association between GBCAs and NSF.

On 8 December 2009, a Joint Meeting of the Cardiovascular and Renal Drugs and Drug Safety and Risk Management Advisory Committees (FDA Advisory Committee) was convened to review data pertaining to the development of NSF in association with GBCAs and to seek the Committee's advice regarding measures to minimize this risk and regarding possible risk differentiations among the marketed agents. Each sponsor (Bayer, Bracco, GE Healthcare, Covidien, and Lantheus) as well as the FDA, provided a briefing document that reviewed the data pertaining to the potential of developing NSF and presented at the FDA Advisory Committee meeting. No formal vote was taken at this FDA Advisory Committee meeting.

In September 2010, FDA issued a Drug Safety Notification announcing changes in the drug label for GBCAs to minimize the risk of NSF. These label changes as recommended by FDA are intended to help ensure that these drugs are used appropriately, and that patients are screened for reduced kidney function and acute kidney injury. Risk factors identified by the FDA in the updated labeling include repeated or higher than recommended dosing, and degree of renal impairment at the time of exposure.

FDA concluded that, based on the available data, three GBCAs (Omniscan, OptiMARK and Magnevist) are considered to be at a greater risk to trigger NSF in at-risk patients than the other marketed GBCAs. FDA also recommended that these three linear extracellular GBCAs should be contraindicated in patients with chronic, severe kidney disease (< 30 mL/min/1.73 m^2) or with Acute Kidney Injury. Other GBCAs still contain strong warnings, including a Boxed Warning, but no contraindication, regarding the risk of NSF. The only macrocyclic GBCA approved in the US, ProHance, is in this lower risk group.

Europe and other countries

In 2007, the European Pharmacovigilance Working Party (PhVWP) also came to the conclusion about a different potential risk of GBCAs based mainly on stability considerations, i.e. the GBCAs' propensity to release Gd-ions. According to their differential risk, this resulted in labeling changes for all GBCA in 2007. The considerations from the PhVWP were confirmed by the Committee for Medicinal Products for Human Use (CHMP) opinion that came into force on 1 July 2010 that identified different NSF risk classes for gadolinium-based contrast agents:

High risk:	a) *Linear non-ionic chelates* including OptiMARK and Omniscan.
	b) *Linear ionic chelate:* including Magnevist.
Medium risk:	*Linear ionic chelates* including Ablavar, Eovist and MultiHance.
Low risk:	*Macrocyclic chelates* including Gadobutrol, ProHance and Dotarem

Note: Ablavar (gadofosveset) and Eovist (gadoexetate) are GBCAs approved in the US for MRA and detection and characterization of lesions in the liver, respectively. Dotarem is not marketed in the US.

In order to minimize the potential risk associated with GBCAs and the development of NSF, the "high risk" GBCAs were contraindicated in patients with severe renal impairment, patients undergoing liver transplantation, and neonates up to 4 weeks of age. Strong warnings are included in the labeling of medium- and low-risk GBCAs in these patient populations.

Other Health Authorities in the world have proposed or implemented recommendations or restrictions similar to the FDA and/or the European Medicines Agency (EMA).

9.2.2. Professional societies

Professional societies, such as ACR (American College of Radiology) (ref:http://www.acr.org/SecondaryMainMenuCategories/quality_safety/contrast_manual/NephrogenicSystemicFibrosis.aspx) in the USA, ESUR (European Society of Urogenital Radiology) (ref: http://www.esur.org/Contrast-media.51.0.html) in Europe, and other professional groups in Canada (ref:

http://www.car.ca/uploads/standard%20guidleines/advisory_nsf_en.pdf) and other countries (ref: RANZCR NSF Guidelines MRI Reference Group, Standards of Practice & Accreditation Committee October 2009), formulated similar recommendations to the radiologists, to provide them with guidance how to use GBCAs in the population at risk. Despite some differences in all of these recommendations, there was an overall consistency in some points:

- The population at risk is mainly patients with severe renal insufficiency and acute renal insufficiency.
- Release of Gd appears to be an important factor for the categorization of risk.
- No agent is without risk, resulting in strong restrictions of use of GBCAs in the population at risk.
- Based on the prevailing theory regarding the potential role of free Gd in the pathogenesis of NSF and the results of various animal and *in vitro* studies, it is believed that there are differential risks between the agents and that macrocyclic agents, including Gadobutrol and ProHance, should be categorized as lower risk.

9.2.3. Summary

The activities of the Health Authorities, GBCA manufacturers, and radiological societies since 2007 appear to have been successful in decreasing the number of new onset NSF reports. The true risk of a particular GBCA to trigger NSF remains unknown. The potential for Gadobutrol (a macrocyclic GBCA) to trigger NSF is similar to other macrocyclic GBCAs, such as ProHance, which have been classified as lower-risk agents.

9.3. Physicochemical properties of Gadobutrol and other GBCAs relevant for NSF

Summary

- All of the GBCAs approved for marketing in the US have a linear structure except for the macrocyclic agent, ProHance. Gadobutrol, with a macrocyclic chelate, belongs to the same structural class as ProHance.
- Macrocyclic Gd-chelates such as Gadobutrol offer a more kinetically stable binding of Gd^{3+} than open chain chelates and are therefore least likely to release free Gd^{3+} from the chelate under physiologic conditions
- Thermodynamic stability constants are useful to describe/compare the stability of linear GBCAs, but for macrocyclic GBCAs, kinetic stability, described by the dissociation half-life, is the key parameter when assessing the risk of macrocyclic GBCAs to release Gd^{3+}.
- Gadobutrol demonstrates a very high kinetic stability (similar to that of ProHance), suggesting a lower potential for Gadobutrol to release Gd^{3+} ions *in vivo* in comparison to all linear GBCAs.
- No relevant difference regarding the risk to release free Gd^{3+} ions from the Gd-chelate complex can be detected between Gadobutrol and ProHance.

GBCAs with a CNS indication can be grouped according to their chemical structure as shown in Text Table 23. GBCA structures are provided in Text Figure 1.

Text Table 23 GBCA structure

Structure		GBCA
Macrocyclic		Gadobutrol
		ProHance
Linear	ionic	MultiHance
		Magnevist
	non-ionic	Omniscan
		OptiMARK

Complex stability of GBCAs

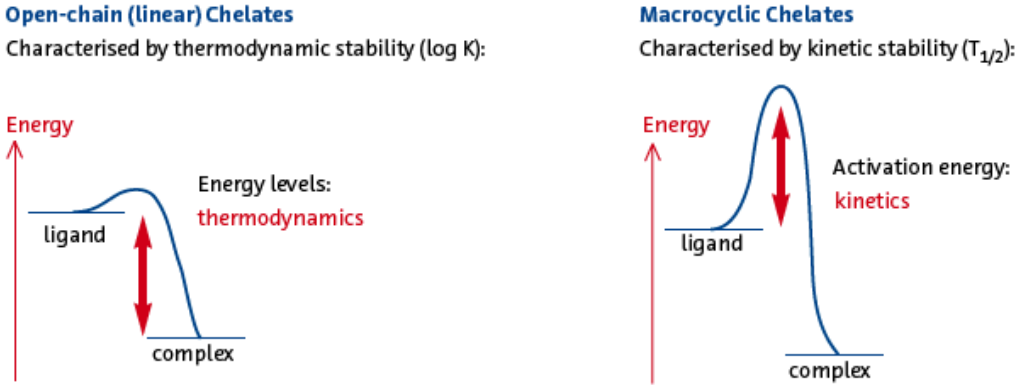
Generally, the complex stability of GBCAs is characterized by both thermodynamic stability (log K) and kinetic inertness ($T_{½}$) (see Text Figure 12). The thermodynamic stability constant represents the concentration of the complex divided by the product of the concentrations of the free Gd and the ligand at equilibrium. Due to its exothermic

nature, the equilibrium of the complexation reaction lies far towards the side of the complex under physiological pH ranges (lower energy levels of the complexes). From the experimental value measured at extreme pH and the protonation constants of the ligand, the apparent thermodynamic stability can be calculated for physiological pH ranges.

However, for macrocyclic GBCAs, it is rather the kinetic inertness that primarily determines the stability of the complex under clinical conditions. This is due to the high activation energy that is needed to incorporate the gadolinium ion into the ligand to form the complex (see Text Figure 12 – right). As a consequence the formation of the complex does not occur at room or physiological temperatures: ligand and free gadolinium need to be heated (e.g. in the case of Gadobutrol, heating of the solution for some minutes at temperatures of > 80°C is required for the process of complexation between Gd^{3+} and ligand) (Sieber et al. 2009). The same holds true for the reverse reaction, the decomplexation or release of Gd^{3+}. Or, in other words, the kinetics of Gd-release from the macrocyclic GBCA is extremely slow at room or physiological temperatures and physiological pH - this facet of complex stability is called kinetic inertness.

The dissociation half-life $T_{½}$ (at physiological conditions), which represents the experimentally derived value to describe the kinetic process of decomplexation, is the key parameter when assessing the risk of this particular group of GBCAs to release Gd^{3+} *in vivo* and *in vitro*. The ligand of Gadobutrol with its macrocyclic structure forms a strong complex with the paramagnetic gadolinium ion, thus resulting in high *in vivo* and *in vitro* kinetic stability and extremely long dissociation half-lives (see Text Table 24).

As a consequence, under physiological conditions (e.g. 37°C, pH 7.4, in serum), there is no measureable release of Gd^{3+} from the macrocyclic chelates (see Section 9.4.1).



Text Figure 12 Stability of gadolinium (Gd^{3+}) chelates

The fundamental difference between linear and macrocyclic chelates is the kinetics of complexation and decomplexation

This is consistent with transmetallation experiments, where no release of Gd-ions was detected, and in line with the results observed for macrocyclics in the non-clinical studies, where Gd concentrations in the skin were below the detection limit.

Due to the high stability of macrocyclics, a dissociation half-life can only be measured under extremely acidic conditions, e.g. at pH 1 (see Text Table 24) and then extrapolated. The calculated dissociation half-life at physiological conditions (37°C and pH 7.4) is greater than 1000 years (Schmitt-Willich 2007); this is similar to the other macrocyclic GBCA, ProHance (Text Table 24).

Text Table 24 Dissociation half-life of macrocyclic chelates

	Dissociation half-life (t1/2)	
	Measured at pH 1	**Extrapolated to pH 7.4**
Gadobutrol	24 h*	>1000 years
ProHance	3 h*	> 1000 years

* Data on file

Values for thermodynamic stability, which are predominantly used to describe the complex stability of open-chain linear Gd-chelates, also exist for the macrocyclic chelates. However, differences in thermodynamic stabilities are not relevant for

macrocyclic GBCAs, as reaching the steady state described by thermodynamic stability constants would take many years under physiological conditions.

In addition, most GBCAs contain a small amount of excess ligand in the drug product. For Gadobutrol, less than 0.1% excess ligand is added to the formulation for the sole purpose of ensuring that potential transmetallation due to metal traces of the glass containers during the process of heat sterilization (i.e. when the activation energy is exceeded) can be compensated.

9.4. Non-clinical studies to investigate the possible relationship between NSF and GBCAs

Summary:

- In contrast with linear agents, Gadobutrol showed no measurable release of Gd in human serum (*in vitro*) even at elevated phosphate levels, a condition frequently occurring in end-stage renal failure (ESRF) patients.
- In contrast to non-ionic linear agents, no skin lesions were observed in animals during non-clinical studies even after repeated administration of extremely high doses of Gadobutrol. No long-term Gd deposition in the skin of healthy or renally impaired rats was detectable.
- The findings in the non-clinical studies are in line with the very high stability of macrocyclic Gadobutrol, even under conditions of renal impairment. According to the prevailing theory of the NSF pathomechanism (in which the release of Gd from chelate plays an inciting role), Gadobutrol can be expected to have a very low propensity to trigger NSF.

