Advisory Committee Briefing Document

Medical Imaging Drugs Advisory Committee (MIDAC)
September 8, 2017

DOTAREM® (gadoterate meglumine) Injection
NDA 204781

Guerbet LLC, 821 Alexander Rd, Princeton, NJ 08540

OPTIMARK® (gadoversetamide) Injection
NDAs 020937, 020975 & 020976

Liebel-Flarsheim Company LLC, 1034 Brentwood Blvd., Richmond Heights, MO 63117

ADVISORY COMMITTEE BRIEFING MATERIALS
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Information provided within this briefing document is based upon medical and scientific information available to date.

EXECUTIVE SUMMARY

Gadolinium-based contrast agents (GdCAs) are essential for use in magnetic resonance imaging (MRI). Although non-contrast-enhanced MRI may be sufficient for use in some clinical conditions, contrast-enhanced MRI (CE-MRI) using GdCA provides additional vital diagnostic information in a number of diseases. It is widely recognized that CE-MRI increases diagnostic accuracy and confidence, and thus can impact the medical and/or surgical management of patients. Based on the chemical structure of the complexing ligand, GdCA are classified as linear (L-GdCA) or macrocyclic (M-GdCA) and can be ionic or nonionic and those characteristics have a dramatic influence on the stability of the GdCA.

Dotarem®, a M-GdCA, was first approved in France in 1989. US-FDA approval was obtained in March 2013 for "*intravenous use with MRI of the brain (intracranial), spine and associated tissues in adult and pediatric patients (2 years of age and older) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity*", at the dose of 0.1 mmol/kg BW. The indication in younger children (0-2 years) is currently being reviewed by the FDA with an expected approval by August 2017. To date, Dotarem® is approved in 79 countries worldwide and more than 65 million doses of Dotarem® have been administered since first launch.

Optimark®, a L-GdCA, was first approved in the USA in 1999, at the dose of 0.1 mmol/kg BW, "*for intravenous use with MRI in patients with abnormal blood-brain barrier or abnormal vascularity of the brain, spine and associated tissues, to provide contrast enhancement and facilitate visualization of lesions with abnormal vascularity in the liver of patients who are highly suspect for liver structural abnormalities on computed tomography.*" Optimark® was integrated into the Guerbet portfolio of contrast agents at the end of 2015 following the acquisition of the contrast media and delivery systems business from Mallinckrodt Inc. **It is important to note that Optimark® is being progressively phased-out worldwide based on an internal business decision by Guerbet (product portfolio rationalization).** In 2016, Guerbet voluntarily proposed a labeling modification for Optimark® to the FDA Division of Medical Imaging Products (DMIP), in order to inform the radiologists and the patients about the potential for brain Gd deposition after repeat administration of L-GdCAs. This labeling change in section "12- Clinical Pharmacology / 12.3 Pharmacokinetics" of the Optimark® US-PI was approved by the FDA in August 2016. To date, Optimark is approved in 33 countries and it is estimated that approximately 22 million people received Optimark® since its first launch.

In 2006, a serious and life-threatening syndrome called Nephrogenic Systemic Fibrosis (NSF), involving fibrosis of the skin, joints and internal organs, occurring in patients suffering from severe to end-stage renal impairment, was associated with the prior administration of some GdCAs. The immense majority of NSF cases were observed after single or repeat administration of L-GdCAs, while few or no cases were observed with M-GdCAs. In particular, for Dotarem®, no confirmed uncounfounded case of NSF has been reported to Guerbet or to the Authorities to date. This has lead to labeling modifications and risk minimisation measures worldwide, including contraindicating L-GdCA in patients with severe renal impairment and in young children. In the USA, Optimark® is contraindicated in patients

with severe chronic kidney disease (GFR <30 mL/min/1.73m^2) and in patients suffering from acute kidney injury; while Dotarem® is not contraindicated for use in those patients.

Since 2014, several publications in international scientific journals have suggested Gd deposition and accumulation in specific regions of the brain (globus pallidus and dentate nucleus) of patients receiving multiple administrations of GdCA, without known risk factors such as renal impairment. At this time, two major drug regulatory bodies (US-FDA and EMA) have been/are reviewing data available on this subject and the potential implications for the clinical use of GdCAs. The EMA has recently concluded its review of gadolinium contrast agents, confirming the EMA's Pharmacovilgance Risk Assessment Committee (PRAC) recommendations to maintain all macrocyclic GdCAs in all their indications, to restrict the use of some linear GdCAs in MRI liver scans and suspend the marketing authorizations of the remaining linear agents. The US FDA has called for a public Medical Imaging Drug Advisory Committee (MIDAC) on September 8, 2017 to discuss the safety of GdCAs and more specifically gadolium retention in the brain and body. This briefing document is provided to the MIDAC members and to the FDA to present scientific data available and Guerbet's position on this issue.

Summary of nonclinical studies

1) Evidence of Gadolinium Retention in the brain :

- Nonclinical results are translational to human results; studies have been performed in healthy and renally-impaired rats.
- GdCA entrance into the brain through the CSF route (plexus choroids) has been demonstrated.
- Based on analytical measurement methods, Gd was detected in brain regions with all GdCA tested, with a 4- to 30-fold increase for linear agents compared to macrocyclic agents. Furthermore, the Gd clearance from brain tissue of macrocyclic agents occurred at a much faster rate.
    - A 30-fold higher total Gd concentration in the cerebellum is observed 5 months after the last injection of gadodiamide as compared to gadoterate (healthy rat model).
    - In cerebellum, for gadoterate, 91±5% of Gd found just after the last injection was cleared 5 months after, unlike gadodiamide where only 29±11% of the Gd was cleared.
    - Total Gd elimination half-life from the cerebellum after gadodiamide is longer than 400 days (healthy rat model).
    - Dose-effect is demonstrated: the higher the cumulated dose, the greater the Gd retention in the case of of linear GdCA.
- Based on MRI, T1 enhancement in the cerebellum including dentate nucleus was observed only with linear agents.
- Based on speciation analysis, it has been evidenced that different chemical forms of Gd were detected after linear agents (insoluble form, soluble form associated to macromolecules, small molecule soluble form attributed to intact GdCA), whereas with the current methods, only small molecule soluble form attributed to intact GdCA was observed after macrocyclic agents.

- Most of the Gd detected in the cerebellum of rats treated with the linear GdCA gadodiamide is no longer under intact chelated form (bound to macromolecule) and to a large extent in the insoluble form.
- Insoluble Gd deposits are found after administration of gadodiamide and gadobenate. It is localized in basal membrane around deep cerebellar nuclei (DCN) microvessels, interstitium (ie. beyond the blood brain barrier (BBB)), and sometimes intracellular (astrocytes, macrophages) where they are associated to a pigment, likely lipofuscin (intracellular). The intact chelated form is the only form found in cerebellum of rats treated with gadoterate.

- Data on kinetic and thermodynamic stability, as well as in vitro and nonclinical studies, strongly suggest that L-GdCAs release gadolinium from the ligand molecules.

2) Retention in the skin, bones, and other tissues

- Based on analytical measurement methods, Gd retention in tissues such as skin, bone have been observed with a similar behavior but in higher quantity than in the brain.
- The higher the stability, (macrocyclic agents) the lower is the Gd retention in all organs and tissues.
- Brain, skin and bone retention of linear GdCAs is potentiated by renal impairment, as well as in juvenile rats (immature renal function).
- Strong evidence of retention of dechelated Gd after L-GdCA
- Hypothesis of deep long-term storage compartment (e.g. bone) is highly probable. So far, there is no experimental evidence of a direct link with brain accumulation.

3) Toxicological risk

- Toxicity of Gd^{3+} release by low stability GdCA has been demonstrated (skin lesions, etc.).
- Increased morbidity is found in animals after repeat administration of the less stable GdCA gadodiamide (weight loss, severe adverse events).
- So far, no neuro-histological consequences of Gd brain uptake have been reported in published nonclinical studies.

Summary of pharmacokinetic data

A recent meta-analysis has compared the pharmacokinetic profiles of the different GdCAs in humans. A long-term residual excretion phase in urine was found suggesting the existence of a deep compartment for gadolinium storage, slow release into the blood stream and slow excretion via the renal route. There was a correlation between the slope of this residual excretion phase and the thermodynamic constant of the GdCAs. This correlation means that the lower the thermodynamic stability of the GdCAs, the more prolonged their residual excretion and thus the higher the Gd accumulation in a deep compartment.

Summary of clinical studies

From all the well designed retrospective studies published in humans, either in adults or children, it can be concluded that there is no T1 shortening effect or T1 hypersignal in the brain

and thus no Gd accumulation in the brain or other tissues after repeat administration of Dotarem®. Its high kinetic and thermodynamic stability considerably limits the possibility of dissociation of the Gd from its ligand. This is particularly true when the data are compared to L-GdCAs but also with other M-GdCAs, Dotarem® being the most stable.

However, this stability does not prevent the transient presence of Gd in the CNS measured after Dotarem® administration, which reduces over time after a physiologic mechanism of wash-out. This elimination phenomenon needs more time in patients with renal failure who clearly benefit from using a more stable GdCA.

As of today, the clinical consequences of this presence of Gd in tissues remains unknown even with L-GdCAs. A careful safety monitoring of literature as well as of individual case safety reports is one of the best ways to detect any potential safety signal in a large scale population.

Summary of pharmacovigilance data

Guerbet Pharmacovigilance department recorded only one case report into our global safety database with a description of T1 hypersignal in brain. This case concerns a female patient with renal insufficiency due to auto-immune disease and who received several linear and macrocyclic GdCAs (including Dotarem®). She was also suspected to experience NSF but the diagnosis based on Girardi score remains to be confirmed. Thirteen years after the first known MRI procedures, and 8 years after the last one, unenhanced MRI revealed hyperintensities in Dentate Nucleus and Globus Pallidus and the patient showed neurological disorders with aphasia and vigilance decreased. The case is lacking important information on history of hypersignal in this patient between her first MRI and the beginning of neurological signs, therefore no conclusion can be drawn on the role of Dotarem, and on the contribution of potential confounding factors such as inflammatory conditions, renal insufficiency, arterial disease or calciphylaxis in the occurrence of these brain intensities.

Guerbet's position, proposed actions and risk mitigation measures

GdCA are indispensable agents for diagnosis and follow-up of many diseases using MRI. Outside the hepato-specific agent gadoxetic acid (Eovist®), which has a corresponding specific clinical use, the other GdCAs all belong to the non-specific category. **While having similar diagnostic efficacy, diagnostic performance and short term (immediate) safety profile, they strongly differ in terms of kinetic and thermodynamic stability.**

Short term (acute) adverse reactions, particularly the severe and potentially life-threatening reactions, are very rare, well-known, and are adequately addressed in the GdCA package inserts (contraindication, warning & precautions, etc) and by the radiological community. The first long-term adverse reaction described with some GdCA was NSF, occurring in patients with severe renal impairement. Gd deposition in skin with subsequent inflammatory reaction was a strongly suggested cause for NSF, and was directly linked with the stability of the GdCA. For this reason, the immense majority of NSF cases were described after L-GdCA exposure or multiple agent exposure but always involving one or several injections of L-GdCAs. NSF risk was associated with a very specific patient population (those with severe renal impairment),

and this risk has been adequately managed by contraindicating the less stable GdCAs in those populations and introducing various warnings and precautions for all GdCAs in patients with moderate renal impairment.

Outside the skin, there is now evidence of Gd deposition in multiple organs after exposing adults or children with normal renal function to less stable GdCAs. Gd deposition is becoming Gd accumulation in cases of repeat exposure to low stability GdCAs. While no adverse effects have been confirmed as related to Gd deposition in the brain, long term consequences are unknown at this time. A significant difference with the NSF issue compared to Gd brain deposition is that it is not restricted to at-risk patient populations. It has been observed in patients, either adults or children, with normal renal function. It is therefore not possible to fully address the problem by restricting the use of some GdCAs in specific at-risk populations.

Regarding the Guerbet/Liebel-Flarsheim Company LLC product portfolio, Dotarem® is a macrocyclic and ionic GdCA with a long worldwide marketing history and a well-established safety profile. Having the highest stability in the class, there has been no unconfounded case of NSF with more than 65 million administrations. No brain T1 hyperintensities have been reported with Dotarem®, either in adults or children, contrary to what has been reported with L-GdCAs. Overall, the Dotarem® benefit/risk balance remains favorable and unchanged.