Exploratory non-clinical *in vitro* and *in vivo* studies were initiated by Bayer shortly after the first reports of a possible association between the administration of GBCAs and NSF. The objective of these studies was to investigate the possible relationship between NSF or NSF-like symptoms and administration of GBCAs and to evaluate in more detail the pathogenesis of this new disease entity. Moreover, it was investigated whether there are possible differences among GBCAs (including Gadobutrol) regarding their propensity to release Gd^{3+} ions and/or to trigger the development of NSF. Additionally, the influence of Gd^{3+} release on NSF development was explored. Caution must be taken when extrapolating the results of these studies to humans.

9.4.1. *In vitro* studies

The rate of Gd release in human serum was investigated for Gadobutrol and several other macrocyclic, ionic and non-ionic linear GBCAs. To differentiate between released and complex-bound gadolinium, a highly sensitive HPLC-ICP-MS method was used. The influence of elevated phosphate concentrations on complex stability was also investigated. High serum phosphate levels are often observed in patients with ESRF which is the population thought to be predominantly at risk for NSF.

In this experimental setting, no measurable Gd release was observed for Gadobutrol and the other macrocyclic GBCAs, ProHance, (i.e. values were below quantification limits), whereas ionic linear GBCAs, Magnevist and MultiHance, had higher release rates. Highest rates were observed for the non-ionic linear GBCAs, Omniscan and OptiMARK (see Text Figure 13).

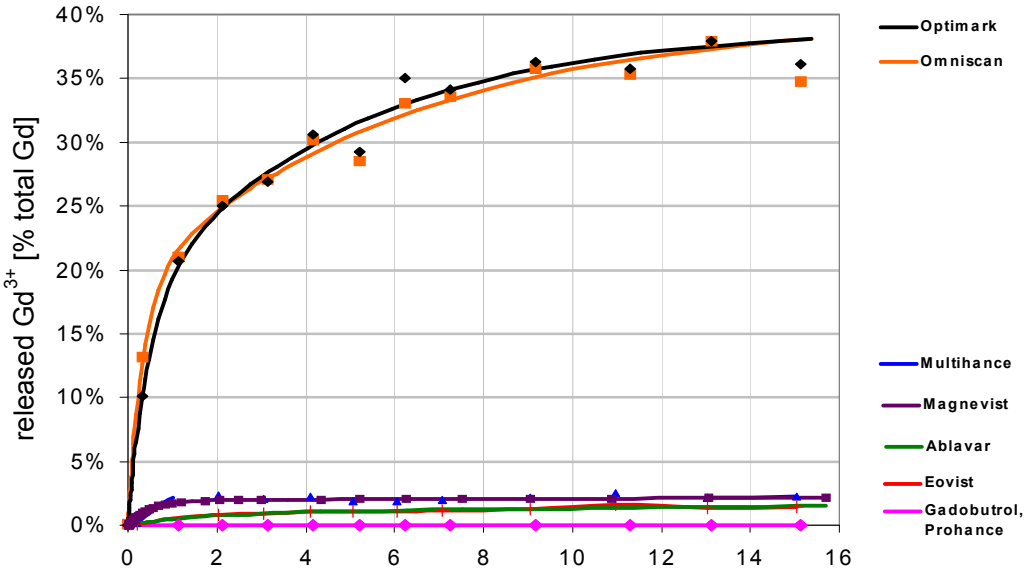
As pointed out above, the propensity for release of gadolinium ions from Gd chelates depends in large part on the chemical structure of the molecule. The release of Gd^{3+} from all linear Gd complexes examined in human serum was several orders of magnitude greater than predicted by their conditional stability constants. After 15 days, release of Gd^{3+} from the non-ionic linear GBCAs was about 10 times higher than from the ionic linear GBCAs. All macrocyclic GBCAs like Gadobutrol remained stable in human serum; no Gd release was observed (Text Table 25).

Text Table 25 GBCA structure and release of gadolinium

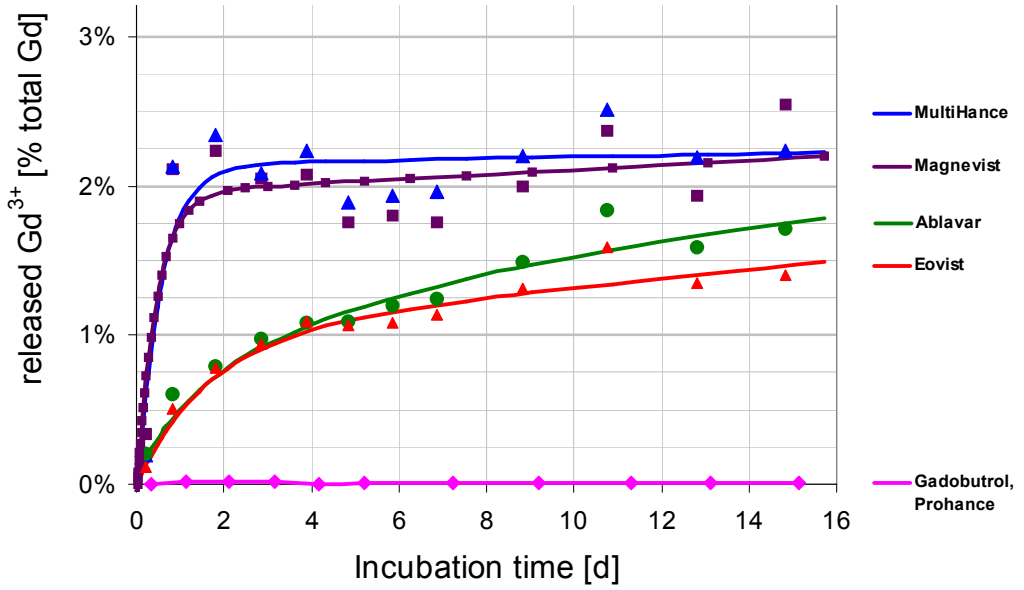
Release of gadolinium in 1 mmol/L solutions of GBCAs in pooled serum
Release expressed as % of total Gd^{3+} in serum after 15 days at 37° C

Structure		GBCA	Gd release
Macrocyclic		Gadobutrol	< 0.1%
		ProHance	< 0.1%
Linear	ionic	MultiHance	1.9%
		Magnevist	1.9%
	non-ionic	Omniscan	20%
		OptiMARK	21%

A **Macrocyclic and <u>all</u> linear GBCAs** (ionic and non-ionic)



B **Macrocyclic and ionic linear GBCAs** (scale zoomed to 10 fold)



Text Figure 13 **Gd^{3+} release from GBCAs**

Comparison of the amounts of Gd^{3+} released from 1 mmol/L solutions of Gadobutrol and several other marketed GBCAs at 37°C in human serum supplemented with 10 mmol/L phosphate. The lower Panel B is enlarged to permit better visualization of the data of the ionic linear and macrocyclic GBCAs (Frenzel et al. 2008).

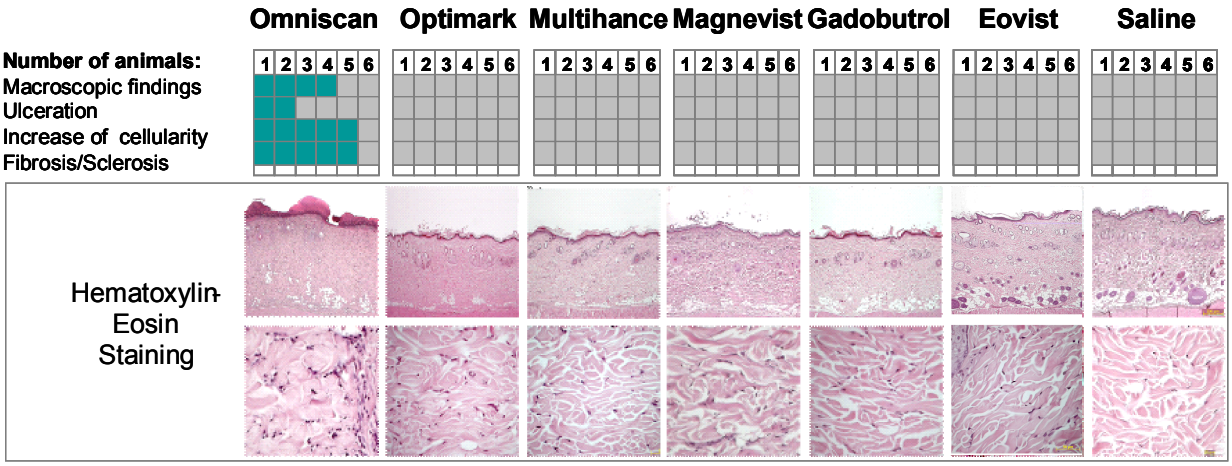
9.4.2. *In vivo* studies

As no established non-clinical animal model for ESRF exists, different Gd-containing contrast agents including Gadobutrol were repeatedly injected i.v. once daily at high doses (i.e. 25 to 40 times the standard clinical dose) into the tail vein of male Wistar rats. The elevated doses generated high serum levels of the contrast agents (far higher than those seen in humans) and also long exposure in order to simulate the exposure situation of patients with severe renal impairment (without hemodialysis).

This non-clinical model was applied in several settings:

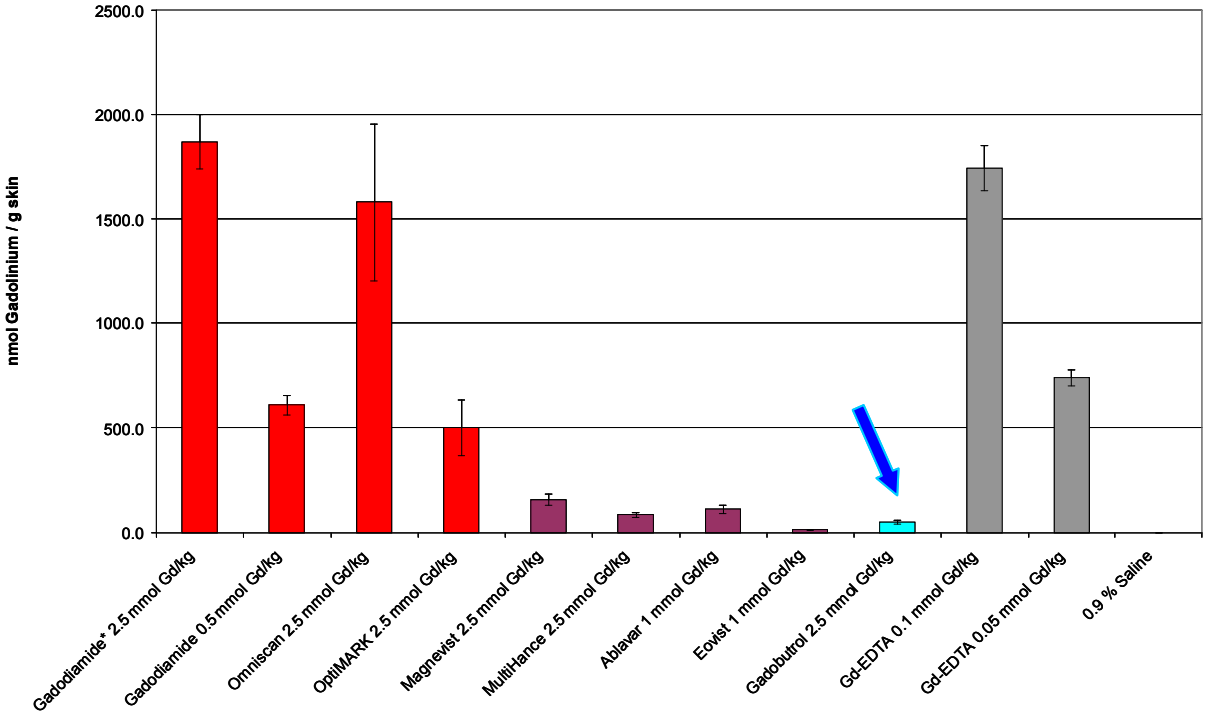
- Different GBCAs including Gadobutrol, several macrocyclic, ionic or non-ionic linear GBCAs, as well as Gd-EDTA were injected over a period of 5 weeks once daily (over 5 consecutive days per week) at high doses into the tail vein. In addition, half of the rats were kept on a zinc-deficient diet for 6 weeks before and during the injection in order to investigate whether occurrence of potential skin lesion would be influenced by zinc levels. A depletion of zinc caused by the excess ligand contained in some formulations of GBCAs was previously hypothesized to be a potential cause for skin lesions observed in rats after administration of non-ionic linear GBCAs.