Given the existence of macrocyclic alternatives with a more favorable benefit/risk balance, as well as for commercial reasons and product portfolio rationalization, Guerbet/ Liebel-Flarsheim Company LLC has decided to progressively phase out Optimark® from the US market. This follows the decision of Guerbet to not to renew the Optimark® EU centralized marketing authorization which has expired on 25 July 2017. Before the decision of phasing out Optimark® from the US market, Guerbet/Liebel-Flarsheim was the only linear GdCA manufacturer to voluntarily propose a labeling change regarding the potential for Gd deposition. This modification for Optimark® was submitted to the FDA medical imaging division to inform the health care professionals and patients of the potential for Gd deposition from administration of a linear agent. In collaboration with FDA, the following statement was added in August 2016 to section "12- Clinical Pharmacology / 12.3 Pharmacokinetics" of the Optimark® US package insert:

Deposition with repeated dosing
Increased signal intensity on non-contrast T1-weighted images within the brain, mainly the globus pallidus and the dentate nucleus, has been observed after multiple administrations of linear (ionic and nonionic) gadolinium-based contrast agents due to gadolinium deposition.

Following repeated GBCA administration, gadolinium deposits may be present for months or years in bone, liver, skin, brain, and other organs. Deposition depends on multiple factors and may be greater following administration of gadoversetamide and other linear GBCAs than following administration of macrocyclic GBCAs. GBCAs have been associated with the development of NSF in patients with renal impairment [see Boxed Warning]. The clinical significance of gadolinium retention in the body and brain is otherwise unknown.

It is in Guerbet's opinion that the precautionary principle should be applied when using a GdCA, particularly in patients susceptible to receive multiple GdCA injections during their

life (patients suffering from cancer, multiple sclerosis, other inflammatory and neurodegenerative diseases, etc) and in fragile populations (pediatric patients). Because it is neither deemed feasible nor justified to restrict repeat use of GdCAs during life, as some patient populations require such repeat imaging procedures for the accurate diagnostic and follow-up of their disease and because it is impossible in practice to properly identify in advance such "at-risk populations", **a restriction of use of non-specific L-GdCAs should be considered**.

Therefore, the following risk mitigation measures are proposed by Guerbet:

- Use the GdCA at the lowest approved diagnostic dose. It is not recommended to use lower doses as the one approved for each GdCA, as there is no robust data to demonstrate effectiveness at a lower dose.
- Choose preferentially a M-GdCA due to the higher stability and a very low propensity to release toxic, free Gd. **Restrict the use of non-specific L-GdCAs to second line agents, if an M-GdCA cannot be used (history of hypersensitivity to an M-GdCA, unavailability of M-GdCA, etc.)**. This is in agreement with the National Institute of Health (NIH) recommendations issued in 2016. All approved indications and populations of L-GdCA are covered by M-GdCA, so there will be no diagnostic gap created by a drastic restriction of use of L-GdCA, or even by an NDA withdrawal of those agents. Gadoxetic acid has to be considered separately here as it is a liver-specific agent needing a separate risk-benefit assessment.

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AIP	All Included Patients
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BBB	Blood-Brain Barrier
BUN	Blood Urea Nitrogen
BW	Body Weight
CE-MRI	Contrast-enhanced Magnetic Resonance Imaging
CHMP	Committee for Medicinal Products for Human Use
CKD	Chronic Kidney Disease
CM	Contrast Medium
CMDh	Co-ordination group for Mutual recognition and Decentralised procedures – human
CMR	Cardiovascular Magnetic Resonance
CNR	Contrast-to-Noise Ratio
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CT	Computerized Tomography
DBP	Diastolic Blood Pressure
DCE-MRI	Dynamic Contrast-enhanced Magnetic Resonance Imaging
DCN	Deep Cerebellar Nuclei
DHCP	Direct Healthcare Professional Communication
DN	Dentate Nucleus
DNMCP	DN-to-MCP
DNP	DN-to-pons
DOTA	Tetraazacyclododecanetetraacetic acid
DTPA	Diethylenetriaminepentacetate
ECG	Electrocardiogram
EDSS	Expanded Disability Status Scale
EEG	Electroencephalogram
EELS	Electron Energy Loss Spectroscopy
EES	Extravascular Extracellular Space
EMA	European Medicines Agency
ENT	Ear, Nose and Throat
ESRD	End Stage Renal Disease
EU	European Union
FAP	Glial Fibrillary Acidic Protein
FAS	Full Analysis Set
FDA	Food and Drug Administration
GBCA	Gadolinium-based Contrast Agent
Gd	Gadolinium

Gd-BTDO3A	Gadobutrol (Gadavist® / gadovist®)
Gd-BOPTA	Gadobenate dimeglumine (MultiHance®)
L-GdCA	Linear Gadolinium-containing Contrast Agent
M-GdCA	Macrocyclic Gadolinium-containing Contrast Agent
GdCA	Gadolinium-containing Contrast Agent
Gd-DOTA	Gadoterate meglumine (Dotarem®)
Gd-DTPA	Gadopentetate dimeglumine (Magnevist®)
Gd-DTPA-BMA	Gadodiamide (Omniscan®)
Gd-EOBDTPA	Gadoxetate disodium (Eovist® / Primovist®)
GFR	Glomerular Filtration Rate
GLC	Gadolinium Liver Concentration
GP	Globus Pallidus
GP:T	Globus Pallidus-to-Thalamus
HG glioma	High Grade glioma
HILIC	Hydrophilic-Interaction-Chromatography
HPLC	High Performance Liquid Chromatography
ICP-MS	Inductively Coupled Plasma Mass Spectrometry
ICU	Intensive Care Unit
ITT	Intent-To-Treat
IV	Intravenous
K_{cond}	Conditional Stability Constant
K_{ep}	Constant flux rate between EES and plasma
K_{therm}	Thermodynamic Stability Constant
K_{trans}	Volume transfer constant between plasma and extravascular extracellular space
KDIGO	Kidney Disease Improving Global Outcomes
LA-ICP-MS	Laser Ablation Inductively Coupled Plasma Mass Spectrometry
LDH	Lactate Dehydrogenase
LG glioma	Low Grade glioma
LIC	Liver Iron Concentration
MAH	Marketing Authorization Holder
MCP	Middle Cerebellar Peduncle
MIDAC	Medical Imaging Drugs Advisory Committee
MPS	Mononuclear Phagocyte System
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NDA	New Drug Application
NIH	National Institute of Health
NSF	Nephrogenic Systemic Fibrosis
PET	Positron Emission Tomography
PI	Prescribing Information
PK	Pharmacokinetics
PMS	Post-Marketing Survey
PND	Postnatal Day
PP	Per-Protocol

PPS	Per-Protocol Set
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PSUSA	PSUR Single Assessment
PT	Preferred Term (MedDRA)
RMP	Risk Management Plan
ROI	Region of Interest
RRMS	Relapsing–Remitting Multiple Sclerosis
SAE	Serious Adverse Event
SBP	systolic blood pressure
SEC	Size Exclusion Chromatography
SI	Signal Intensity
SMQ	Standardised MedDRA Query
SmPC	Summary of Product Characteristics
SNR	Signal-to-Noise Ratio
SNx	Subtotal Nephrectomy
SOC	System Organ Class
SOP	Standard Operating Procedure
SPECT	Single Photon Emission Computed Tomography
TEM	Transmission Electron Microscopy
TH	Thalamus
$T_{1/2}$	Half Life Time
TOF	Time of Flight
USA	United States of America
US-PI	US-Prescribing Information
V_e	Fractional distribution volume of the GdCA molecules in the EES

1 INTRODUCTION

Gadolinium-based contrast agents (GdCAs) are essential for use in magnetic resonance imaging (MRI). Although non-contrast-enhanced MRI may be sufficient for use in some clinical conditions, contrast-enhanced MRI (CE-MRI) using GdCA provides additional vital diagnostic information in a number of diseases. It is widely recognized that CE-MRI increases diagnostic accuracy and confidence, and thus can impact the medical and/or surgical management of patients.

During CE-MRI procedures using GdCA, contrast is obtained by signal enhancement produced by the paramagnetic metal, gadolinium (Gd^{3+}; also referred to as Gd in this document). Gd^{3+} enhances the magnetic resonance signal by shortening the relaxation times of extracellular water protons in blood and tissues, which results in increased signal intensity in T1-weighted sequences and reduced signal intensity in T2-weighted sequences. Since free Gd^{3+} is highly toxic in humans, it must be linked to a complexing agent (ligand) when administered in order to suppress its toxicity and ensure rapid excretion from the body. Therefore, it is crucial to ensure a very strong chelation of Gd^{3+} ion to avoid any release of toxic free Gd in the human body. Based on the chemical structure of the complexing ligand, GdCA are classified as linear (L-GdCA) or macrocyclic (M-GdCA) and can be ionic or nonionic and those characteristics have a dramatic influence on the stability of the GdCA (see section 2.1). Several GdCAs have been approved since the late 80's, in the US and other regions of the world, for various clinical uses in adults and pediatrics (approved indications and populations can vary between products and countries):

- Cranial and spinal CE-MRI
- Whole-body CE-MRI
- MR angiography
- Liver imaging (with hepato-specific agents)

Dotarem® is a M-GdCA and contains a 0.5 mol/L aqueous solution of the meglumine salt of gadoteric acid (gadoterate meglumine). Optimark® is a L-GdCA and contains a 0.5 mol/L aqueous solution of gadoversetamide. The chemical structures of both compounds are presented in Figure 1 and Figure 2.

Figure 1: Chemical structure of gadoterate meglumine (Dotarem®)

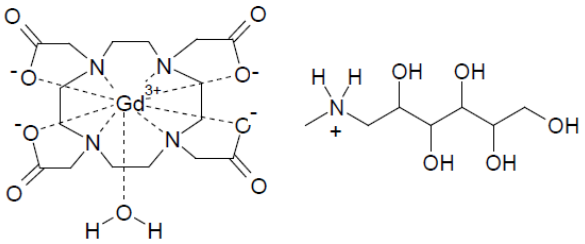
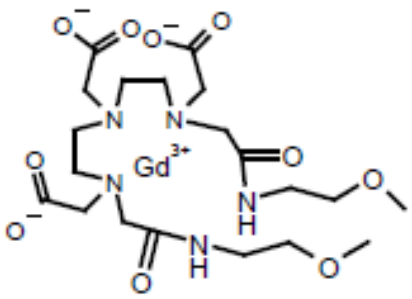


Figure 2: Chemical structure of gadoversetamide (Optimark®)



Dotarem® was first approved in France in 1989. US-FDA approval was obtained in March 2013 for "*intravenous use with MRI of the brain (intracranial), spine and associated tissues in adult and pediatric patients (2 years of age and older) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity*", at the dose of 0.1 mmol/kg BW. The indication in younger children (0-2 years) is currently being reviewed by the FDA and the anticipated approval expected by end of August 2017. To date, Dotarem® is approved in 79 countries worldwide and more than 65 million doses of Dotarem® have been administered since its first launch (see Section 3.1 for more details).

Optimark® was first approved in the US in 1999, at the dose of 0.1 mmol/kg BW, "*for intravenous use with MRI:*

- *Brain, spine and associated tissues*
- *to provide contrast enhancement and facilitate visualization of lesions with abnormal vascularity in the liver of patients who are highly suspect for liver structural abnormalities on computed tomography.*"

Optimark® was integrated into the Guerbet portfolio of contrast agents end 2015 following to the acquisition of the contrast media and delivery systems of Mallinckrodt Inc. **Guerbet has decided to initiate a global phase out of Optimark® based on an internal business decision (product portfolio rationalization).** At the date of submission of this briefing document, it is approved in 33 countries and it is estimated that approximately 22 million doses of Optimark® have been administered since its first launch (see Section 3.2 for more details).