  Similar to the other investigated macrocyclic GBCAs, very low Gd levels were observed in the skin of Gadobutrol-treated animals 5 days after the last injection. These trace amounts are most likely attributable to intact compound still circulating in the microvasculature of the tissue. No effects on skin were observed in these animals, and the histology of the skin in the Gadobutrol group was undistinguishable from that of the saline control group (see Text Figure 14). In contrast, skin lesions (erythema, multifocal ulcerations, multiple crusts, increased dermal cellularity, loss of interstitial space and dermal fibrosis), with concomitant high Gd concentrations in the skin, were observed in the animals treated with Gd-EDTA and gadodiamide (drug substance of Omniscan, without excess ligand) and to a lesser extent in some of the animals treated with Omniscan. These skin findings were accompanied by high Gd skin levels (see Text Figure 15). No evidence was found that the observed skin lesions were attributable to zinc depletion.



5 days after the 20th i.v. injections of compounds (2.5 mmol/kg)

Text Figure 14 Macroscopic and microscopic skin findings following the treatment with GBCAs in rats



Text Figure 15 Gd-concentrations in rat skin following treatment with GBCAs

Skin samples were taken 5 days after the last Gd injection.

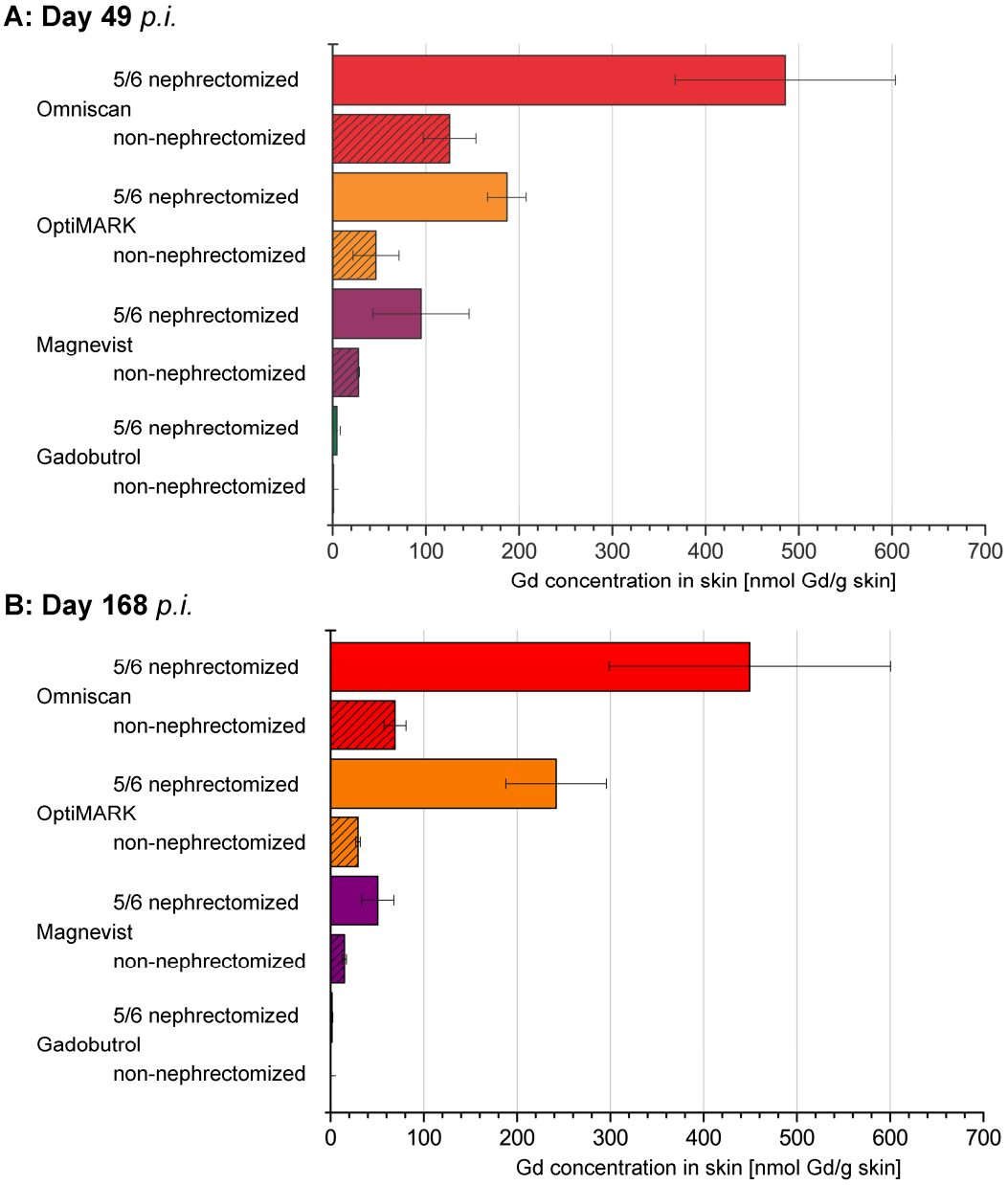
Dark grey:	Gd-EDTA [Gd chelate of low stability not used as GBCA]
Red:	non-ionic linear GBCAs
Purple:	ionic linear GBCAs
Light blue:	macrocyclic GBCA
Arrow:	Gadobutrol

- In another study investigating the long-term retention of Gd, six male rats per group were injected with Gadobutrol or several other macrocyclic, ionic or non-ionic linear GBCAs into the tail vein once daily on five consecutive days at doses of 2.5 mmol Gd/kg BW. Skin biopsies were taken at various time points up to 365 days post-injection and analyzed for Gd content.

  Following the treatment with Gadobutrol and the other macrocyclic GBCAs, long-term deposits could not be observed, since the Gd values in skin tissue were back to the same range as observed for the control animals from about Day 10 post-treatment onwards, whereas they were significantly higher for the ionic linear and highest for the non-ionic linear GBCAs (see Text Figure 16) (Pietsch et al. 2009a).

- Renally impaired (5/6 nephrectomized) Wistar rats were injected with Gadobutrol or some ionic or nonionic linear GBCAs. The contrast agents were administered once daily for five consecutive days into the tail vein at a dose of 2.5 mmol Gd/kg BW, 25 times the proposed clinical dose. Skin biopsies were taken at various time points, and the Gd concentration was determined over an observation period of 168 days post injection (Pietsch et al. 2009b).

  Again lowest skin levels were found after administration of Gadobutrol. Though in the renally impaired animals treated with linear GBCAs significantly higher Gd values in skin were observed compared to healthy animals, such differences were not detected for Gadobutrol. The extremely low Gd levels determined in the skin resulted in no statistically significant difference between renally impaired or healthy animals (see Text Figure 16). The study shows the importance of GBCA stability, especially if the circulation time of the compounds is prolonged.



Text Figure 16 Gd concentration in rat skin
Skin of 5/6-nephrectomized rats (solid bars) and non-nephrectomized animals (striped bars). Skin biopsies were taken on Day 49 (A) and Day 168 (B) after administration of Omniscan (red), OptiMARK (orange), Magnevist (purple), and Gadobutrol (green).

9.5. Comparative pharmacokinetics of Gadobutrol and other GBCAs in the context of NSF

Summary

- The pharmacokinetics of Gadobutrol are similar to other GBCAs with CNS indications.
- All available GBCAs currently marketed for CNS indications are predominantly eliminated by the kidneys via glomerular filtration with similar elimination half-lives.
- In patients with renal impairment, the excretion of GBCAs is prolonged.
- Gadobutrol is dialyzable. Approximately 68%, 94% and 98% of the administered dose were recovered in the dialysate after the 1st, 2nd and 3rd dialysis, respectively.

Gadobutrol is distributed rapidly into the extracellular space. Plasma protein binding in humans is negligible. Gadobutrol is rapidly excreted in urine by glomerular filtration. The urinary excretion of Gadobutrol is nearly complete 12 hours after administration in subjects with normal renal function. Gadobutrol is not metabolized and is therefore renally excreted as unchanged drug.

9.5.1. Elimination of GBCAs in healthy volunteers

A summary of the available data on elimination half-life and elimination pathways for various Gd-containing contrast agents in healthy volunteers is displayed in Text Table 26. The mean terminal half-life of Gadobutrol for elimination is 109 minutes (80 to 128 minutes). This is similar to the excretion of other extracellular GBCAs in healthy volunteers which ranged between 70 and 103 minutes (Text Table 26).

Text Table 26 Pharmacokinetics in healthy volunteers of GBCAs with CNS indication

Chemical structure	Charge	Contrast agent	Protein binding	Serum elimination half-life*	Elimination pathway
Macrocyclic chelate		Gadobutrol	None	80 - 128 min	Kidney
		ProHance	None	96 min	Kidney
Linear chelate	Ionic	MultiHance	< 5%	72 – 102 min	Kidney ≥ 96% Bile ≤ 4 %
		Magnevist	None	90 min	Kidney
	Non-ionic	Omniscan	None	ca. 70 min	Kidney
		OptiMARK	None	103 min	Kidney

* In healthy subjects

References: US or European Package Inserts

9.5.2. Elimination of GBCAs in patients with renal impairment

Glomerular filtration via the kidney is the primary elimination pathway for all GBCAs currently marketed in the US for CNS imaging. Accordingly, the elimination half-life for all these contrast agents can be significantly prolonged in patients with renal impairment (reduced GFR). Dedicated studies to investigate the safety and tolerability as well as pharmacokinetics in patients with different degrees of renal impairment were performed for some of the marketed GBCAs including Gadobutrol. These studies showed similar pharmacokinetics in renally-impaired patients for other GBCAs as compared to Gadobutrol.

See Section 6.3.1.2 for a summary of PK results in a clinical study in renally-impaired patients.

In patients with moderate renal impairment, urinary excretion of the administered Gadobutrol dose was completed within 72 hours, but was not completed 120 hours post dose in severely renally impaired patients due to a markedly prolonged $t_{1/2}$.

Dialyzability of Gadobutrol was investigated in 11 patients with ESRF who required hemodialysis treatment. The first 3-hours hemodialysis eliminated 68.2 ± 12.7% of the administered Gadobutrol dose. After the second and third hemodialysis sessions, the total amount of eliminated Gadobutrol increased to 94.1 ± 4.3% and 98.0% ± 1.8%, respectively. After 30 min of the first hemodialysis session, the mean and SD of Gadobutrol clearances were 126.1 ± 17.8 mL/min showing that dialysis is similarly effective as the renal elimination of Gadobutrol in healthy volunteers.

9.6. NSF data from clinical studies and post-marketing safety surveillance for Gadobutrol

Summary:

- No cases of NSF or NSF-like symptoms were reported from 4549 patients who were administered Gadobutrol during clinical trials.
- After an estimated total of 6.1 million post-marketing administrations of Gadobutrol, 2 single agent reports of NSF or NSF-like symptoms have been received for Gadobutrol in which the available clinical and histological information is consistent with NSF according to the criteria of Cowper et al. One additional report fulfilling the same criteria is a multiple agent report. In addition, there were 7 reports involving Gadobutrol that do not fulfill these criteria or do not provide sufficient information. The majority of all reports had onset of symptoms in 2008 or earlier.
- To assess the magnitude of the potential risk of Gadobutrol for the development of NSF, Bayer has voluntarily initiated a prospective non-randomized (pharmaco-epidemiologic) cohort study ("GRIP"; open-label, multicenter) with a similar design that the FDA requested for the other marketed GBCAs in patients with moderate to severe renal impairment. The 349 patients in follow-up include 123 patients with severe renal impairment. To date, no reports of NSF or NSF-like symptoms were received.
- Taking all available information into account, the potential risk for NSF for patients in the identified at-risk population receiving Gadobutrol is similar to that of other macrocyclic GBCAs with a labeled lower risk for NSF, such as ProHance.