In 2006, a serious and life-threatening syndrome called Nephrogenic Systemic Fibrosis (NSF), involving fibrosis of the skin, joints and internal organs, in patients suffering from severe to end-stage renal impairment, was associated with the prior administration of some GdCAs. This adverse condition is strongly suspected to be related to a Gd release and deposition in the skin after administration of some GdCAs in this population in which the elimination of the GdCA is delayed due to the impaired renal function. The immense majority of NSF cases were observed after single or repeat administration of L-GdCA, while few or no cases were observed with M-GdCA. In particular, for Dotarem®, no confirmed uncounfounded case of NSF has been reported to Guerbet or to the Authorities so far. This has lead to labeling modifications and risk minimisation measures worldwide, including contraindicating L-GdCA in patients

with severe renal impairment and in youg children. In the European Union, the European Medicine Agency (EMA) has classified the GdCAs in 3 categories for the risk of NSF (low, medium and high risk). Dotarem® was classified by the EMA as a low risk product, while Optimark® was classified as a high risk product for NSF. In the USA, Optimark® is contraindicated in patients with severe chronic kidney disease (GFR <30 mL/min/1.73m^2) and in patients suffering from acute kidney injury; while Dotarem® is not contraindicated and no dose adjustment is recommended or necessary for use in these patients.

More recently (since end 2014), several publications in international scientific journals have suggested Gd deposition and accumulation in specific regions of the brain (globus pallidus and dentate nucleus) of patients receiving multiple administrations of GdCA, without known risk factors such as renal impairment. At this time, two major drug regulatory bodies (US-FDA and EMA) have been/are reviewing data available on this subject and the potential implications for the clinical use of GdCAs. The US FDA has called for a public Medical Imaging Drug Advisory Committee (MIDAC) on September 8, 2017 and this briefing document is provided to the MIDAC members and FDA to present the available scientific data and Guerbet's position on this issue.

2 BACKGROUND ON GDCA AND MEDICALCONTEXT

2.1 DIFFERENT SUB-CLASSES OF GDCAS AND THEIR CHARACTERISTICS

2.1.1 Characteristics of GdCAs for MRI

All GdCAs are made of the same principle components: a Gd ion linked to a complexing agent (i.e. the ligand). GdCAs can differ in a number of properties, such as:

- Chemical structure (macrocyclic versus linear [open-chain], ionic versus non-ionic)
- Thermodynamic stability (i.e., the affinity of Gd^{3+} for its ligand)
- Kinetic stability (i.e., time course of dissociation of gadolinium)
- Relaxivity (a measure of their ability to enhance tissue during MRI exams)
- Non-specific or specific distribution (e.g. hepato-specific agents like gadoxetic acid – Eovist®)

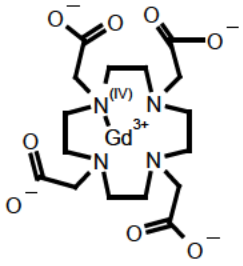
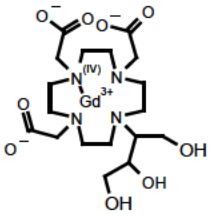
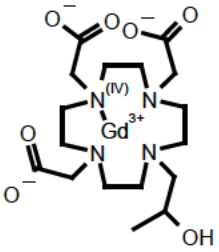
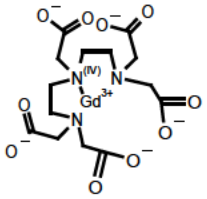
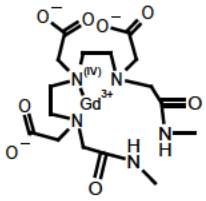
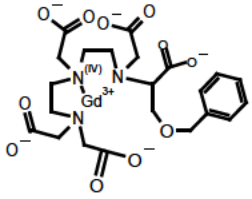
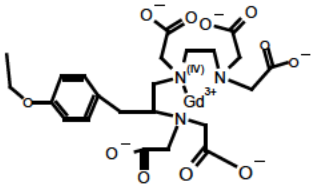
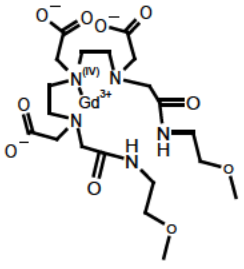
These characteristics are key for safety and diagnostic performance. In particular, the thermodynamic and kinetic stabilities are essential properties that determine the long term safety profile of GdCAs.

Based on the structural association of the gadolinium atom with its ligand, currently marketed GdCAs can be categorized as having either macrocyclic structure or open-structure (linear) (Figure 3). Macrocyclic chelates offer strong binding to Gd^{3+} by virtue of their pre-organized, optimally sized rigid ligands that surround the gadolinium atom. Compared to non-ionic GdCAs, ionic chelates are more stable since the binding between Gd^{3+} with the negatively charged carboxyl group is stronger.

2.1.2 Relationship between structure, stability and in vivo Gd dissociation

High stability is desirable for GdCAs, as when gadolinium dissociates from its chelate resulting in free gadolinium, it can cause both acute and chronic toxicity, and has been linked with the risk of developing NSF. The GdCAs complex stability is characterized by a thermodynamic stability constant (log K_{therm}), the corresponding conditional stability constant at physiological pH (log K_{cond}) and kinetic stability ($T_{1/2}$, dissociation half-life).

Figure 3: Structure of currently marketed GdCAs in the USA

	Ionic	Non ionic
Macrocyclic*	 Dotarem® (gadoterate meglumine)	 Gadavist® (gadobutrol)
		 ProHance® (gadoteridol)
Open-chain (linear)**	 Magnevist® (gadopentetate dimeglumine)	 Omniscan® (gadodiamide)
	 MultiHance® (gadobenate dimeglumine)	
	 Eovist® (gadoxetate disodium)	 OptiMARK® (gadoversetamide)

* Macrocyclic structure (complexes are derived from Tetraazacyclododecanetetraacetic acid [DOTA])
** Open-chain structure (complexes are based on the Diethylenetriaminepentacetate [DTPA] backbone)

2.1.3 Stability characteristics of GdCAs

Thermodynamic stability
By definition, as gadolinium is chelated, a thermodynamic equilibrium exists between the gadolinium [Gd], the ligand [L] and the chelate [GdL]. The stability of this equilibrium is expressed as log K_{therm}:

$$[Gd^{3+}] + [L] \leftrightarrows [GdL] \qquad K_{therm} = \frac{[GdL]}{[Gd^{3+}] \times [L]}$$

As the value of log K_{therm} does not take into account the protonated species, the conditional thermodynamic stability constant log Kcond is calculated at pH 7.4 on the basis of log K_{therm} values and protonation constants of the ligand. Consequently, log K_{cond} represents the equilibrium at physiological pH 7.4.

Kinetic stability
The dissociation rates of gadolinium chelates are slow at pH 7.4, but these molecules dissociate much more rapidly in acidic solutions. Consequently, the kinetic stability of the Gd^{3+} chelates is classically studied by measuring the dissociation half-life ($T_{1/2}$) of the Gd complex in acidic media.

In vivo, in order to avoid any likelihood of free gadolinium release, the highest stability, i.e., the highest log Kcond, along with the highest kinetic stability ($T_{1/2}$), is desirable.

The thermodynamic and kinetic stability values of the different marketed GdCAs in the USA are presented in Table 1.

Table 1: Thermodynamic and Kinetic Stability Measurements of Gadolinium Chelates

Gadolinium Chelate	Type of structure	Thermodynamic stability		Kinetics stability
		Log Ktherm	Log Kcond (at pH 7.4)	$T_{1/2}$ at pH 1.0 at 25°C
DOTAREM	Macrocyclic ionic	25.6	19.3	338 hrs
GADAVIST	Macrocyclic non-ionic	21.8	14.7	43 hrs
PROHANCE	Macrocyclic non-ionic	23.8	17.1	3,9 hrs
MULTIHANCE	Open-chain ionic	22.6	18.4	<5 s
MAGNEVIST	Open-chain ionic	22.1	17.7	<5 s
EOVIST	Open-chain ionic	23.5 (1)	18.7	<5 s *
OMNISCAN	Open-chain non ionic	16.9	14.9	<5 s
OPTIMARK	Open-chain non ionic	16.6	15.0	<5 s

Abbreviations: K_{cond} = conditional stabilityconstant at physiological pH; K_{therm} = thermodynamic stability constant; $T_{1/2}$ = half life time; ND = Not determined
Source : Port *et al*, Biometals, 2008 (1), except * Internal (unpublished) data

Due to its unique chemical structure, Dotarem® presents the highest stability constants for both thermodynamic stability and conditional stability, as well as the largest kinetic inertness (dissociation T½). This reduces the risk of dissociated gadolinium release *in vivo*, where free gadolinium is strongly suggested to be linked to the risk of triggering NSF, and overall reduces the risk of Gd deposition in multiple organs.

2.1.4 Effectiveness of GdCAs for Signal Enhancement

Among all the physico-chemical properties characterizing a gadolinium chelate, the efficacy of an MRI contrast agent is measured in terms of relaxivities, i.e., the longitudinal (r1) and transverse (r2) relaxation rates of the water protons observed at a millimolar concentration of contrast agent. These 2 parameters are acting in simultaneous, but opposing ways on the signal enhancement:

- r1 induces a positive effect on signal enhancement (namely "T_1 effect"), which is seen as brightening.
- r2 induces a negative effect on signal enhancement (namely "T_2 effect"), which is seen as darkening.

In Table 2, typical relaxivities of marketed non-specific GdCA are reported (Eovist®, as a hepatospecific agent, is not considered here as it is not comparable to a non-specific agent). **The T_1 effectiveness and diagnostic efficacy, of all non-specific GdCAs marketed in the USA are comparable.**

Table 2: Relaxivities at 1.5T and 37°C of non-specific GdCAs

Gadolinium Chelate	Type of Structure	r1 ($mM^{-1}.s^{-1}$)	r2 ($mM^{-1}.s^{-1}$)	Calculated % of reduction of brain T1 at a 0.12 mM tissue concentration	
				ΔT1 (%)	[min ; max] * (%)
DOTAREM	Macrocyclic ionic	3.0	3.5	29 %	[26 ; 31]
GADAVIST	Macrocyclic non-ionic	3.3	3.9	31 %	[29 ; 32]
PROHANCE	Macrocyclic non-ionic	2.9	3.4	28 %	[25 ; 30]
MULTIHANCE	Open-chain ionic	3.8	4.4	33 %	[32 ; 35]
MAGNEVIST	Open-chain ionic	3.3	3.9	31 %	[29 ; 32]
OMNISCAN	Open-chain non-ionic	3.3	3.9	31 %	[29 ; 32]
OPTIMARK	Open-chain non-ionic	3.6	4.1	32 %	[31 ; 34]

2.2 MEDICAL CONTEXT OF BRAIN T1-HYPERSIGNALS AND GD TISSUE ACCUMULATION

Since 2014, many publications in international scientific journals have reported Gd deposition and accumulation in specific regions of the brain (globus pallidus and dentate nucleus) of patients with normal renal function, either adults or children, receiving multiple administrations of GdCA. At this time, two major drug regulatory bodies (US-FDA and EMA) have been/are reviewing data available on this subject and the potential implications for the clinical use of GdCAs.

The EMA has recently concluded its review of gadolinium contrast agents, confirming the former Pharmacovigilance Risk Assessment Committee (PRAC) recommendations to restrict the use of some linear gadolinium agents used in MRI body scans and suspend the marketing authorizations of the remaing linear agents:

- *"The intravenous linear agents gadoxetic acid and gadobenic acid can continue to be used for liver scans# because they are taken up in the liver and meet an important diagnostic need. In addition, gadopentetic acid given intra-articularly (into the joint) can continue to be used for joint scans because the dose of gadolinium used for joint injections is very low.*
- *All other intravenous linear products (gadodiamide, gadopentetic acid and gadoversetamide) should be suspended in the EU.*
- *Another class of gadolinium agents known as macrocyclic agents (gadobutrol, gadoteric acid and gadoteridol) are more stable and have a lower propensity to release gadolinium than linear agents. These products can continue to be used in their current indications but in the lowest doses that enhance images sufficiently and only when unenhanced body scans are not suitable".*

 # Guerbet note: it is important to note that the only remaining approved indication in EU for gadobenic acid (Multihance®) is not approved in the US.

The US FDA has called for a Medical Imaging Drug Advisory Committee (MIDAC) meeting on September 8, 2017.