9.6.1. Clinical trials

In the 4549 patients studied in Phase 2 to 4 clinical trials, no cases of NSF or NSF-like symptoms were reported from patients who were administered Gadobutrol at doses up to 0.51 mmol/kg BW.

9.6.2. Post-marketing data on NSF

9.6.2.1. Assessment of NSF risk: Methodological considerations

In its Briefing Document for the 8 December 2009 FDA Advisory Committee (FDA 2009), the FDA described a number of significant limitations of the crude report analysis as presented by the FDA's Office of Surveillance and Epidemiology (OSE). "Spontaneous reporting data are generally not useful for determining incidence rates, due to uncertainties in factors that influence reporting of adverse events." However, even

with the limitations, OSE indicated it considers the single-agent reports more interpretable than those listing multiple agents.

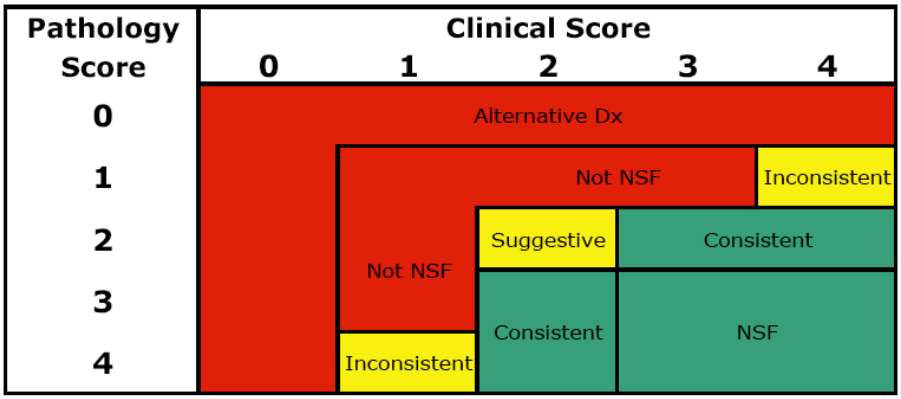
Some of the many potential limitations of utilizing spontaneous reports for a relative assessment of the potential risk of NSF include:

- Differences across GBCA manufacturers in their handling of NSF reports
- Stimulated reports can affect the numbers of all cases of NSF reported globally
- Geographical scope for the estimated number of administrations (worldwide [in the case of agents not currently marketed in US such as Gadobutrol] versus US only)
- Double reporting/counting
- Quality of the report, such as incomplete information, including lack of
  - Confirmation of the disease (NSF) (e.g. lack of biopsy)
  - Information on the product identity
  - Information for dosing per injection
  - Information for cumulative number of administrations
  - Information for the time between multiple administrations
  - Information for the delay in the time of onset following administration
  - Information for the patient's renal status

Typically, even intense follow-up activities by the sponsor cannot overcome some of these reporting limitations. Given the limitations noted above, a report does not necessarily equal a proven case.

9.6.2.2. Analysis according to the criteria of Cowper

To evaluate whether the patient has NSF, Bayer relies on the clinico-pathological definition of NSF proposed by Cowper et al. (personal corespondence). Clinical and pathology scoring are each based on a scale from 0 ("Excluded") to 4 ("Highly Consistent"). The resulting diagnostic grid is shown in Text Figure 17.



Ref: Cowper et al. (2010).

Text Figure 17 Diagnostic grid of clinico-pathological definition of NSF

This combined clinico-pathological score is used to arrive at one of six possible diagnoses or conclusions:

- A diagnosis of "NSF" is considered when a patient scores at least a "3" on both the clinical and the histological criteria (i.e. at least one major clinical criterion and at least three histologic criteria).
- A score of "consistent" with NSF means the patient has scored at least a 3 on the clinical criteria, and at least a 2 on the histological criteria (i.e. at least one major clinical criterion and at least two histologic criteria).
- Anything less than "consistent with NSF" (suggestive of NSF; inconsistent with NSF; not NSF/NSF ruled out; or alternative diagnosis/diagnostic of an entity other than NSF), according to Cowper et al., has not met the criteria for NSF and should be considered non-diagnostic of NSF unless and until more compelling evidence is obtained.

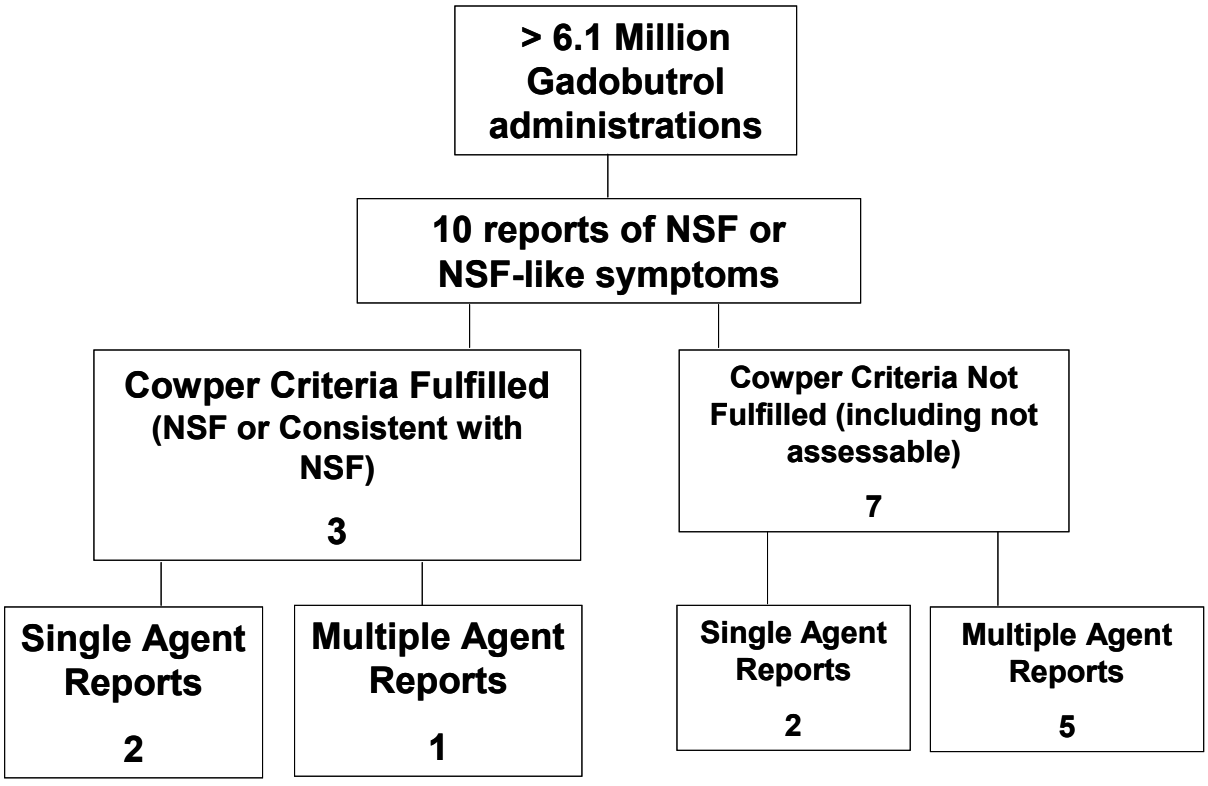
In order to evaluate reports of NSF or NSF-like symptoms for possible association with Gadobutrol and to evaluate whether the patient has NSF, Bayer applies the criteria described above based on Cowper et al.

9.6.2.3. Reports received by Bayer

A report need only consist of 4 basic data elements: an identifiable patient, identifiable reporter, a suspect drug, and an adverse event. Detailed information or positive confirmation of these elements, or assessment or proof of causality, are not required. The characteristics of these reports with regard to (i) the fulfilment of the diagnostic NSF criteria and (ii) the number of GBCAs involved are summarized Text Figure 18.

Through 15 November 2010, 10 reports of NSF or NSF-like symptoms had been received in patients who were administered Gadobutrol. All reports are followed up intensively to receive as much information as possible.

When evaluating all available information concerning these reports, only 3 fulfill both the clinical and histological description of NSF as defined by Cowper et al. Two of these are single agent reports in which patients are reported to have received Gadobutrol only before development of NSF, and one is a multiple agent report, in which a patient received multiple GBCAs before development of NSF.



Text Figure 18 Reports of NSF or NSF-like symptoms associated with Gadobutrol

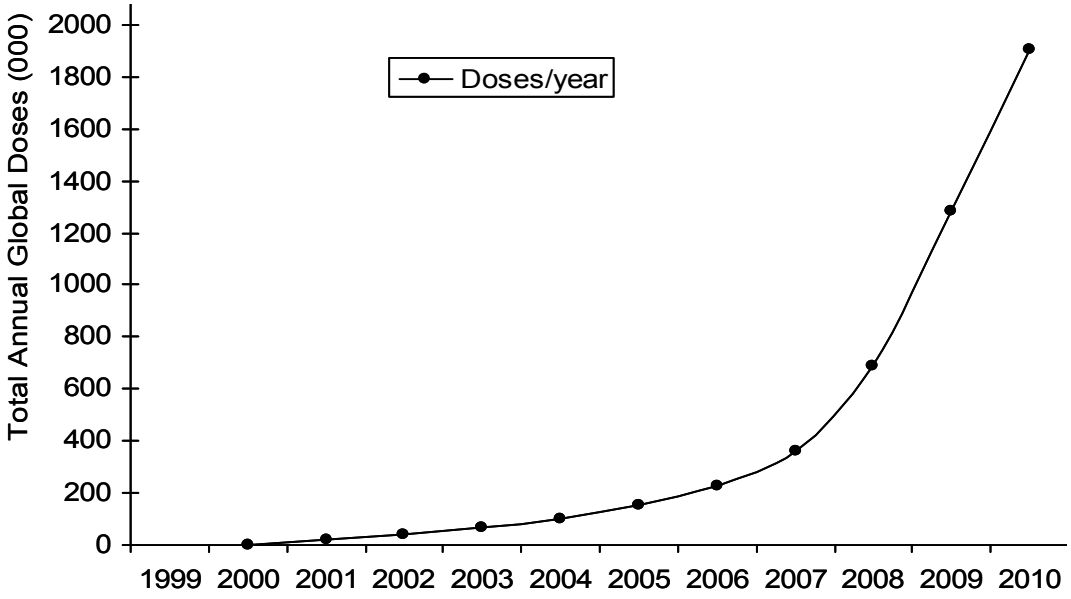
9.6.2.4. Additional analyses of NSF reports

9.6.2.4.1. NSF reports by year

Between the launch of Gadobutrol (1999) and the cut-off date for this analysis (31 October 2010), more than 6.1 million patients are estimated to have been exposed to Gadobutrol (approved in doses up to 0.3 mmol/kg BW for CNS imaging or other indications).

From February 2005 through February 2010, the estimated number of administrations of Gadobutrol has increased approximately 8 fold to approximately 1.9 million administrations for the 12 months ended in February 2010. The increase in usage of Gadobutrol was especially pronounced since 2007 when first regulatory actions were taken in the context of GBCAs and the potential to trigger NSF.

Text Figure 19 shows the increasing number of world-wide Gadobutrol administrations, while Text Table 27 shows that the number of NSF or NSF-like reports each year have remained low.