3 BACKGROUND INFORMATION ON DOTAREM® AND OPTIMARK®

3.1 DOTAREM®

3.1.1 Regulatory history

Dotarem was developed by Guerbet in the 1980's and was first approved in France in 1989 for examinations of the central nervous system (CNS). To date, Dotarem® is approved in 79 countries worldwide for various indications, including CNS examinations, whole body examinations and for MR angiography (MRA).

In March 2013, FDA approved Dotarem after priority review for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissues in adult and pediatric patients (2 years of age and older) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity.

3.1.2 Approved indications

The current US approved indication is as follows: "*Dotarem is a gadolinium-based contrast agent indicated for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissues in adult and pediatric patients (2 years of age and older) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity.*" In addition, a prior-approval supplement (S-0001) with clinical data for the CNS indication in the term neonate (less than 2 years old) population was submitted to FDA on October 27, 2016 and is currently under review with an expected approval date of August 2017.

Outside the US, Dotarem is approved in most countries for CNS examinations and whole body examinations in adults and pediatrics (0-17 years old) and for MRA in adults (approved indications vary per country/region).

3.1.3 Overview of efficacy data

3.1.3.1 CNS imaging

In adults, the clinical benefit of Dotarem®-enhanced MRI in the CNS imaging is supported by 2 controlled Phase III pivotal studies and 20 supportive, controlled clinical studies (3 double-blind, randomised, comparative studies comparing Dotarem with gadopentetate dimeglumine (Magnevist®) or gadobutrol (Gadovist®/ Gadavist®) and 17 open, non-randomised studies: 14 at single dose, 1 at double dose and 2 at triple dose).

In pediatric patients, the efficacy of Dotarem® in CNS imaging was demonstrated in 5 clinical studies: one pivotal Phase III study that also included pediatric patients (2-<18 years) in addition to adults, 3 open-label, non-randomised studies exclusively conducted in pediatric population (0-<18 years) and one study conducted to assess the pharmacokinetics, safety and efficacy of Dotarem® in the specific population of pediatric patients <2years old.
These studies are summarised in Table 3 and detailed in the following sections.

Table 3: Studies conducted by Guerbet for CNS indication.

Study	Phase	Year	Design	Patients	Number of patients*	
					safety	efficacy
DGD-44-050	III	2010-11	R, DB, C*, M	Adult	240	239
			O, NR, M	Pediatric 2-<18	38	37
DGD-44-051	III	2010-11	Re-read of DGD-03-044	Adult	-	149
DGD-03-017	II	1988	R, DB, PG, C*, S	Adult	10	10
DGD-03-031	III/IV	1989-90	R, DB, PG, C*, M	Adult	149	149
DGD-44-058	IV	2014-15	R, DB, CO, C*, M	Adult	258	258
DGD-03-044	III	2003-04	O, NR, M	Adult	150	129
DGD-03-001	II	1987	O, NR, S	Adult	10	10
DGD-03-003	II	1987-88	O, NR, S	Adult	30	30
DGD-03-004	II	1987	O, NR, S	Adult	20	20
DGD-03-005	II	1987-88	O, NR, S	Adult	10	10
DGD-03-007	II	1986-87	O, NR, S	Adult	56	53
DGD-03-008	III	1987	O, NR, S	Adult	54	54
DGD-03-009	II	1987-88	O, NR, S	Adult	22	22
DGD-03-011	II	1987-88	O, NR, S	Adult	19	19
DGD-03-012	II	1987	O, NR, S	Adult	50	50
DGD-03-014	III	1987	O, NR, S	Adult	55	55
DGD-03-020	III	1988	O, NR, S	Adult	48	48
DGD-03-021	III	1987-88	O, NR, S	Adult	50	50
DGD-03-023	III	1988	O, NR, S	Adult	50	50
DGD-03-033	III	1994-95	O, NR, M	Adult	65	61
DGD-03-034	III	1994-95	O, NR, M	Adult	45	44
DGD-03-040	IV	1999-2000	O, NR, M	Adult	59	57
DGD-03-015	II	1988	O, NR, S	Pediatric <18 years	29	29
DGD-03-016	II	1988	O, NR, S	Pediatric <18 years	20	20
DGD-03-029	IV	1990-91	O, NR, S	Pediatric <18 years	50	50
DGD-44-063	IV	2015	O, NR, M	Pediatric <2 years	45	28

DB: double-blind; O: open-label; R: randomised; NR: not randomised; PG: parallel groups; CO: cross-over; M: multicenter; S: single center. All clinical studies included intraindividual comparison Dotarem-enhanced vs. unenhanced images; *Number of patients who received Dotarem

C*: + comparator arm (Magnevist®): 117 patients in DGD-44-050; 10 patients in DGD-03-017 and 150 patients in DGD-03-031; cross-over design in DGD-44-058: 259 patients received Gadavist®

3.1.3.1.1 CNS imaging in adult population

(a) Pivotal studies

- Study DGD-44-050 is a multicenter, randomised, double-blind, comparative Phase III study to determine the safety and efficacy of Dotarem® in patients referred to contrast-enhanced (CE)-MRI of the CNS. In this study, 364 adult patients were randomised in 2 parallel arms to undergo unenhanced MRI followed by an MRI with Dotarem or an MRI with Magnevist® (with 2:1 ratio), each administered at 0.1 mmol/kg intravenously, and 38 pediatric patients aged 2-17 years were included in one open-label Dotarem® arm (refer to CNS Imaging in pediatric population).

- Study DGD-44-051 is a blinded centralized re-read of the previously conducted Phase III study DGD-03-044. This study is a multicenter, open label study conducted in Europe to determine the safety and efficacy of Dotarem in 151 patients presenting or suspected of cerebral or spinal tumors, referred to CE-MRI of the CNS.

The two pivotal studies were designed in a manner similar to that for other GdCAs. The study sites of both studies were instructed to consistently perform MRI examination using predefined acquisition parameters for all patients at each site.

The reading of images obtained in both studies was conducted in an independent and blinded manner using a Blinded Image Evaluation Charter. The studies used the central image interpretation process that is typical for contrast agent studies.

For each study, 3 experienced neuroradiologists were selected and trained for the independent reader role. Readers of study DGD-44-050 were different from and independent from readers of study DGD-44-051. No changes in readers occurred during the course of the assessments.

The images (made anonymous) received from sites were entered in a central database and accumulated into 3 different sets per patient by the imaging core lab:
Set “Pre”: MR images without contrast agent administration (unenhanced MRI)
Set “Paired”: combined unenhanced and contrast-enhanced MRI
Set “Post”: MR images after contrast agent administration (contrast enhanced MRI)

Every batch of images (“Pre”, “Paired” and “Post” sets) available for 20 to 40 patients was randomised and presented to the 3 independent readers. A wash-out period of at least two weeks between the evaluations of 2 different sets for a single patient was ensured to minimize recall bias. In addition, the order of presentation of different sets to the readers was randomly determined for each batch of images.

Each off-site blinded reader reviewed all images from “Pre” and “Paired” MRI modalities and graded border delineation, internal morphology and degree of contrast enhancement of each lesion up to a limit of the 5 largest representative lesions identified, using a 3-point scale: unevaluable (0), seen but imperfectly (1) or seen completely/perfectly (2). For each of the 3 co-primary endpoints, the patient scores (sum of all lesion scores within patient for “Paired” and “Pre” assessments, giving a patient “Paired” score and a patient “Pre” score, respectively)

were computed. To compute the difference between the mean "Paired" score and the mean "Pre" score, the sum of lesions' scores was used for the patient score instead of mean of lesions' scores within individual patients, in order to reflect the number of lesions detected.

The primary statistical assessment was based on the comparison of the "Pre" (unenhanced) versus the "Paired" (unenhanced + enhanced) images of each patient within the Dotarem arm. "Post"-contrast images were reviewed in a secondary analysis.

Statistically significant ($p \leq 0.025$) superiority in lesion visualisation on "Paired" images (unenhanced plus Dotarem-enhanced MRI) over "Pre" images (unenhanced MRI) was to be demonstrated for at least 2 out of the 3 off-site blinded readers simultaneously for all three co-primary endpoints: lesion border delineation, lesion internal morphology and lesion contrast enhancement.

In study DGD-44-050, as part of the secondary efficacy analysis, a comparator arm (Magnevist®) provided confirmation of validity of scoring and interpretation methodology.

Statistical methods

Co-primary endpoints

Each co-primary criteria was analysed using a multiple regression model, modelling the patient's score as a function of the MRI modality ("Pre" and "Paired") with adjustment on centers and repeated measures on the patient due to the pairing of MRI modalities in patient (no random effect on the patient). Results were presented per reader. The superiority of the "Paired" MRI modality over the "Pre" was statistically demonstrated if the one-sided p-value was ≤ 0.025 when using a T-test.

The primary analyses were performed at patient level on the Full Analysis Set (FAS, all patients with valid co- primary endpoint assessments) and Per-Protocol (PP) set (FAS patients without protocol deviations) and took into account the off-site blinded assessments. Data from all sites were pooled.

Secondary efficacy endpoints

For the study DGD-44-050 secondary efficacy endpoints were analysed, for both off-site and on-site readers. For the study DGD-44-051 analysis of secondary parameters involved off-site assessments (re-reading study).

In study DGD-44-050 only:

- Comparison of the lesion visualisation parameters between "Paired" and "Pre" images with Magnevist was performed for internal validation of the outcomes with Dotarem®.

In both studies:

- **"Post" versus "Pre" image readings**: Patient lesion visualisation scores (border delineation/ internal morphology/degree of contrast enhancement) were calculated for the "Post" MRI modality (patient level) and compared to "Pre" scores in the Dotarem group in the same way as for the primary analysis.

- **Analysis at lesion-level:** Each co-primary criterion was analysed at lesion-level using a logistic regression model, modelling the probability of the "Seen perfectly" classification as a function of the MRI modality (unenhanced MRI "Pre" and unenhanced + Dotarem-enhanced MRI "Paired") with adjustment on centers and repeated measures on the patient due to multiple lesions in patients.
- **Classification of scores:** For each co-primary endpoint, patients were sorted in different subgroups according to their patient scores as “worse” (“Paired/Post” score less than “Pre” score), “same” (“Paired/Post” score equal to “Pre” score) or “better” (“Paired/Post” score greater than “Pre” score). A logistic regression model was used to modelling the probability of the classification "better" as a function of the contrast agent administered and the center.
- **Number of lesions:** For each patient, the number of lesions in "Pre", "Paired" and "Post only" MRI modalities was counted. A Poisson regression model was used to modelling the per-patient number of lesions as a function of the MRI modality (3 measures within patients) and the center.
- **Image Quality:** Image quality was evaluated for each lesion on a 3-point scale: poor (1), fair (2) or good (3) and an overall score per patient was calculated. A multiple regression model was built to modelling the patient quality score as a function of the MRI modality ("Pre", "Post only" and "Paired" measures within patient) and the center.
- **Diagnostic confidence:** Level of diagnostic confidence was graded using a 5-point scale as: nil (1), poor, (2), moderate, (3), high, (4), and excellent (5). A multiple regression model was used to modelling the per-patient confidence score as a function of the MRI modality and the center.
- **Signal and contrast intensity:** Using the "Paired" MRI modality, off-site readers measured the signal intensity (lesion/healthy tissue/background) in "Pre" and "Post" images so that the percentage of enhancement (% Enhancement) and the contrast-to-noise ratio (CNR) could be computed. A multiple regression model was used to compute the adjusted average on centers of the percentage of enhancement and the CNR, with repeated measures on the patient due to multiple lesions in patients.
- **Intra and inter off-site readers variability:** For each MRI modality, the inter-readers agreement for the co-primary endpoints was assessed using kappa coefficient. A subgroup of 10% randomly selected patients had their images read twice by off-site readers so that the intra reader agreement could be assessed.
- **Safety:** Descriptive statistics were performed on safety data (quantity of contrast product injected, adverse events, clinically significant changes of laboratory values, vital signs and electrocardiogram).

Study population

In the population included in both studies, age ranged from 18 to 85 years, with a median of 55 years old. The percentage of female patients was 53.5% in study DGD-44-050 and 44.4% in study DGD-44-051. The large majority of patients were Caucasian. Mean (±SD) weight was 76 (±17) kg and 73 (±14) kg, respectively.

Results

As shown in Table 4 the evaluation of the primary endpoints demonstrated statistically significant (p<0.001) superiority of "Paired" images over "Pre" (unenhanced) images for lesion visualisation for all three readers in both studies.