Text Figure 19 Gadobutrol total annual doses
Global data

Text Table 27 Reports of NSF-like symptoms by year

Onset of signs and symptoms suggestive of NSF by year in all reports in which Gadobutrol was mentioned.
Observation period: Launch (1999) to 15 November 2010

Year of onset of signs and symptoms	Number of multiple-agents reports	Number of single-agents reports
2005	1	0
2006	1	1
2007	0	0
2008	2	2
2009	1	1
2010	0	0
Unspecified or unclear	1	0
Total	6	4

All reports were received from 2007 onward, however the onset (when known) occurred between November 2005 and November 2009 (Text Table 27). These reports were received by Bayer between July 2007 and November 2010. The last documented administration of Gadobutrol in any of these 10 reports was September 2009 in a patient who had previously received Omniscan and Magnevist.

9.6.2.4.2. NSF reports by age and gender

When known, the age ranged from 37 years to 79 years (Text Table 28). The gender of the patients in the reports of NSF or NSF-like symptoms was composed of 4 males, and 5 females; for one subject, the gender is not known.

Text Table 28 NSF reports by age and gender

		Number of reports
Age (years)	30 - 39	1
	40 - 49	2
	50 - 59	1
	60 - 69	4
	>70	1
	Unknown	1
Gender	Male	4
	Female	5
	Unknown	1

9.6.2.4.3. NSF reports by patient's renal and dialysis status

The majority of patients in these reports (at least 7 out of 10) had severe renal impairment.

Seven patients were on dialysis, and the remaining three patients are summarized below:

- In one patient, there was no specific reference to the patient's renal status, although his underlying multiple myeloma is known to be associated with kidney damage and renal impairment.

- One patient was reported to have renal insufficiency with a "creatinine clearance 15 to 20 mL/min" at the time of contrast administration, with no reference to dialysis.

- One patient had chronic renal failure since 2003 but was not on dialysis either before or after contrast administration. Although he was reported to be in CKD stage 3, with Modification-of-Diet-in-Renal-Disease (MDRD) GFR estimated to be 34 mL/min based on a serum creatinine of 190+ µmol/L one month before contrast administration (14 May 2008), examination of the patient's serum creatinine and eGFR values over the subsequent months showed fluctuating values as shown below:

	Creatinine (µmol/L)	eGFR - MDRD formula (mL/min)
14 May 2008	190+	34
01 Jul 2008	201	31
07 Aug 2008	181	35
15 Oct 2008	214	29
14 Jan 2009	229	27
19 Mar 2009	214	29
22 Sep 2009	283	21
29 Dec 2009	264	23

9.6.2.4.4. NSF reports by gadolinium administration

The patients described in the 10 reports received between 1 and 7 GBCA administrations, with 7 out of 10 of these patients known to have received more than one GBCA administration (Text Table 29; which includes one patient who received two administrations of Gadobutrol only).

Text Table 29 NSF reports: Number of GBCA administrations

Number of GBCA administrations	Number of patients
1	3
2	4
3	2
7	1

The doses of Gadobutrol and other GBCAs are not known for 2 reports. In 2 other reports, limited information regarding the GBCA doses is available. Where the information was provided, patients received Gadobutrol at individual dose volumes ranging from 5 mL to 30 mL, with individual Gadobutrol doses ranging from 0.1 mmol/kg to 0.49 mmol/kg.

In the 2 single-agent reports of NSF or NSF-like symptoms in which the Cowper criteria were fulfilled, the reported doses of Gadobutrol before the onset of symptoms were 0.49 mmol/kg BW in one patient and 0.19 mmol/kg BW in the other.

For the multiple-agent report fulfilling the Cowper criteria, the patient had 7 injections which included Magnevist, Gadobutrol and Dotarem. The maximum known single dose was 0.25 mmol/kg BW, and the patient received a total of 1.14 mmol/kg BW plus an additional unquantified GBCA dose.

9.6.2.4.5. NSF reports by identity of GBCA administered

The GBCAs identified in the 10 reports of NSF or NSF-like symptoms in association with Gadobutrol reports are provided in Text Table 30. Four patients reportedly received Gadobutrol only (single agent reports), while 6 patients reportedly received Gadobutrol in addition to other GBCAs (multiple agent reports).

Text Table 30 GBCAs identified in NSF reports received by Bayer

Observation period: Launch (1999) to 15 November 2010

	Gadobutrol	ProHance	Dotarem*	Magnevist	Omniscan	Number of patients
Single-agent	•					4
Multiple-agent	•		•	•		1
	•				•	1
	•			•		2
	•	•				1
	•			•	•	1

* macrocyclic agent not approved in the US

9.6.2.4.6. NSF reports by country

The geographical origin of all 10 reports are provided in Text Table 31. No particular conclusion can be drawn from this data, although 5 of the 10 reports have been received from Denmark.

Text Table 31 Reports of NSF-like symptoms by geographical origin

Observation period: Launch (1999) to 15 November 2010

		Number of reports
Geographical origin	Denmark	5
	Germany	2
	Switzerland	2
	Norway	1
	Total	10

9.6.2.4.7. Literature reports

There are case reports in the literature describing four of the patients with reports of NSF or NSF-like symptoms (Wollanka et al. 2009 and Collidge et al. 2010; Elmholdt et al. 2010, Morcos et al 2010 and Elmholdt 2010; Becker et al. 2010). These reports are included in the summary of reports described above.

9.7. GRIP study (Safety of Gadovist in Renally Impaired Patients)

The Food and Drug Administration, in 2007, required manufacturers of GBCAs to conduct post-marketing studies to assess the magnitude of potential risk of GBCAs in patients with moderate to severe renal impairment. Bayer voluntarily initiated, outside of the US, the "GRIP" study (Safety of Gadovist in Renally Impaired Patients), a prospective non-randomized (pharmaco-epidemiologic) cohort study (open-label, multicenter) to assess the magnitude of potential risk with the administration of Gadobutrol in patients with moderate to severe renal impairment for the development of NSF based on diagnostically specific clinical and histopathologic information. The design is similar to the post-marketing studies required by the FDA for GBCAs approved in the US. The study has voluntarily been initiated by Bayer with the first patient entered in 2008.

At least 1000 patients are scheduled to undergo contrast-enhanced MRI with Gadobutrol, including 600 with moderate (eGFR from 30 to 59 mL/min/1.73 m^2) and 400 with more severe (eGFR < 30 mL/min/1.73 m^2) renal impairment. Standardized active follow-up contacts with study participants at pre-defined time points (follow-up visits at 12 and 24 months post-injection and telephone contacts at 1, 3, 6, and 18 months post-injection) are designed to provide all necessary information on any NSF-related events or changes in health status of the study patients after administration of Gadobutrol for contrast-enhanced MRI for a follow-up period of two years.

The primary objective is to assess the magnitude of potential risk with the administration of Gadobutrol in patients with moderate to severe renal impairment for the development of NSF, based on diagnostically specific clinical and histopathological information.

The first patient was enrolled on 8 December 2008. As of 30 November 2010:

- 43 study sites in countries with Marketing Authorization in Europe, Asia Pacific and Canada have been activated.
- A total of 453 patients have been enrolled.
- Among these, 349 patients are in follow-up (211 moderate, 123 severe, 14 eGFR 60 to 65 mL/min, 1 unknown [no central laboratory]).

As of 30 November 2010, no reports of NSF have been received from this study.

9.8. Labeling

Summary:

- Proposed US package label is consistent with the labeling for products labeled as having a lower NSF risk (no contraindications regarding NSF)
- Proposed labeling contains a Boxed Warning, Warnings and Precautions and Patient Counseling Information for patients with chronic or severe renal impairment (< 30 mL/min/1.73m^2) or Acute Kidney Injury.

9.8.1. Labeling considerations

In September 2010, FDA issued a Drug Safety Communication requiring changes in the drug label for marketed GBCAs. These changes, based on FDA's review of the safety of GBCAs and discussions by the FDA Advisory Committee on 8 December 2009, consist of recommendations to not to use three GBCAs (Omniscan, OptiMARK, and Magnevist) in patients with chronic, severe kidney disease (< 30 mL/min/1.73m^2) or Acute Kidney Injury. These three GBCAs are contraindicated in these patients.

Based on its structure, stability, physicochemical properties, non-clinical data, clinical data and post-marketing data, as well as other general information regarding the relationship of GBCAs and the potential risk of NSF, Bayer proposes that Gadobutrol should have the same warning concerning the potential risk of NSF in the identified patient population (acute kidney injury; and chronic, severe kidney disease) as for the other US-marketed GBCAs approved for the CNS indication and labeled as having a lower risk for NSF, such as the macrocyclic ProHance.

9.8.2. Proposed Gadobutrol NSF labeling

Consistent with all other GBCAs that have been approved for marketing in the US, a Boxed Warning is included in the proposed US product label for Gadobutrol.

WARNING: Nephrogenic systemic fibrosis (NSF)

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities. NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs.

- The risk for NSF appears highest among patients with:
  - Chronic, severe kidney disease (GFR < 30 mL/min/1.73m^2), or
  - Acute kidney injury.
- Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (for example, age > 60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.
- For patients at highest risk for NSF, do not exceed the recommended Gadobutrol dose and allow a sufficient period of time for elimination of the drug from the body prior to re-administration *[see Warnings and Precautions]*.

Additional information in the Warnings and Precautions section of the proposed US product label for Gadobutrol advises on screening procedures, dosing considerations in the renally impaired population, information that prompt hemodialysis might help to clear gadolinium from the body (although it is unknown whether hemodialysis prevents NSF) and reporting instructions.

The proposed Warnings and Precautions section states:

> Gadolinium-based contrast agents (GBCAs) increase the risk for nephrogenic systemic fibrosis (NSF) among patients with impaired elimination of the drugs. Avoid use of GBCAs among these patients unless the diagnostic information is essential and not available with non-contrast enhanced MRI or other modalities. The GBCA-associated NSF risk appears highest for patients with chronic, severe kidney disease (GFR <30 mL/min/1.73m^2) as well as patients with acute kidney injury. The risk appears lower for patients with chronic, moderate kidney disease (GFR 30- 59 mL/min/1.73m^2) and little, if any, for patients with chronic, mild kidney disease (GFR 60- 89 mL/min/1.73m^2). NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs. Report any diagnosis of NSF following Gadobutrol administration to Bayer HealthCare Pharmaceuticals (1-888-842-2937) or FDA (1-800-1088 or www.fda.gov/medwatch).
>
> Screen patients for acute kidney injury and other conditions that may reduce renal function. Features of acute kidney injury consist of rapid (over hours to days) and usually reversible decrease in kidney function, commonly in the setting of surgery, severe infection, injury or drug-induced kidney toxicity. Serum

creatinine levels and estimated GFR may not reliably assess renal function in the setting of acute kidney injury. For patients at risk for chronically reduced renal function (for example, age >60 years, diabetes mellitus or chronic hypertension), estimate the GFR through laboratory testing.

Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of a GBCA and degree of renal impairment at the time of exposure. Record the specific GBCA and the dose administered to a patient. For patients at highest risk for NSF, do not exceed the recommended Gadobutrol dose and allow a sufficient period of time for elimination of the drug prior to re-administration. For patients receiving hemodialysis, physicians may consider the prompt initiation of hemodialysis following the administration of a GBCA in order to enhance the contrast agent's elimination. The usefulness of hemodialysis in the prevention of NSF is unknown.

Further measures to minimize risk of NSF for GBCAs include, in addition to the warnings in the product labeling described above, patient counseling information in the product labeling.

The proposed Patient Counseling Information section states:

GBCAs increase the risk of NSF among patients with impaired elimination of drugs. To counsel patients at risk of NSF:

- Describe the clinical manifestation of NSF
- Describe procedures to screen for the detection of renal impairment

Instruct the patients to contact their physician if they develop signs or symptoms of NSF following Gadobutrol administration, such as burning, itching, swelling, scaling, hardening and tightening of the skin; red or dark patches on the skin; stiffness in joints with trouble moving, bending or straightening the arms, hands, legs or feet; pain in the hip bones or ribs; or muscle weakness.