Table 4: Lesion visualisation (primary endpoint): results of pivotal studies (Patient level).

	Study DGD-44-050						**Study DGD-44-051**					
	Reader 1		**Reader 2**		**Reader 3**		**Reader 1**		**Reader 2**		**Reader 3**	
Modality	Pre	Paired	Pre	Paired	Pre	Paired	Pre	Paired	Pre	Paired	Pre	Paired
Border Delineation							**Border Delineation**					
Mean score	1.06	3.30	1.62	4.49	1.43	2.54	0.94	1.98	1.41	2.18	0.34	1.62
Difference*	2.26		2.92		1.15		1.05		0.77		1.28	
Internal Morphology							**Internal Morphology**					
Mean score	0.97	3.70	1.76	4.49	1.45	2.93	1.09	2.23	1.34	2.28	0.67	2.41
Difference*	2.75		2.77		1.54		1.14		0.94		1.74	
Contrast Enhancement							**Contrast Enhancement**					
Mean score	0.01	3.11	0.01	3.73	0.01	2.95	0.00	2.06	0.00	2.11	0.00	2.21
Difference*	3.13		3.76		2.99		2.06		2.10		2.21	

*Difference calculated from least square mean (LS mean) scores.
All differences are statistically significant (p<0.001).

Table 5 shows the improvement in the 3 visualisation endpoints. The percentage of patients with improved lesion visualisation for Paired images compared to Pre images ranged from 60% to 97.8% for study DGD-44-050, and 67.6% to 97.3% for study DGD-44-051.

Table 5: Lesion visualisation improvement.

Better Score / Endpoints	**Study DGD-44-050** Better score (Paired-Pre)			**Study DGD-44-051** Better score (Paired-Pre)		
Reader	Reader 1 N=231	Reader 2 N=232	Reader 3 N=237	Reader 1 N=149	Reader 2 N=149	Reader 3 N=149
Border Delineation N (%)	195 (87.4%)	215 (96.8%)	132 (60.0%)	114 (77.0%)	100 (67.6%)	114 (77.0%)
Internal Morphology N (%)	218 (97.8%)	214 (96.4%)	187 (85.0%)	131 (88.5%)	121 (81.8%)	144 (97.3%)
Contrast Enhancement N (%)	208 (93.3%)	216 (97.3%)	208 (94.5%)	143 (96.6%)	136 (91.9%)	139 (93.9%)

The proportion of lesions assessed as seen "perfectly" on "Paired" and "Post" images was statistically significantly superior to "Pre" images for all 3 readers.
In both studies, the superiority of "Post" over "Pre" images for all 3 co-primary variables for lesion visualisation was demonstrated for all 3 readers (p<0.001) with the exception of internal morphology for one of the readers in study DGD-44-050 (p=0.037).

In study DGD-44-050, more lesions were detected on both "Paired" images and on "Post" images compared to "Pre" images. In study DGD-44-051, the number of detected lesions was

similar between the different imaging modalities, due to the fact that the majority of the patients included in this study presented only one lesion. Both studies showed better lesion visualisation on "Paired" and "Post" images. "Paired" images also demonstrated superiority for the image quality and diagnostic confidence compared to "Pre" images.
Significant ($p<0.001$) increases in mean CNR in "Post" images compared to "Pre" was seen for all 3 readers in both the pivotal studies.
The inter-reader comparison showed that globally the agreement for "Paired" images was better than for "Pre" images.
The comparison between Dotarem and Magnevist in study DGD-44-050 did not show significant differences between the 2 contrast agents.

Conclusion of pivotal studies in CNS imaging in adults:
The efficacy of Dotarem® in MRI of the CNS was demonstrated in these two adequate and controlled Phase-III studies. All prospectively defined primary and important secondary efficacy analyses were positive and support the effectiveness of Dotarem® at a standard dose of 0.1 mmol/kg for use in MRI of the CNS.

(b) Supportive randomized studies
Two randomised, comparative, double blind and parallel group studies, DGD-03-017 and DGD-03-031 (2), were conducted to compare the diagnostic efficacy and clinical safety of Dotarem® with Magnevist® in patients who underwent MRI for various neurological reasons. Both groups received standard dose of contrast agent. The results of these studies are summarised in Table 6.

Table 6: Results of Supportive Randomised Studies (CNS MRI -Adults).

Study	Studied agents	Number of patients	Diagnostic contribution		Change in diagnosis	Modification of therapeutic management
			Good	Excellent		
DGD-03-017	Dotarem® 0.1 mmol/kg	10	40%	60%	82%	
	Magnevist® 0.1 mmol/kg	10	60%	30%	40%	
DGD-03-031	Dotarem® 0.1 mmol/kg	149	35%	59%	13%	7%
	Magnevist® 0.1 mmol/kg	150	33%	63%	10%	10%

A dose of 0.1 mmol/kg corresponds to 0.2 mL/kg.

In study DGD-03-017, modification of the diagnosis was seen in 82% of the cases after Dotarem® injection and 40% of the cases after Magnevist®, thus providing good or excellent diagnostic contribution.

In study DGD-03-031, post-contrast images were good or excellent in 94% of patients with Dotarem and in 95% of patients with Magnevist. The use of the contrast agent made the diagnosis more precise in 68% of patients with Dotarem® and 69% with Magnevist®. Management decisions were facilitated in 65% of patients in the Dotarem group and 62.5% of patients in the Magnevist® group. There was no significant difference between the two agents regarding their diagnostic efficacy.

There was no significant difference in efficacy between the 2 agents in both studies.

A recent double-blind, randomised, controlled intra-individual and cross-over study (REMIND study, DGD-44-058) was conducted by Guerbet to compare Dotarem® and gadobutrol (Gadavist®) in MRI diagnosis of brain tumours (3). Patients with known or highly suspected primary intracranial tumours detected by previous CT or MRI examination were included and randomised to undergo two identical MRIs with Dotarem and then Gadavist® or Gadavist and then Dotarem®. The two contrast agents were administered at a dose of 0.1 mmol/kg and MRIs were spaced out with a time interval of at least 48 hours for contrast washout to prevent any effect of carryover. A total of 268 patients received at least one contrast agent injection (male: 35.8%, mean (±SD) age: 53.6 ± 15.1 years) and 234 patients were included in the Per Protocol Set (PPS). The primary endpoint was overall lesion visualisation and characterization, assessed by 3 independent blinded off-site neuroradiologists on a 4-point scale ranging from "poor" to "excellent".

Table 7: Patients with overall lesion visualisation and characterization scored "good" or "excellent" (PPS).

Reader	**Contrast Agent**	**n / N (%)**	**GEE Estimate Difference [CI 95%]**
Reader 1	Gadavist® (reference)	220/234 (94.0%)	2.3 [-1.3 ; 5.9]
	Dotarem®	225/234 (96.2%)	
Reader 2	Gadavist® (reference)	218/234 (93.2%)	-2.5 [-6.5 ; 1.4]
	Dotarem®	212/234 (90.6%)	
Reader 3	Gadavist® (reference)	233/234 (99.6%)	NE
	Dotarem®	234/234 (100.0%)	

CI: Confidence Interval; GEE: Generalized Estimating Equations; NE: Not Evaluable.

Overall lesion visualisation and characterization was "good" or "excellent" in more than 90% of patients for all three readers and non-inferiority of Dotarem® *vs.* Gadavist® was statistically demonstrated (non-inferiority margin set at -10%). (Table 7) Patients with overall lesion visualisation and characterization scored "good" or "excellent" (PPS).No significant differences were observed between the two contrast agents regarding qualitative secondary endpoints: lesion border delineation, internal morphology and degree of contrast enhancement. Regarding quantitative signal assessments, mean SNR and CNR were found to be around 5% and 15% higher, respectively, for Gadavist® compared to Dotarem®.
Diagnostic confidence was high or excellent for the three readers in more than 81% of the patients with both contrast agents.

In conclusion, using a cross-over design, the REMIND study demonstrates non-inferiority of Dotarem® *vs*. Gadavist® in the diagnosis of brain tumours by MRI. Although quantitative signal intensity measurements showed a small difference in favour of gadobutrol that is explained by its slightly higher relaxivity, this did not result in any clinical benefit since no differences were demonstrated for overall diagnostic evaluation of the images for any of the off-site readers.

Conclusion of the supportive randomised studies in CNS imaging in adults:
These studies demonstrated that Dotarem® provided similar diagnostic contribution as other GdCAs, and that it is an efficacious contrast agent for detection and better visualisation of CNS lesions.

(c) Supportive non-randomized studies at single dose

Dotarem® has been evaluated in a series of 14 open, comparative, non-randomised studies, which involved a total population of 596 patients who benefited from MRI procedures for the diagnosis of various suspected cerebral lesions, the detection of local recurrence of disease, the exploration of the anatomical structure of lesions or as a routine procedure for therapeutic follow-up reasons. All patients were administered Dotarem® at a single dose of 0.2 mL/kg (0.1 mmol/kg) as IV bolus injection and the studies followed comparable protocols.

In one study (DGD-03-020), patients were investigated for neuro-ophtalmological or ENT diseases. In the other studies, brain or spinal cord imaging was performed, with a total of 426 lesions detected: 70% in brain and 30% in spine. For any given patient, the same pre- and post-injection T1-weighted sequences were used for the efficacy evaluation.

The diagnostic contribution of Dotarem®-enhanced MRI, as scored by the investigator on a 4-point scale, was found to be superior to both unenhanced MRI and preliminary exam like CT scan. Diagnostic contribution of Dotarem was scored “Good” or “Excellent” in 70% to 100% of patients across the studies. Dotarem-enhanced MRI led to change in diagnosis in 15% to 94% of patients and modification of therapeutic management in 29% to 96% of patients across all supportive non-randomised studies. Dotarem® had a notable advantage for detecting tumour recurrences, regardless of their nature, by allowing for a distinction between their necrotic components and their active components within lesion. Dotarem® contributed to the preoperative assessment of the dimensions of the tumour, better anatomical relations and adjacent structures.

The main efficacy results are summarised in Table 8.

Table 8: Supportive non-randomised studies in CNS imaging at single dose

Study ID	n patients	Diagnostic Contribution		Change in Diagnosis	Modification of therapeutic management
		Good	Excellent		
DGD-03-001	10	60%	10%	70%	60%
DGD-03-003	30	17%	77%	80%	67%
DGD-03-004	19	10%	90%	75%	85%
DGD-03-005	9	50%	50%	50%	30%
DGD-03-007	53	40%	40%	51%	45%
DGD-03-008	54	91%-89% [a]		94% [b]	96%
DGD-03-009	22	27%	68%	45%	36%
DGD-03-011	19	37%	47%	68%	47%
DGD-03-012	50	42%	38%	67%	61%
DGD-03-014	55	22%	69%	69%	73%
DGD-03-020	48	35%-79% [c]		44% [d], 60% [e]	6% [d], 77% [e]
DGD-03-021	48	69%-95% [f]		78%	74%
DGD-03-023	50	70%-97% [g]		15%	29%
DGD-03-044	129	37.5%	77%		53.5%

[a] MRI with Dotarem® (T1-weighted) superior to preliminary CT scan in 91% of patients and to MRI (T2-weighted) in 89% of patients.
[b] Change from initial unenhanced- MRI based diagnosis in 94% of patients and detection of new small lesions in 37% of patients.
[c] MRI with Dotarem (T1-weighted) superior to CT in 79% of cases and to unenhanced MRI in 35% of patients
[d] Neuro-opthalmic diseases; [e] ENT lesions
[f] 95% in 22 patients in comparison with CT, 80% improvement in comparison with the same sequence without Dotarem and 78% in comparison with T2-weighted spin echo sequence. Lesion-healthy tissue delineation improved in 69% of patients.
[g] 70% improvement of the diagnostic contribution in comparison with plain MRI, T1- and T2-weighted sequences. Better delineation of lesion limits in 97% of patents in comparison with the same T1 sequence without Dotarem®.

Conclusion of the supportive non-randomised studies in CNS imaging at single dose in adults:

All supportive studies generally confirmed the findings of the pivotal studies that diagnostic performance of Dotarem®-enhanced MRI is superior to unenhanced MRI and provides clinical relevant information that has impact on patient management.

(d) Supportive non-randomized studies at double and triple dose

While gadolinium complexes are usually used at a dose of 0.1 mmol/kg, numerous studies have documented the interest of injecting higher than the standard dose (4-7). This approach has been shown in various settings to improve diagnostic contribution and to allow detection of small tumours (less than 10 mm in size) or of recent metastases. Furthermore, a quantitative

correlation between tumour/normal tissue contrast and dose injected has been demonstrated (4, 8-13) . **These higher doses are not approved by the FDA for Dotarem®.**

A dose of 0.2 mmol/kg Dotarem® ("double dose") in a single administration was used to evaluate in 59 patients cerebral functional MR imaging with Dotarem® in the diagnosis of Alzheimer disease (DGD-03-040). The study results did not permit any conclusions to be drawn as to whether functional MR investigation could be used in the early diagnosis of Alzheimer disease (predemential status). However, perfusion sequences could be performed with satisfactory image quality.

Most interestingly efficacy and safety of triple dose of Dotarem® has been evaluated in two open, non-randomised clinical studies conducted in 1994. (Table 9) The first trial, DGD-03-034, included 45 patients and was mainly performed to evaluate the safety of a Dotarem® triple dose administration but efficacy was also evaluated. Overall, the high dose of Dotarem® enabled to identify one or more lesions not visualized with the usual dose. Dotarem® administered at the dose of 0.3 mmol/kg provided more diagnostic information in terms of lesion delineation and/or characterization in comparison to the usual dose in over 67% of the patients included in this analysis.

The second study, DGD-03-033, was planned to demonstrate superior diagnostic efficacy of the 0.3 mmol/kg cumulative dose in comparison to the standard dose in the detection of brain metastases. In this multicenter study, 65 patients were evaluated by MRI after injection of a 0.1 mmol/kg dose. Within 20 to 30 min after the first dose, a second dose of 0.2 mmol/kg was injected and MRI immediately repeated in the same conditions. The main efficacy criterion was the number of visualized metastases with the second MRI compared to the 0.1 mmol/kg injection. This study demonstrated that a triple Dotarem® dose significantly increased the number of definitively established metastatic lesions and improved lesion delineation in more than 80% of the patients.

Table 9: Results of Supportive Non-Randomised Studies at Triple Dose (CNS MRI -Adults).

			Number of additional detected lesions (2^{nd} – 1^{st} dose)		Supple-mentary detected lesions	Overall improvement of triple dose compared with simple dose		
Study, Location	**Study design**	**No. of patients**	**Confirmed lesions**	**Doubtful lesions**		**Detection of lesions**	**Character-ization of lesions**	**Delineation of lesions**
DGD-03-034 France	O, NR, M Neurological MRI for various reasons. On-site reading. Safety study.	45*			0.7 ± 2.2	20%	2%	66%
DGD-03-033 France Belgium	O, NR, M Detection of brain metastases On-site reading.	65**	1.7 ± 10.0 p=0.001	-0.1 ± 0.6 NS	1.6 ± 10.1 p=0.07	19.7%	9.8%	80.3%

Mean ± SE; *: only 44 patients received the "triple dose" administration. ** 61 patients evaluable for imaging.
Dotarem® 0.1 mmol/kg followed 30 min later by an additional 0.2 mmol/kg IV bolus injection.

Conclusion of the supportive non-randomized studies in CNS imaging at double or triple dose in adults:

From both studies it was concluded that doses higher than 0.1 mmol/kg BW of Dotarem® may be beneficial 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. More accurate information has been obtained regarding the number of detected lesions, lesion size, improved visualisation, tumour classification and outline definition. However, it should be stated that, in current clinical practice, taking both safety and improved imaging technology into account, the dose of 0.1 mmol/kg is considered a standard dose as it adequately answers all questions for the majority of patients. **In the US, only the standard dose of 0.1 mmol/ kg BW is approved.**

In summary, in the adult population, Dotarem® demonstrates a superiority to unenhanced MRI in CNS indications, and provides clinically relevant information that has an impact on patient management, similarly to other contrast agents.

3.1.3.1.2 CNS Imaging in pediatric population

The efficacy of Dotarem® in CNS imaging for pediatric patients was demonstrated in a total of 5 clinical studies (Table 10): one pivotal Phase III study (DGD-44-050) including adults and pediatric patients (38 pediatric patients aged 2-17 years included in the Dotarem® group), 3 open, non-randomised studies conducted in pediatric population (DGD-03-016; DGD-03-015; DGD-03-029) and 1 open, non-randomised study conducted to assess pharmacokinetics, safety and efficacy of Dotarem® in children <2 years old (this study is presented below in the section "(b) Sub-population of pediatric patients <2 years old").

Table 10: Overview of the studies in CNS imaging in Pediatric patients

Study ID	Year	Study Design	Dotarem dosing	Number of Pediatric Patients	
				Evaluable for Safety	Evaluable for Efficacy
DGD-44-050	2010-2011	O, C, M	0.1 mmol/kg	38	37
DGD-03-016	1988	S, O, NR, C	0.1 mmol/kg	20	20
DGD-03-015	1988	S, O, NR, C	0.1 mmol/kg	29	29
DGD-03-029	1991	S, O, NR, C	0.1 mmol/kg	50	50
DGD-44-063	2015	M, O, NR	0.1 mmol/kg	45	28
			Total	**182**	**164**

C: Comparative (before and after Dotarem® injection); M: Multicenter O: Open; S: Single center; NR: Not Randomised
A dose of 0.1 mmol/kg Dotarem corresponds to 0.2 mL/kg

(a) Sub-population of pediatric patients 2 - 17 years old

As part of the secondary analyses in the pivotal study DGD-44-050, the co-primary efficacy endpoints were also assessed in an open-label arm of 38 pediatric patients, with a reasonable representation of age groups from 2 to 17 years of age. It was found unnecessary to expose pediatric patients to the comparator product.

Dotarem® was administered during the course of MRI procedures for the diagnosis of various suspected cerebral lesions, the detection of local recurrence of disease, the exploration of the anatomical structure of lesions or as a routine procedure for therapeutic follow-up.
A total of 22 female (58%) and 16 male (42%) pediatric patients, ranging in age from 2 to 17 years (mean ±SD of 9 ± 4 years), participated in the study DGD-44-050. The majority of pediatric patients (68.4%) were Caucasian. The mean weight was 36 ± 19.7 kg and mean BMI was 18.6 ± 4.2 kg/m^2. The 3 supportive pediatric studies (0-<18 years) included a total of 99 children who received Dotarem®. There were 40 girls and 59 boys with a mean age of 8.8 ± 5.0 years (range 2 weeks to 17 years), mean body weight of 30.0 ± 15.7 kg.

Table 11 presents lesion visualisation data for each of the 3 co-primary variables for the pediatric population enrolled in study DGD-44-050. For all 3 readers, mean scores for each endpoint were higher for “Paired” (contrast-enhanced + unenhanced images) relative to “Pre” (unenhanced) mean scores according to descriptive statistics. Dotarem®-enhanced MRI improved lesion border delineation, lesion internal morphology, and lesion contrast enhancement compared to non-contrast MRI and these results were comparable to those seen in adults.

Table 11: Lesion visualisation (primary endpoint): results of pivotal CNS study for pediatric patients (Patient level)

Study DGD-44-050							
Readers		**Reader 1**		**Reader 2**		**Reader 3**	
Modality		**Pre**	**Paired**	**Pre**	**Paired**	**Pre**	**Paired**
N Patients		**31**	**32**	**34**	**35**	**33**	**36**
Border Delineation	Mean scores (SD)	1.42 (1.09)	2.47 (1.52)	1.18 (1.03)	3.51 (2.50)	1.06 (0.66)	1.36 (1.10)
Internal Morphology	Mean scores (SD)	1.13 (0.88)	2.75 (1.50)	1.41 (0.78)	3.51 (2.48)	1.06 (0.56)	1.81 (1.09)
Contrast Enhancement	Mean scores (SD)	0	1.81 (1.09)	0	2.69 (2.03)	0	1.64 (1.25)

Abbreviations: Paired = MRI scans obtained before and after Dotarem® administration; Pre = before Dotarem® administration; SD = standard deviation

Overall, the results observed in the 3 supportive studies were similar to those already described with adult patients. Dotarem®-enhanced MRI allowed better visualisation of lesions with a more accurate delineation of the lesion/normal tissue or lesion/oedema borders. Furthermore, blood supply was more easily imaged. This better visualisation modified the planned therapeutic approach in 15% to 34% of cases (Table 12).

Table 12: Results of supportive pediatric CNS MRI study with Dotarem®

Study	**Efficacy Results**
DGD-03-016	**Diagnostic contribution:** Better diagnosis with Dotarem MRI in 94% of patients compared to plain (unenhanced) MRI Contrast-enhanced T1 -weighted MR1 better than unenhanced T1 -weighted MR1 in 84% of patients and better than unenhanced T2-weighted MRI in 24% of patients **Modification in therapeutic approach**: in 15% of patients. **Image quality:** Visualisation of blood supply in 42% of patients.
DGD-03-015	T1-weighted MRI after injection of Dotarem considered better than T1-weighted MRI without injection in 69% of patients and better than T2-weighted MR1 without injection in 62% of patients. Better lesion/normal tissue delineation in 52% to 55% of patients. **Modification in therapeutic approach**: 34% patients
DGD-03-029	Confirmation of the value of Gadolinium complex, particularly in investigation of extra-axial tumours (neuromas, meningiomas and pituitary lesions). Improvement in image quality of T1 sequences in staging of lesions (21 out of 27 patients) and in distinction between cystic and necrotic components of some tumours (12 out of 14 patients)

Conclusion of the clinical studies in CNS imaging in pediatric patients aged 2 – 17 years:

Dotarem® has been shown to improve lesion border delineation, lesion internal morphology, and lesion contrast enhancement compared to unenhanced MRI, with results comparable to those seen in adults.

(b) Sub-population of pediatric patients <2 years old

The efficacy of Dotarem® in CNS imaging for pediatric patients aged <2 years is shown from results of the Phase IV study DGD-44-063 including 28 patients undergoing Dotarem®-enhanced MRI for CNS indication out of 51 patients aged <2 years, and the results for 7 patients aged <2 years included in the 3 supportive, open, non-randomised studies conducted in pediatric patients.

Additionally, 7 prospective PMS observational studies including 258 patients aged <2 years (including 213 with CNS indication evaluable for efficacy), gave supportive results for CNS indication in this population (Table 13).

All clinical studies that provided efficacy data on Dotarem® for CNS imaging in pediatric patients aged <2 years were non-randomised, open-label, single-group studies. Efficacy was assessed by comparing MR images before and after administration of Dotarem within the same patient. Each patient served as his/her own control as it was found unnecessary to expose pediatric patient to a comparator product. In all studies, the dose of Dotarem® planned to be administered to the patients was 0.2 mL/kg (0.1 mmol/kg) in accordance with the recommendations.

Table 13: Overview of the Supportive PMS Observational Studies for CNS Imaging in Pediatric Patients Aged <2 Years

Study ID Author Year	Study Location	Dotarem Dosing (mmol/kg)[a]	Number of Patients <2 years		
			Total enrolled	Evaluable for Efficacy	
				All	For CNS MRI
Neiss 1991	France, Belgium, Switzerland	0.1	6	6	6
Briand 1992[b]	France	0.1	26	26	26[c]
Ishiguchi 2010 2001-2005	Japan	0.1	2	2	1
DGD-55-002[d] (Emond 2011)	France	0.1	104	104	85
PMS Maurer (Maurer 2012) 2004-2011	Germany	0.1	10	10	6
DGD-55-004 2011-2012	Korea	0.1	4	4	4
DGD-55-001 (SECURE) (Soyer 2017) 2008-2013	Argentina, Austria, China, France, Germany, India, Italy, Saudi Arabia, Spain, and United Kingdom	0.1	106	104	85
Total number of patients			**258**	**256**	**213**

Abbreviations: CNS, central nervous system; MRI, magnetic resonance imaging; PMS, post-marketing surveillance.
[a] A dose of 0.1 mmol/kg of Dotarem corresponds to 0.2 mL/kg.
[b] Entire study population ≤17 years of age.
[c] The exact number of patients who had CNS imaging could not be determined; therefore, it was considered that all 26 patients were evaluable for efficacy in CNS.
[d] Entire study population <2 years of age.
Source: publication for Neiss 1991(14); abstract for Briand 1992 (15); publication and Clinical Study Report for Ishigushi 2010 (16); statistical report, patient database, and publication (Emond 2011) (17) for DGD-55-002; Final Clinical Study Report and publication with interim results (Maurer 2012) for PMS Maurer (18); Clinical Study Report for DGD-55-004; Clinical Study Report, patient database and publication for DGD-55-001 (19).