9.9. Summary and conclusions

NSF is a rare, but serious disease that has been predominantly observed in patients with chronic, severe kidney disease (GFR < 30 mL/min/1.73 m^2) or Acute Kidney Injury. Exposure to GBCAs has been identified since 2006 as a potential risk factor for acquiring this serious and often disabling disease.

In the at-risk population, use of GBCAs should be carefully considered to determine if the expected benefit for an individual patient outweighs the individual NSF risk. The choice of a GBCA in the at-risk population should be limited to those products not contraindicated in this population.

Based on all available data and analysis:

- Gadobutrol demonstrates a very high stability (similar to that of the other US marketed macrocyclic GBCA ProHance), suggesting a lower potential for Gadobutrol to release Gd^{3+} ions in vivo in comparison to linear GBCAs
- Non-clinical studies did not reveal any macroscopic or microscopic effects of the Gadobutrol administration on skin or signs of NSF, and, as with the other macrocyclic GBCAs, had no measurable release of Gd in human serum
- Gadobutrol can be effectively removed from the body by hemodialysis
- After an estimated total of 6.1 million post-marketing administrations of Gadobutrol, 2 single agent reports of NSF or NSF-like symptoms have been received for Gadobutrol in which the available clinical and histological information is consistent with NSF according to the criteria of Cowper et al. One additional report fulfilling the same criteria is a multiple agent report. In addition, there were 7 reports involving Gadobutrol that do not fulfill these criteria or do not provide sufficient information.
- No cases of NSF have been reported in clinical studies and the ongoing GRIP study

Conclusion

Taking all available information into account, the potential NSF risk for patients in the identified at-risk population receiving Gadobutrol is similar to that of the macrocyclic ProHance with a labeled lower risk for NSF.

The proposed US labeling for Gadobutrol includes the same Boxed Warning, Warnings and Precautions, and Patient Counseling language as the other GBCAs (including the other macrocyclic ProHance) which are labeled as having a lower risk for NSF (i.e not contraindicated in the at-risk population).

10. Risk management

Summary:

NSF and dose misadministration, especially in the population at risk for NSF, are risks that will be specifically addressed in the risk management plan for Gadobutrol.

- Bayer will implement similar risk minimization measures for NSF as those currently in place for other GBCAs including a class labeling (Boxed Warning, Warnings and Precautions, Patient Counseling Information) and quarterly summaries of all NSF reports for FDA.
- Bayer has proactively initiated a pharmacoepidemiology study in renally impaired patients (GRIP) in line with FDA post-marketing requirements of other GBCAs marketed in the US.
- Bayer proposes measures to minimize the risk for dose misadministration in all patients with special attention to the at-risk of NSF population (those with chronic, severe kidney disease (glomerular filtration rate [GFR] < 30 mL/min/1.73m^2), or Acute Kidney Injury). These measures include:
  - Conspicuous labeling and packaging that highlights Gadobutrol's high concentration and low dose volume
  - Dosing charts
  - Educational initiatives for health care providers

10.1. Nephrogenic systemic fibrosis (NSF)

The medical community has developed an increased awareness of the NSF risk of all GBCAs in patients with severe renal impairment. Clinically, contrast enhancement and alternative imaging modalities must be considered carefully in these patients. Current risk management measures (e.g. label warnings) have been effective in educating providers on appropriate use of these agents and on the population at risk. As a result, reports of NSF associated with GBCAs have declined considerably.

10.1.1. Proposed labeling

Gadobutrol's structure, physicochemical properties, non-clinical, clinical and safety data are similar to that of the other macrocyclic GBCA (ProHance) for which the FDA has not required a contraindication in patients with severe renal impairment. Bayer proposes that Gadobutrol's label contain the same Boxed Warning, Warnings and Precautions and Patient Counseling Information language as those GBCAs with a lower risk of NSF. (See Section 9.8 for details).

10.1.2. Pharmacovigilance

Upon marketing approval of Gadobutrol by the FDA, Bayer Global Pharmacovigilance (GPV) will continue its ongoing pharmacovigilance and risk assessment programs in both the postmarketing and clinical research settings. Quarterly summaries of all NSF reports have been submitted to the FDA since 2006.

Any report of NSF received by Bayer is evaluated for possible association with any of Bayer's marketed MR contrast media according to the criteria of Cowper et al. (as discussed in Section 9.6.2.2).

In addition to ongoing monitoring of all incoming adverse events, safety surveillance efforts include monitoring of the scientific literature, and careful follow-up of new and potential NSF reports using a targeted questionnaire.

Any reports of NSF or NSF-like symptoms will continue to be promptly reported to health authorities, including the FDA.

10.1.3. GRIP

Bayer has voluntarily initiated a pharmacoepidemiology study (GRIP; described in detail in Section 9.7), to assess the risk of NSF in patients with moderate and severe renal disease. This study is in line with similar studies required by FDA of other GBCAs. As an additional initiative to assess the risk of NSF with the use of Gadobutrol, Bayer proposes as a post-marketing commitment expanding the GRIP study to include study sites located in the US.

10.2. Dose misadministration

One of the measures now required by the FDA in the risk management of NSF is the adherence to the standard dose in patients having a greater risk of NSF. Gadobutrol is the only GBCA formulated at a 1.0 M concentration; all other GBCAs approved for CNS imaging are formulated at a 0.5 M concentration. Consequently, to deliver the recommended target dose, Gadobutrol requires only half of the injection volume needed for all other GBCAs (0.1 versus 0.2 mL per kg BW; Text Table 32).

Text Table 32 Volume per application dependent on concentration

	Target dose (mmol/kg BW)	**Concentration** (mmol/mL)	**Target volume** (mL/kg BW)
Gadobutrol	0.1	1.0	0.1
Other GBCAs	0.1	0.5	0.2

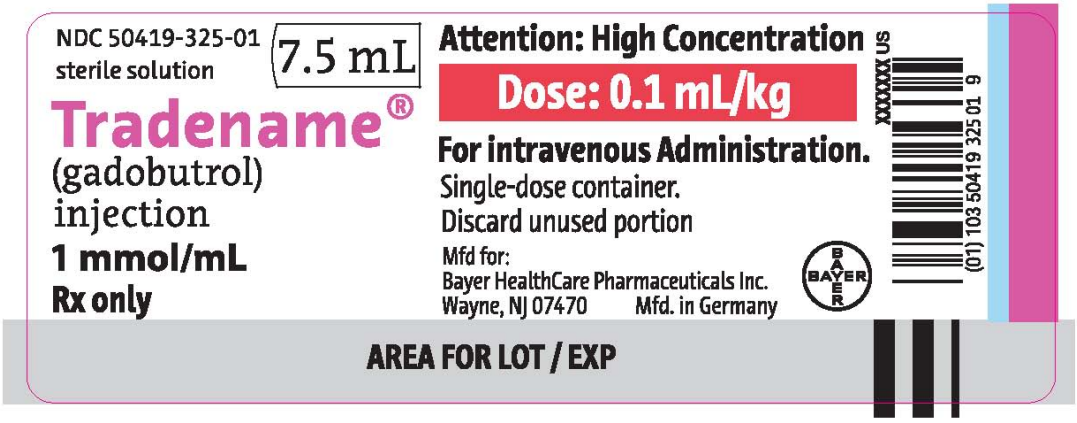
For example, for a 75 kg patient, the proposed volume of administration of Gadobutrol would be 7.5 mL (75 kg * 0.1 mmol/kg), while for other GBCAs indicated for CNS MR imaging, the corresponding volume would be 15 mL (75 kg * 0.2 mmol/kg).

Radiologists are accustomed to using different contrast agents with different concentrations and volumes. If the volume of Gadobutrol is erroneously calculated based on the dosing algorithm for other GBCAs, there is potential for administering a double dose of Gadobutrol. FDA has concluded in September 2010 that all GBCAs should carry the following label statement: "Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of a GBCA and degree of renal impairment at the time of exposure."

Though the risk of dose misadministration for the general population is very low, Bayer is committed to facilitating the safe and appropriate use of all of its products. Reports of dose misadministration were noticed in routine monitoring in the two Phase 3 studies 310123 and 310124 (See Section 8.1.3.3 for details). Good communication with the investigator sites on proper dosing of Gadobutrol by way of simple reminders in two study newsletters helped to prevent further dosing errors in these studies. Also of note, the clinical trial material labels for these studies did not highlight Gadobutrol's higher concentration or the recommended dose volume. Drawing from this experience, Bayer is proposing additional labeling, packaging and educational efforts to facilitate proper dosing of Gadobutrol post-approval.

10.2.1. Labels and cartons: Display of Gadobutrol's higher concentration and recommended dose

Bayer plans to prominently and conspicuously display Gadobutrol's higher concentration and recommended lower dosing volume on all labels and cartons for Gadobutrol vials, pre-filled syringes, and Pharmacy Bulk Packs. The proposed labels and cartons contain the words "Attention: High Concentration" in bold as well as the recommended dose volume ("Dose: 0.1 mL/kg") highlighted in a red box. An example of the proposed labeling is provided in Text Figure 20. Moreover, the individual package volumes are differentiated using different colors to highlight the total volume contained in the package. In addition, the proposed Pharmacy Bulk Pack labels contain tear-off labels for labeling individual doses.



Text Figure 20 Proposed 7.5 mL label for Gadobutrol

10.2.2. Package insert labeling: Dosing chart

To reduce the potential for medication administration errors, Bayer will prominently and conspicuously emphasize Gadobutrol's concentration and recommended dose volume (0.1 mL/kg BW) in the prescribing information.

In addition, as required by FDA of other GBCAs, Bayer proposes to include the following statement in Gadobutrol's Boxed Warning: "For patients at highest risk for NSF, do not exceed the recommended Gadobutrol dose and allow a sufficient period of time for elimination of the drug from the body prior to re-administration".

Bayer also proposes to include in the package insert a graded dosing chart that clearly and accurately indicates the recommended dose volume (in mLs) for a patient's weight. (A draft dosing chart is shown in Text Table 33.)

Text Table 33 Injection volume by body weight

Volume of Gadobutrol by body weight		
Body weight		**Total volume**
lb	kg	mL
22	10	1
33	15	1.5
44	20	2
55	25	2.5
66	30	3
77	35	3.5
88	40	4
99	45	4.5
110	50	5
132	60	6
154	70	7
176	80	8
198	90	9
220	100	10
242	110	11
264	120	12
286	130	13
298	140	14

10.2.3. Communication and education initiatives

Bayer has more than 20 years of experience in the field of MR imaging and a long tradition of helping to educate Health Care Providers, technologists and radiology suite personnel on the safe and appropriate use of its contrast media products.

Bayer proposes an extensive communication plan to create awareness of proper dosing and use of Gadobutrol among physicians, radiology technologists and radiology nurses with the following key dosing and safety information objectives:

- The Gadobutrol concentration (1.0 M), is twice the concentration of many other extracellular GBCAs with CNS indications (0.5 M). Therefore, the recommended dose of 0.1 mmol/kg BW has a lower dose volume (half the volume in mL/kg BW).
- Boxed Warning and Warning and Precautions label language common to Gadobutrol and other GBCAs with a lower potential risk of NSF, including the importance of avoiding repeat or higher dose administration
- Instruct providers to counsel patients at risk for NSF

- The importance of, and process for, reporting adverse events and dose misadministration with any GBCA including Gadobutrol

The educational and communication plan for providers will be executed as follows:

- Bayer plans to develop a field force sales training program that includes education on the 1.0 M concentration of Gadobutrol, how it differs from other GBCAs currently marketed in the US, and the potential for administration errors. Before communicating with Health Care Providers, the field force will be required to pass both a written and an oral test intended to demonstrate their understanding of prescribing information in the label, including proper dosing.
- Bayer proposes to provide Health Care Providers with a dosing chart in addition to that found in the prescribing information to facilitate accurate dosing of patients with Gadobutrol. The dosing chart will be in both pounds and kilograms.
- Bayer proposes to include the dosing chart in launch branded detail pieces, Gadobutrol formulary kits, and to provide this chart to new customers receiving Gadobutrol via samples or trade product.
- Bayer branded educational program speakers will be trained to effectively communicate to other Health Care Providers Gadobutrol's proper dosing schedule.
- Bayer branded educational web-based programs for Health Care Providers will emphasize Gadobutrol's 1.0 M formulation compared to other extracellular GBCAs (0.5 M) and the correct dose and volume to be administered. At the end of each program, post-program surveys will evaluate participants' understanding of the key learning objectives listed above. For incorrect answers, online immediate explanation with the correct information will be provided to the participant and a re-test administered. In addition, the content of the web-based programs will be evaluated and modified based on Health Care Providers performance in and feedback on the after-program survey.
- Bayer proposes to distribute leave-behind materials such as a Gadobutrol presentation and a dosing chart for Health Care Providers who want to educate other Health Care Providers in their individual institutions on the appropriate dosing and administration of Gadobutrol
- We propose including the dosing chart in a Gadobutrol branded website.
- Bayer proposes including a standard statement on drug dosing and administration in Gadobutrol Medical Content Letters.
- The Bayer HealthCare Medical Communications contact center (888-84BAYER) will be trained on Gadobutrol. This training will include correctly responding to dosing questions. Dosing FAQs will be developed and made available for all contact center employees for their reference in their working system.

- Bayer plans to survey a sample of Health Care Providers at specified intervals for the first year after launch to assess their knowledge of key learning objectives stated above.

10.2.4. Conclusion

Bayer intends to minimize and manage risk for NSF and dose misadministration with Gadobutrol by:

- A Boxed Warning and Warning and Precautions, and Patient Counseling Information label language that highlights the risks of NSF, higher than standard doses, and re-administration with Gadobutrol, in patients with chronic, severe kidney disease or Acute Kidney Injury renal impairment
- Expansion to the US of an on-going observational study to further characterize the risk of NSF with Gadobutrol
- Conspicuous packaging and labeling that prominently displays Gadobutrol's higher concentration and recommended lower dosing volume
- Comprehensive communication and education to providers to facilitate safe and appropriate dosing of Gadobutrol and prompt reporting of adverse events and dose misadministration

11. Benefit-risk considerations

This application focuses on the efficacy and safety of 0.1 mmol/kg BW of Gadobutrol for contrast-enhanced MRI of the CNS. One-molar Gadobutrol was first approved in 1998 and is marketed now in 65 countries worldwide. Through 31 October 2010, Gadobutrol is estimated to have been administered to over 6.1 million patients. Since about 2007, worldwide usage of Gadobutrol has increased significantly, indicating a positive benefit-risk ratio also after NSF labeling changes introduced outside the US. Numerous regulators worldwide and radiological societies such as the ACR consider Gadobutrol as belonging to GBCAs with lower NSF risk.

11.1. Benefit

Gadobutrol has the highest relaxivity amongst all macrocyclic GBCAs. The 1.0 M concentration, combined with high r1, yields the highest T1-shortening effect per unit volume. The high complex stability of Gadobutrol as a macrocyclic GBCA with regard to the release of gadolinium from the chelate reduces the potential to trigger NSF. This high relaxivity and high T1-shortening effect contributed to Gadobutrol's improved diagnostic imaging and visualization qualities as compared to conventional 0.5 M GBCA

at equimolar doses. Despite the higher concentration, the viscosity of 1.0 M Gadobutrol is similar to 0.5 M GBCAs. The higher concentration reduces the injection volume and may provide further advantages in dynamic imaging procedures.

The two Phase-3 trials undertaken for the development in the US independently met all of their pre-specified primary and secondary efficacy objectives as have previous development studies conducted for approval in Europe, China and rest of the world. Additional pooled analyses of efficacy in the two US studies demonstrated that the efficacy of Gadobutrol is consistent across demographic and disease subgroups. Both studies showed consistent improvements over non-enhanced MRI despite inclusion of all-comers as compared to clinical routine where only about 40% of patients receive an additional contrast-enhanced scan to assess the clinical question.

One of these Phase-3 studies compared Gadobutrol with ProHance and showed – in pre-specified secondary endpoints - improved sensitivity and accuracy of 1.0 M Gadobutrol over the 0.5 M comparator (ProHance) in detecting malignant lesions. Likewise, improved image quality and preference of the blinded Gadobutrol images was consistently shown for all 3 blinded readers.

In conclusion, 1.0 M macrocyclic Gadobutrol offers significant diagnostic properties and improved contrast-enhanced imaging in patients requiring contrast-enhanced MRI of the CNS including patients with severe renal impairment.

11.2. Risks

General GBCA class risks

The general risks associated with GBCAs are well known and are similar across all agents, including Gadobutrol, for which the safety profile has been established in over 11 years of clinical and post-marketing use. Risk management measures currently in place in the US for all GBCAs are also proposed for Gadobutrol, as they have proven to adequately mitigate risks. Similar measures have been introduced by other regulators, such as EMA, for GBCAs including Gadobutrol. Recently introduced measures for all GBCAs focus on the NSF risk, predominantly in patients with chronic, severe kidney disease or Acute Kidney Injury.

<u>NSF</u>

GBCAs have been used in the US for over 20 years and have a well-established safety profile. Following the occurrence of NSF in 2006, FDA has further enhanced labeling and risk management for all GBCAs on the US market in 2010, differentiating agents into those with the highest number of reports from those with fewer reports. FDA-mandated risk management, including risk mitigation activities for all manufacturers, combined with increased awareness and modified prescribing behavior of the professional radiological and medical community has led to a sharp decline of new NSF reports since 2008.

The relative potential for macrocyclic Gadobutrol to trigger development of NSF in patients with severely impaired kidney function as compared to other GBCAs can be considered low. This is also reflected in the labeling of Gadobutrol outside the US.

Specific risk

Dose misadministration

The higher concentration of 1.0 M macrocyclic Gadobutrol as compared to other, 0.5 M GBCAs licensed and used in the US warrants consideration of a potential for dose misadministration, i.e. inadvertently doubling the proposed dose of 0.1 mL/kg, as the administration volume to achieve equimolar doses is halved for Gadobutrol. The overall safety profile, including anaphylactic reactions and local tolerance for Gadobutrol as known from 11 years of post-marketing experience is very similar to that of 0.5 M agents.

Of note, while dose misadministration should be avoided in all patients, a specific risk may only be associated in the population at risk for developing NSF, i.e. those with a GFR <30 mL/min/1.73 m^2. In the general population, dose misadministration is very unlikely to be associated with an additional risk as the resulting dose is well within the approved dose range outside the US (up to 0.3 mmol/kg BW) and because Gadobutrol has a very large safety margin.

For the at-risk population, the risk also appears well manageable. In the radiological community, there is a very high awareness of the risks of NSF. Since the association between NSF and renal impairment and initial regulatory action in 2007, the use of GBCAs in the at-risk patient population has decreased substantially. Very high scrutiny prevails when administering GBCAs to patients with impaired kidney function in whom the individual benefit still outweighs the potential risk. This scrutiny, together with the risk management measures proposed by Bayer to manage the risk of dose misadministration in this population, will help ensure the risk of NSF for Gadobutrol remains low.

11.3. Conclusion

Gadobutrol has demonstrated convincing efficacy, both with respect to superior diagnostic and visualization performance compared to unenhanced imaging. Gadobutrol has high relaxivity (the highest relaxivity amongst all macrocyclic GBCAs), which combined with the unique 1.0 M formulation, yields the highest T1-shortening effect per mL compared to other GBCAs. This highest relaxivity amongst all macrocyclic GBCAs is reflected in a Phase-3 study that compared Gadobutrol with ProHance and showed – in pre-specified secondary endpoints - improved sensitivity and accuracy of 1.0 M Gadobutrol over the 0.5 M comparator (ProHance) in detecting malignant lesions.

The safety of Gadobutrol has been extensively characterized in both clinical studies and in the post-marketing setting outside the US. The overall safety profile of Gadobutrol has been established in clinical programs in more than 4500 patients, and in the post-approval setting in more than 6.1 million patients throughout 11 years of marketing. At the proposed dose of 0.1 mmol/kg BW (equivalent to 0.1 mL/kg BW) (one third of the approved dose of 0.3 mmol/kg BW outside the US), Gadobutrol has a large safety margin and is approved in doses up to 0.3 mmol/kg BW outside the US. The potential risk for NSF after receiving Gadobutrol appears to be similar to that for other macrocyclic GBCAs with a labeled lower risk for NSF, such as ProHance. The risk management measures proposed by Bayer will help ensuring that the risk for a dose misadministration of Gadobutrol, especially in the at-risk population, remains low.

Based on all clinical trial and post-marketing safety data, the benefit-risk assessment of Gadobutrol is considered to be favorable and supports the use of this GBCA for CNS imaging in adults and children aged 2 to 17 years at a dose of 0.1 mmol/kg BW.
A favorable benefit-risk assessment also applies to patients with severe renal impairment.

Approval of 1.0 M Gadobutrol will add another, diagnostically highly effective, macrocyclic agent understood to be associated with a low risk for triggering NSF to the armamentarium of the radiologist.

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13. Appendix

13.1. List of clinical studies for Gadobutrol

Study number	Region	No. of subjects	Gadobutrol conc.	Doses studied	Indication	Study design
Pivotal Phase-3 clinical studies						
310123	US, South America & Asia	403	1.0 M	0.1 mmol/kg	CNS	2-period cross-over with Gadobutrol and ProHance
310124	US, Asia South America	343	1.0 M	0.1 mmol/kg	CNS	Single arm Gadobutrol
Additional key clinical studies						
308200	US & South America	229	1.0 M	0.03, 0.1 or 0.3 mmol/kg	CNS	Phase 2: 2-period cross-over with Gadobutrol and OptiMARK
310788	Europe and Canada	138	1.0 M	0.1 mmol/kg	Pediatric	Phase 1/3; single arm Gadobutrol
Phase-1 clinical studies						
92001	Europe	55	0.5 M	0.04, 0.1, 0.2, 0.3, and 0.4 mmol/kg	healthy volunteer	Single-dose safety, tolerability and pharmacokinetics study in healthy Caucasian adult men
92010	Europe	36	1.0 M	0.3, 0.4, and 0.5 mmol/kg	healthy volunteer	Single-dose tolerability study in three dose levels
93016	Japan	32	0.5 M	0.05, 0.1, 0.2, and 0.4 mmol/kg	healthy volunteer	Japanese single-dose safety, tolerability and pharmacokinetics study in healthy Japanese adult men
96063	Europe	20	0.5 M and 1.0 M	0.05, 0.1 or 0.2 mmol/kg (multiple injections)	healthy volunteer	Pilot study in healthy volunteers on bolus geometry, resulting from different application schemes and dosages
97113	Europe	48	1.0 M	0.3, 0.5, 0.75, 1.0, 1.25, or 1.5 mmol/kg	healthy volunteer	Single-dose safety, tolerability and pharmacokinetic study in healthy Caucasian adult men
98098	Europe	45	0.5 M and 1.0 M	0.3 mmol/kg	healthy volunteer	Intraindividual controlled, randomized, crossover concentration comparison study of 0.5 and 1.0 molar Gadobutrol injection in MR brain perfusion imaging in healthy volunteers
307362	US	64	1.0 M	0.1, 0.3 and 0.5 mmol/kg	healthy volunteer	Thorough QT study in healthy adults of different ethnicities including pharmacokinetics
308183	Europe	23	1.0 M	0.1 mmol/kg	healthy volunteer	Single-dose safety, tolerability and pharmacokinetics study in healthy non-elderly and elderly male and female healthy subjects
310865	Japan	40	1.0 M	0.1, 0.2, 0.3 or 0.1+ 0.1 mmol/kg	healthy volunteer	Japanese single-dose safety, tolerability, pharmacokinetic and divided dose study in healthy Japanese adult men