The anatomic CNS imaging being a steady state imaging, the acquisition of T1 sequence images is normally done at least 5 to 10 minutes after injection, after uptake of the contrast agent by the lesion (resulting from BBB disruption). Consequently, injection rate of the product does not significantly impact the efficacy of Dotarem® in anatomical CNS imaging and Dotarem® efficacy can be considered similar when the product is injected slowly (infusion) or rapidly (bolus). Due to the low body weight of pediatric patients aged <2 years, the injection volume is very small, and consequently, clinical practice cannot accurately calculate the rate of injection. However, the injection should be manually controlled when administering bolus to avoid any damage to the delicate veins of pediatric patients.

The parameters of the sequences for both unenhanced and Dotarem®-enhanced MRI were prospectively defined and were similar to the parameters that are currently used to evaluate CNS pathologies. Efficacy endpoints were mainly related to the contribution of Dotarem® for making a diagnosis and improving image quality.

(i) Study DGD-44-063

Design

The study DGD-44-063 was designed according to the FDA recommendations to provide data that would support the approval of Dotarem® for CNS imaging in patients aged <2 years in the USA. The study was to include at least 40 patients to adequately characterize the PK of Dotarem® in this age group, with a sufficient number of patients to adequately support the safety and efficacy of Dotarem® for CNS MRI. The comparison of pre + post contrast images vs. pre-contrast images was used to determine Dotarem® efficacy in the subset of patients with CNS indication. The on-site radiologist analysed the pre- and post-contrast images to determine the number of lesions and their localization. Lesions (up to 5 largest) were scored using a 3-point scale for 3 co-endpoints of lesion visualisation: lesion border delineation, internal morphology and contrast enhancement. Image quality was also categorized as poor, fair, or good. In addition to these subjective assessments, objective quantitative assessment on signal intensity and contrast-to-noise ratio (CNR) were also evaluated.

Study Population

Of the 51 patients enrolled and scheduled for routine gadolinium-enhanced MRI, 45 patients actually received Dotarem®. Approximately half of the 45 analysed patients presented with neoplasms (n=23, 51.1%), the most frequent being neuroblastoma (n=7, 15.6%). Nine patients (20.0%) presented with nervous system disorders, the most frequent being epilepsy (n=5, 11.1%). Of these 45 patients, 28 were scheduled for CNS MRI due to suspected or known CNS lesions: 15 boys and 13 girls. Mean (±SD) age was 8.2 months (±7.2), with 5 patients aged 0-1 month, 6 patients aged 1-3 months and 17 patients aged 3-23 months.

Results

The overall quality of images was considered “good” for 26 patients (92.9%) and “fair” for 2 patients (7.1%) with pre-contrast images while it was “good” for all patients with pre + post-contrast images. Lesions were identified in 15 patients with pre-contrast images and in 16 patients with pre + post-contrast images. The number of lesions detected per patient ranged from 0 to 11, with a median of 1 lesion per patient.
Dotarem®-enhanced MRI improved lesion border delineation, lesion internal morphology, and lesion contrast enhancement relative to non-contrast MRI and these results were comparable to those seen in adults and older children.

Based on 3 co-endpoints, lesion visualisation was improved whether the analysis was performed at lesion level (considering up to 5 largest lesions per patient) or at patient level.
At lesion level (

Table 14), an improvement was noted with pre + post-contrast images compared to pre-contrast images with more lesions having the highest score. With pre + post-contrast images, contrast enhancement was clear and bright for 23 lesions (76.7%), fair for 4 lesions (13.3%) and remained null for 3 lesions (10.0%).

At patient level (Table 15), the mean sum of scores (summing the scores of lesion visualisation for up to 5 lesions) was higher with pre + post-contrast images compared to pre-contrast images, with however a large variability between patients. The mean (SD) increase was 0.7

(1.0) for lesion border delineation, 0.9 (1.6) for internal morphology and 3.1 (3.2) for contrast enhancement.

Regarding the quantitative assessments, a mean increase in CNR and signal-to-noise ratio (SNR) was reported in pre + post-contrast images compared to pre-contrast images. At lesion level, mean (SD) SNR increased from 112.3 (57.8) in pre-contrast images to 212.6 (198.3) in pre + post-contrast images, and mean CNR increased from 9.3 (27.8) to 79.4 (109.9). At patient level, mean pre-post variation was 5.7 (12.6) for CNR and 0.6 (0.4) for signal intensity while median values were 2 and 1, respectively. Mean absolute pre-post CNR difference was 64.0 (139.0), while median value was 24.

Table 14: Lesion Border Delineation, Lesion Internal Morphology and Lesion Contrast Enhancement at Lesion Level (up to 5 Largest Lesions per Patient) in Study DGD-44-063

	All Patients Evaluable for Efficacy (N=28)	
	Pre-contrast (N=28 lesions[a])	**Pre + Post-contrast (N=30 lesions[a])**
Lesion Border Delineation Score		
1-None	2 (7.1%)	0 (0.0%)
2-Moderate	15 (53.6%)	8 (26.7%)
3-Clear and complete	11 (39.3%)	22 (73.3%)
Internal Morphology Score		
1-Poorly visible	5 (17.9%)	0 (0.0%)
2-Moderately visible	9 (32.1%)	7 (23.3%)
3-Sufficiently visible	14 (50.0%)	23 (76.7%)
Contrast Enhancement Score		
1-None	28 (100.0%)	3 (10.0%)
2-Weak	0 (0.0%)	4 (13.3%)
3-Clear and bright	0 (0.0%)	23 (76.7%)

[a] Lesions identified in pre- and post-contrast images could be different.
No missing data.

Table 15: Lesion Border Delineation, Lesion Internal Morphology and Lesion Contrast Enhancement at Patient Level (Sum of Scores) in Study DGD-44-063

Sum of Scores	**Pre-contrast N=28 patients**	**Pre + Post-contrast N=28 patients**	**Difference[a] N=28 patients**
Number of Patients with Lesions Detected	**N=15**	**N=16**	**N=15**
Lesion Border Delineation			
Mean (SD)	4.3 (3.7)	5.1 (4.0)	0.7 (1.0)
Median (min; max)	3 (2; 15)	3 (2; 15)	0 (0; 3)
Internal Morphology			
Mean (SD)	4.3 (3.9)	5.2 (4.3)	0.9 (1.6)
Median (min; max)	3 (1; 15)	3 (2; 15)	0 (0; 6)
Contrast Enhancement			
Mean (SD)	1.9 (1.5)	5.0 (4.5)	3.1 (3.2)
Median (min; max)	1 (1; 5)	3 (1; 15)	2 (0; 10)

Abbreviations: max, maximum; min, minimum; SD, standard deviation.
[a] Difference: Pre + Post-contrast minus Pre-contrast.

(ii) Results of supportive studies

Supportive non-randomised studies

In the 3 supportive non-randomised pediatric studies (completed earlier: 1988-1991), the assessment of Dotarem® efficacy was based on the comparison of post- vs. pre-contrast MRI images. The reading was performed by an on-site radiologist.

The 7 patients aged <2 years from these studies included 3 boys and 4 girls, with age ranging from 0.1 to 1.8 years, All patients had known or suspected CNS and were scheduled for a CNS MRI for etiological diagnosis (n=3), staging of a lesion (n=2), post-surgical control (n=1) or treatment follow-up (n=1).

In the 3 supportive pediatric clinical studies, Dotarem®-enhanced MRI images allowed better visualisation of lesions with a more accurate delineation of the lesion/normal tissue or lesion/oedema borders. They contributed to establish a diagnosis, either by confirming the absence of a lesion or by providing information on the type of lesion (based on the uptake -or absence of uptake- of the contrast agent by the lesion) in the 7 patients aged <2 years. Dotarem-enhanced MRI also facilitated patient management.

PMS studies

In the 7 supportive PMS observational studies, Dotarem® efficacy was evaluated based on the comparison between pre- and post-contrast images, or simply on the analysis of post-contrast images. The efficacy results could not be pooled for the whole population due to the variability of efficacy endpoints. Results obtained in the 2 largest studies confirmed that Dotarem®-enhanced images improve lesion visualisation and contributed to the diagnosis. MRI image quality was rated as good or very good/excellent for 97.6% of the patients in DGD-55-002 and 98.8% in DGD-55-001 (98.8%). a definite diagnosis could be made for 97.6% of the patients in DGD-55-002 and 98.8% in DGD-55-001.

The impact of Dotarem®-enhanced images on therapeutic management was also investigated in DGD-55-002. The therapeutic decision was impacted mainly regarding the choice of initial treatment (n=39, 45.9%), but also the continuation of treatment (n=16, 18.8%), the change of treatment (n=5, 5.9%) or the decision not to treat (n=25, 29.4%).

Conclusion of the clinical studies in CNS imaging in pediatric patients aged 0 – 2 years:
Dotarem®-enhanced MRI improved lesion border delineation, lesion internal morphology assessment, and lesion contrast enhancement relative to non-contrast MRI and these results were comparable to those seen in adults and older children.

In summary, in pediatric patients from neonates to 17 years of age, through Guerbet-sponsored clinical program, Dotarem®-enhanced MRI has demonstrated efficacy for detection and visualisation of areas with disruption of the BBB and/or abnormal vascularity in brain (intracranial), spine and associated tissues.

Efficacy of Dotarem® in the CNS indication in pediatric patients was assessed in 164 patients enrolled in 5 studies, including 35 patients aged <2 years. Efficacy results obtained in the pediatric population were consistent with those obtained in the adult population. Dotarem®-enhanced MRI produced significant improvement in the ability to detect and visualize CNS lesions and the overall image quality, showing clinically significant diagnostic contribution and facilitating patient management. Results of observational PMS studies on larger numbers of pediatric patients (including 213 patients <2 years) also supported these findings.

3.1.3.1.3 Analysis of the Literature about CNS imaging

In the recent literature, two multicentric clinical studies sponsored by competitors have compared to Dotarem® the diagnostic performances of higher relaxivity contrat agents – gadobenate dimeglumine (Multihance®) and gadobutrol (Gadavist®) – in CNS imaging.

The study conducted by Vaneckova et al. (20) is a multicenter, prospective, randomised, intraindividual, crossover, 2-arm study. Adult patients with suspected or known brain tumours were randomised to Arm 1 (70 patients) or Arm 2 (107 patients) and underwent 2 identical examinations at 1.5 T. The agents were injected in randomised-sequence order, and the 2 examinations were separated by 2-14 days.