Study number	Region	No. of subjects	Gadobutrol conc.	Doses studied	Indication	Study design
Phase-2 to 4 clinical studies						
92095	Europe	64	0.5 M	0.3 mmol/kg	CNS	single arm Gadobutrol
92096	Europe	103	0.5 M	0.1, 0.2, or 0.3 mmol/kg	Body	single arm Gadobutrol
92097	Europe	47	0.5 M	0.1+ 0.1 + 0.1 mmol/kg (total 0.3 mmol/kg)	CNS	single arm Gadobutrol
93017	Japan	18	0.5 M	0.1 mmol/kg	CNS	single arm Gadobutrol
93018	Japan	38	0.5 M	0.1 mmol/kg	Body	single arm Gadobutrol
94061	Europe	89	1.0 M	0.1, 0.2, 0.3, 0.4, or 0.5 mmol/kg	CNS (Brain Perfusion)	single arm Gadobutrol
94368	Japan	114	0.5 M	0.1 mmol/kg	CNS	two parallel arms with Gadobutrol and Magnevist
94369	Japan	62	0.5 M	0.1 + 0.1 + 0.1 mmol/kg (total: 0.3 mmol/kg)	CNS	single arm Gadobutrol
94383	Japan	13	0.5 M and 1.0 M	0.15 mmol/kg	CNS (Brain Perfusion)	two period cross-over with different Gadobutrol concentrations
97035	Europe	241	1.0 M	0.05, 0.15 or 0.25 mmol/kg	MR Angio-graphy	three parallel arms with different Gadobutrol doses
305501	Europe	226	1.0 M	0.01, 0.025 or 0.05, or 0.1 mmol/kg; two injections (Total: 0.02, 0.05 or 0.1, or 0.2 mmol/kg)	Myocardial perfusion	single arm Gadobutrol
310864	Japan	164	1.0 M	0.1+ 0.1 mmol/kg (Total: 0.2 mmol/kg)	CNS	two period cross-over with Gadobutrol and ProHance
94052	Europe	305	0.5 M	0.1 mmol/kg	CNS	two parallel arms with Gadobutrol and Omniscan
94054	Europe	296	1.0 M	0.1 and 0.2 mmol/kg (total 0.3 mmol/kg)	CNS	single arm Gadobutrol
94055	Europe	182	1.0 M	0.1 mmol/kg	Body	single arm Gadobutrol
95062	Europe	32	1.0 M	0.1 or 0.3 mmol/kg	Renally-impaired	two parallel arms with different Gadobutrol doses
95064	Europe	44	1.0 M	0.3 mmol/kg	CNS	single arm Gadobutrol
95359	Japan	175	0.5 M	0.1 mmol/kg	Body	single arm Gadobutrol
95361	Japan	196	0.5 M	0.1 mmol/kg	CNS	single arm Gadobutrol
95362	Japan	134	0.5 M	0.1 mmol/kg	Body	single arm Gadobutrol
95363	Japan	100	0.5 M	0.1+ 0.2 mmol/kg (total: 0.3 mmol/kg)	CNS	two parallel arms with different Gadobutrol doses
95364	Japan	39	0.5 M	0.05 or 0.1 mmol/kg	Body	two parallel arms with different Gadobutrol doses

Study number	Region	No. of subjects	Gadobutrol conc.	Doses studied	Indication	Study design
97099	Europe	179	1.0 M	7.5 mL for patients <75 kg BW; 10 mL for patients ≥75 kg BW	MR Angio-graphy	single arm Gadobutrol
302722	Europe	203	1.0 M	15 mL for patients <75 kg BW; 20 mL for patients ≥75 kg BW	MR Angio-graphy	single arm Gadobutrol
304300	Europe	53	1.0 M	7.5 or 15 mL for patients <75 kg BW; 10 or 20 mL for patients ≥75 kg BW	MR Angio-graphy	single arm Gadobutrol
304561	Europe	466	1.0 M	0.1 mmol/kg	Body	two parallel arms with Gadobutrol and Magnevist
304562	Europe	572	1.0 M	0.1 mmol/kg	Body	two parallel arms with Gadobutrol and Magnevist
309761	China	146	1.0 M	0.1 mmol/kg	CNS	two parallel arms with Gadobutrol and Magnevist
309762	China	83	1.0 M	0.2 mmol/kg (up to 0.3 mmol/kg)	MR Angio-graphy	two period cross-over with Gadobutrol and Magnevist
302600	Europe	49	1.0 M	2 injections (≥3 hours apart) of 12 or 15 mL depending on body weight (approx. 0.2 mmol/kg)	CNS	single arm Gadobutrol

13.2. Efficacy summaries of additional supportive studies in CNS imaging

The efficacy results obtained from these supportive studies are consistent with those from the pivotal Phase 2 and 3 studies. In brief, all four supportive studies demonstrated that Gadobutrol-enhanced images were superior to unenhanced images with regard to clinically relevant imaging parameters.

Study 94052

This multicenter, two-arm, parallel-group, double-blind, randomized Phase-3 study was conducted between 1994 and 1995 to compare the safety and diagnostic efficacy of 0.5 M Gadobutrol with that of Omniscan (gadodiamide) in patients presenting with evidence of brain lesions, i.e. primary tumors, metastases or inflammatory lesions. Subjects were randomly assigned to receive either contrast agent as a single i.v. dose of 0.1 mmol/kg BW. A total of 298 subjects (Gadobutrol: 153; Omniscan: 145) were included in the efficacy evaluations.

For the majority of subjects, the overall visualization clearly improved after injection of either contrast medium, giving more than 90% good and excellent post-contrast ratings.

Additional radiological information was provided by post-contrast scans for half to three quarters of the subjects regarding each of the parameters lesion size, lesion localization, lesion demarcation and lesion characterization. Diagnostic confidence improved in 90% of subjects in each treatment group.

Both Gadobutrol-enhanced and Omniscan-enhanced MR scans showed clear superiority to unenhanced MR scans. For all efficacy variables, comparable results were obtained with both contrast media. Minor variations, however, were found in some cases in favor of Gadobutrol, in others in favor of Omniscan.

In this study, Gadobutrol was shown to be at least as effective as Omniscan.

Study 94054

This dose-response study was conducted between 1994 and 1995 to evaluate the safety and diagnostic efficacy of two different i.v. doses of Gadobutrol 1.0 M in subjects presenting with evidence of brain or spine lesions. Each subject received two consecutive doses:

1st dose: 0.1 mmol/kg BW (standard dose) and

2nd dose: 0.3 mmol/kg BW (cumulative high dose) – given as an additive dose of 0.2 mmol/kg BW 10 minutes after the 1st dose.

The primary efficacy variable was the investigator's assessment of the change in diagnostic confidence (none, low, moderate, high). The secondary efficacy variables were as follows: qualitative evaluation, quantitative evaluation, global evaluation (i.e. additional radiological information after 1st and 2nd injection) and change in diagnosis.

The diagnostic confidence increased from pre- to 1st post-contrast scans in 95% of subjects regardless of the pre-assessment. After the 2nd injection, diagnostic confidence was further improved, especially in subjects with metastases (70%) and those with multiple sclerosis (65%).

The results for the secondary efficacy parameters (signal intensity ratio; overall visualization; global evaluation; number of lesions) were consistent with the findings for the primary efficacy variable.

It was concluded that 0.1 mmol/kg BW of Gadobutrol remains the recommended standard dose because it adequately answers all questions for the majority of patients; however, in patients in whom additional or more accurate information or the exclusion of any abnormality is expected to influence the patient's therapy or management, it may well be beneficial to give an additional dose of contrast medium to reach the optimal therapy.

The use of higher doses in patients with poorly visualized lesions had been consistent with clinical practice in the 1990s when this study was conducted. In current clinical practice with improved imaging technology, doses above 0.1 mmol/kg BW are very rarely used for CNS imaging.

Study 309761

This two-arm, parallel-group, randomized, single-blind study was conducted between April and July 2007 to demonstrate the non-inferiority of Gadobutrol 1.0 M (dose of 0.1 mmol/kg BW) relative to Magnevist (gadopentetate dimeglumine) 0.5 M (dose of 0.1 mmol/kg BW) with regard to efficacy in Chinese patients.

The primary efficacy variable was the change in contrast-to-noise ratio (CNR) in MRI post-contrast images compared to pre-contrast images of the lesions for both contrast agents as measured by one independent blinded reader off-site. The study was conducted in a total of 147 randomized subjects.

For the change of CNR, the lower limit of the one-sided 95% confidence interval of the difference in the mean change between Gadobutrol and Magnevist was -3.897, which was well above the pre-specified non-inferiority margin of -15%. Hence, non-inferiority of Gadobutrol was statistically confirmed.

The results for the secondary efficacy variables (lesion detection, diagnostic confidence, contrast enhancement, border delineation) were consistent with the findings for the primary efficacy variable.

Study 310864

This randomized, controlled, single-blind study was conducted between 2007 and 2008 to demonstrate the non-inferiority of Gadobutrol 1.0 M (given at a dose of either 0.1 or 0.2 mmol/kg BW) in comparison with ProHance (gadoteridol) 0.5 M (given at a dose of 0.2 mmol/kg BW) in subjects with known or suspected brain metastasis scheduled to undergo a routine contrast-enhanced MRI of the CNS.

Each subject underwent two MRI study sessions, separated by an interval of 24 hours to 2 weeks. One session included pre-contrast imaging and post-contrast imaging with first and second injection of Gadobutrol; the other session included pre-contrast imaging and post-contrast imaging with second injection of ProHance. Thus, five imaging sessions were carried out for each subject.

Assignment to the two Gadobutrol doses was randomized on a 1:1 basis; the same held true for the assignment to the two possible sequences (Gadobutrol followed by ProHance, or vice versa).

The primary efficacy variable was the number of lesions detected in the PPS. For evaluation of the primary variable, three independent blinded readers and one investigator (non-blinded) evaluated the following images separately and recorded the total number of metastatic lesions detected (unenhanced and enhanced lesions):

- Post-contrast image of Gadobutrol first injection (dose of 0.1 mmol/kg BW)
- Post-contrast image of Gadobutrol second injection (total dose of 0.2 mmol/kg BW)
- Post-contrast image of ProHance second injection (total dose of 0.2 mmol/kg BW)

Secondary efficacy variables included contrast enhancement of lesions, border delineation of lesions, patient management, lesion size, and CNR of lesions and normal white matter.

Subjects included into this study (male or female, ≥ 18 years of age) had to present with either known or highly suspected focal areas of disruption in blood-brain barrier (e.g. primary and secondary tumors, focal inflammatory or demyelinating disorder) and/or abnormal vascularity in the CNS.

Of the total of 175 subjects enrolled into the study, 164 subjects received at least one dose. Among these, all were Asian, with a slightly higher proportion of males (54.9%) than females (45.1%); the median age was 63 years, ranging from 27 to 88 years. Primary focus of the subjects was lung cancer (75.0%), breast cancer (12.2%), and others (12.8%). Most of the subjects (> 95%) were diagnosed as having brain metastases at baseline; the mean number of brain metastases was 4.0 (range: 1–40).

A total of 164 subjects completed the first study period, and 159 subjects completed the whole study.

For the PPS, the mean numbers of detected lesions of three blinded readers' average per subject was 6.28, 6.92, and 6.87 for 0.1 mmol/kg BW and 0.2 mmol/kg BW of Gadobutrol, and 0.2 mmol/kg BW of ProHance, respectively. The point estimate and 95% CI (lower limit, upper limit) of the difference (Gadobutrol minus ProHance) was –0.58 (–0.87, –0.29) for 0.1 mmol/kg BW of Gadobutrol and 0.06 (–0.23, 0.36) for 0.2 mmol/kg BW of Gadobutrol. Because the lower limit of 95% CI of the difference was greater than the prospectively defined non-inferiority margin of –1 for both doses of Gadobutrol, the non-inferiority of 0.1 mmol/kg BW and 0.2 mmol/kg BW of Gadobutrol to 0.2 mmol/kg BW of ProHance was proved. Similar results were obtained in the FAS analysis.