- In Arm 1, the objective was to demonstrate the superiority of a full dose of Multihance (0.1 mmol/kg) vs. a full dose of Dotarem® (0.1 mmol/kg). The primary endpoint was the overall diagnostic preference of the readers for one GdCA. Results showed a significant superiority in favour of MultiHance®. The conclusion was "gadobenate is significantly superior to gadoterate for qualitative and quantitative enhancement of brain lesions when these agents are administered at an equivalent dose of 0.1 mmol/kg"
- In Arm 2, the objective was to ascertain whether MultiHance® at half-dose (0.05 mmol/kg) provides diagnostic information similar to that of Dotarem® (0.1 mmol/kg), using the same primary endpoint. Results showed no significant differences between the two GdCAs. The conclusion was "a half-dose of gadobenate (0.05 mmol/kg body weight) is equivalent to a full dose (0.1 mmol/kg body weight) of gadoterate and may prove advantageous when a clinical requirement is to administer a low GdCA dose"

Table 2: Qualitative assessment of patients with brain tumors: intraindividual comparison of 0.1-mmol/kg gadobenate and 0.1-mmol/kg gadoterate[a]

Diagnostic Information End Point	Reader	Gadobenate Preferred	No Difference	Gadoterate Preferred	Significance (*P* Value)[b]	3-Reader Agreement κ Value (% Agreement)
Global diagnostic preference	1	31 (49.2%)	31 (49.2%)	1 (1.6%)	<.0001	0.273 (50.8%)
	2	51 (82.3%)	9 (14.5%)	2 (3.2%)	<.0001	
	3	43 (69.4%)	17 (27.4%)	2 (3.2%)	<.0001	
Lesion-border delineation	1	29 (46.0%)	33 (52.4%)	1 (1.6%)	<.0001	0.271 (44.3%)
	2	34 (54.8%)	27 (43.5%)	1 (1.6%)	<.0001	
	3	25 (40.3%)	35 (56.5%)	2 (3.2%)	<.0001	
Definition of disease extent	1	15 (23.8%)	48 (76.2%)	0	<.0001	0.286 (57.4%)
	2	18 (29.0%)	43 (69.4%)	1 (1.6%)	<.0001	
	3	15 (24.2%)	45 (72.6%)	2 (3.2%)	.0023	
Visualization of lesion internal morphology	1	10 (15.9%)	53 (84.2%)	0	.002	0.215 (54.1%)
	2	14 (22.6%)	48 (77.4%)	0	.0001	
	3	23 (37.1%)	38 (61.3%)	1 (1.6%)	<.0001	
Lesion contrast enhancement	1	31 (49.2%)	31 (49.2%)	1 (1.6%)	<.0001	0.249 (49.2%)
	2	51 (82.3%)	9 (14.5%)	2 (3.2%)	<.0001	
	3	43 (69.4%)	17 (27.4%)	2 (3.2%)	<.0001	

51.7%

[Table from Vaneckova et al 2015 (20)]

As stated in the response letter published in the journal (21), some biases limit the interpretation of the results and lead to wrong assertions. The statistics were not adapted to the objectives of the study. As shown by the kappa value (< 0.3), the inter-reader agreement was only fair reflecting a moderate level of agreement and leading to some doubts about the robustness of the interpretations. Most importantly, arm 2 was not designed as equivalence or a non-inferiority trial. And thus, the failure to show a difference should not have been interpreted as equivalence between both GdCAs and clearly the authors made a biased interpretation of the results. In addition, some image analysis discrepancies were not explained. The number of lesions subjected to signal intensity measurements with the T1GRE sequence differed from that of the T1SE sequence. Fewer lesions were considered with the T1GRE sequence, though they were all larger than 5 mm. This discrepancy between sequences may have created a bias in the analysis of the images. As both GdCAs assessed the same number of lesions, it is likely that the choice of sequence is more important than the differences in relaxivity between GdCAs. Finally, the primary endpoint, overall diagnostic preference, is qualitative and subjective by nature and it should be highlighted that, as shown in the table 2 of the paper, the "no difference" between GdCAs ranged from 14.5% up to 84.2%, with an average of 51.7% when all diagnostic information and all readers are taken into account.

In common with all previous studies of this type, a principal limitation is that the clinical impact of MultiHance® superiority, if any, on patient management and outcome was not directly evaluated. This statement is in line with the conclusions of a previous comparative study between these two contrast agents: "*Further investigation is warranted […] to evaluate any possible clinical impact"* (22).

Anzalone et al. (23) reported the results of a multicenter, randomised, single-blind, intra-individually controlled study that compared two macrocyclic extracellular contrast agents, 1.0M gadobutrol and 0.5M gadoterate meglumine, for diagnostic imaging of cerebral tumours. The aim was to determine the overall preference for one or the other in a clinical setting.

A total of 160 patients with known cerebral intra axial or extra axial neoplastic lesions (primary or secondary enhancing lesions) were randomised prospectively into group A (n= 80 patients) who received a single dose of gadobutrol in their first MRI and a single dose of gadoterate meglumine in their second MRI examination 48 hrs to 7 days later and group B (n=80) who received the contrast agents in reversed order. Efficacy analysis was based on 136 patients who underwent identical MRI examinations. Three independent blinded readers assessed off-site their overall diagnostic preference (primary efficacy parameter) based on a matched pairs approach.

The results are summarized in the following tables.

Table 1
Overall preference of gadobutrol versus gadoterate meglumine MR examination following post contrast evaluation.

Observer	N[a]	Reader overall preference			p-Value[b]
		Preference for gadobutrol, N (%)	No preference, N (%)	Preference for gadoterate meglumine, N (%)	
Reader 1	124	67(54)	24(19)	33(27)	0.0005
Reader 2	120	22(18)	91(76)	7(6)	0.0034
Reader 3	130	42(32)	60(46)	28(22)	0.0945
Clinical investigator	136	58(43)	42(31)	36(26)	0.0224

[a] The clinical investigators performed their qualitative assessments on all examinations. The blinded readers evaluated the preference only in cases, where at least one enhancing lesion was detected by the reader.
[b] p-Value of the two-sided Wilcoxon signed rank test.

Table 2
Overall preference of gadobutrol versus gadoterate meglumine MR examination by qualitative assessment parameter.

Observer	N[a]	Reader overall preference			p-Value[b]
		Preference for gadobutrol, N (%)	No preference, N (%)	Preference for gadoterate meglumine, N (%)	
A. Intensity of lesion enhancement					
Reader 1	124	68(55)	24(19)	32(26)	0.0002
Reader 2	120	21(18)	92(77)	7(6)	0.0057
Reader 3	130	49(38)	51(39)	30(23)	0.0316
Investigator	136	55(40)	51(38)	30(22)	0.0060
B. Lesion delineation					
Reader 1	124	26(21)	81(65)	17(14)	0.1727
Reader 2	120	6(5)	109(91)	5(4)	1.0000
Reader 3	130	19(15)	99(76)	12(9)	0.2140
Investigator	136	24(18)	92(68)	20(15)	0.5526
C. Internal structure					
Reader 1	124	32(26)	74(60)	18(15)	0.0466
Reader 2	120	7(6)	110(92)	3(3)	0.3438
Reader 3	130	24(18)	89(69)	17(13)	0.2797
Investigator	136	38(28)	74(54)	24(18)	0.0752

[a] The blinded readers gave a qualitative assessment, if enhancing lesions were present and combined images were evaluable, whereas the pre-requisite of the presence of an enhancing lesion was not given for the clinical investigators.
[b] p-Value of the two-sided Wilcoxon signed rank test.

(Tables from Anzalone et al. 2013 (23))

Across readers and when excluding the 175 assessments "no preference" in the ITT population, "gadobutrol better then gadoterate meglumine" was reported in a proportion of 66% [95%CI: 57% to 74%] (131 out of 199 assessments, in which preference for one of the two contrast agents was stated), i.e., in significantly more than 50% of cases.

Preference in lesion enhancement was found significantly in favour of gadobutrol while there was no statistically significant difference between the 2 contrast agents regarding lesion delineation for all readers and internal structure for 2 out of 3 readers.

The authors concluded that contrast-enhanced MRI of neoplastic brain lesions at a dose of 0.1 mmol Gd/kg body weight, assessed in a standardized off-site blinded reading, results in a significantly higher qualitative and quantitative preference for gadobutrol compared to gadoterate meglumine.

As stated in the response letter published in the journal (24), this conclusion needs to be interpreted in the context of the endpoints, reading methods and study design used in that trial. First, regarding the primary endpoint (overall diagnostic preference), from a methodological viewpoint it would have been better to have the evaluation of images done separately than simultaneously to provide maximal information. Furthermore, there was a major bias in the analysis due to the exclusion from the analysis of the "no preference" assessment group which was clearly the largest group (43% of the assessment when pooling all observers). In addition, the blinded readers evaluated the preference only in cases where at least one enhancing lesion was detected by the reader, thus not the same number of cases per reader and less than the total

examinations (136 patients) evaluated by the clinical investigators. Also, it is surprising that no statistically significant difference was observed for reader 3 (130 patients), while the results are statistically different with less patients for reader 1 (124 patients) and reader 2 (120 patients). Finally, as in the Anzalone study, the inter-reader agreement was only fair (0.26–0.33) based on the weighted Kappa statistics. Regarding the secondary efficacy parameters, the only difference statistically significant for all three readers concerned the intensity of lesion enhancement. For the two other important clinical efficacy parameters lesion delineation from its surrounding tissue and information on the internal lesion structure, no significant difference was reported (except for one reader). From a clinical perspective, this strongly suggests that the benefit of having a higher enhancement for a better diagnosis is highly questionable. Interestingly, although a higher enhancement was observed with gadobutrol ($p = 0.0003$) as well as a significant difference in lesion-to-brain ratio ($p = 0.0003$) there was no statistically significant difference ($p = 0.2372$) in contrast-to-noise ratio (CNR) between gadobutrol (129.3±335.1) and gadoterate meglumine (98.3±146.2), probably due to the high standard deviation reported with gadobutrol.

Finally, some comments should be made regarding the study design. A single-blind study could induce a bias in the way the contrast media is used/injected during the MRI scan and could lead to the on-site reading unreliable. The study results should have been presented according to each group (A and B) in order to evaluate the impact of the injection sequence on the results as it is usually done for any cross-over study.

Conclusion of the published comparative clinical studies in CNS imaging:
Altogether, studies comparing gadobenate dimeglumine or gadobutrol to gadoterate meglumine (gadoteric acid) failed to demonstrate a superiority of the former in terms of diagnostic preference. Moreover, none of these studies showed any clinical benefit in terms of diagnostic confidence or performance.

3.1.3.2 Other indications approved outside USA

3.1.3.2.1 Magnetic resonance angiography (MRA)

Guerbet has conducted 15 controlled clinical trials in this indication, including 892 patients who underwent Dotarem-enhanced MRA to investigate different territories (Table 16). These territories are representative of the whole body (supra-aortic region, thorax, abdomen, limbs, heart), and represent major indications in terms of therapeutic impact. Most studies were open, non-randomised studies. Two single-blind randomised studies (DGD-3-37; DGD-3-39) compared 2 doses of Dotarem® and two double-blind randomised studies (DGD-44-045 and DGD-44-052) used an active comparator (Gadavist®). In all studies, the main efficacy criteria were the accuracy or the sensitivity, specificity and the predictive values of the technique in comparison with the selected standard of reference.

Table 16: Summary of Studies conducted by Guerbet in Magnetic Resonance Angiography (MRA) in Adults

Study ID	year	MRA Indication	Phase	Design	Number of patients[a]
DGD-44-060	2013-14	Carotid/vertebral basilar arterial disease (Re-Read of DGD-44-048)	III/IV	O, NR, M	200[b]
DGD-44-061	2013-14	Carotid/vertebral basilar arterial disease (Re-Read of DGD-44-049)	III/IV	O, NR, M	187[c]
DGD-44-048	2009-10	Carotid/vertebral basilar arterial disease	III/IV	O, NR, M	200
DGD-44-049	2009-10	Carotid/vertebral basilar arterial disease	III/IV	O, NR, M	187
DGD-03-038	1997-98	Carotid artery stenosis	III	O, NR, M	40
DGD-44-038	2003-05	Diagnosis of clinically significant non-coronary arterial disease	III	O, NR, M	100
DGD-44-042 (17)	2006-08	Diagnosis of clinically significant non-coronary arterial disease	IV	O, NR, S	92
DGD-03-037	1997-98	Pulmonary embolism	III	SB, R, PG, S	35
DGD-03-039	1997-98	Lower limb artery	III	SB, R, PG, M	40
DGD-44-045	2009-12	Suspected infrarenal aorta or chronic lower limb ischemia	IV	DB, R, C*, M	92
DGD-44-052	2009-10	Peripheral Arterial Occlusive Disease stage II or III	IV	DB, R, C*, cross-over, S	17
DGD-03-042	2000	Coronary artery stenosis	IV	O, NR, S	6
DGD-03-036	1997-98	Renal artery	III	O, NR, M	41
DGD-44-046	2009-10	Renal artery	III	O, NR, M	32
DGD-44-047	2009-10	Renal artery	III	O, NR, M	10

DB, double-blind; SB, single-blind; O, open-label; R, randomised; NR: not randomised; PG: parallel groups; M: multicenter; S: single center. C*: + comparator group (Gadavist®); All clinical studies included intraindividual comparison Dotarem-enhanced vs. unenhanced images.
[a]: number of patients who received Dotarem; [b]: same patients as DGD-44-048; [c]: same patients as DGD-44-049.

MRA of Supra-Aortic Arteries

The efficacy and safety of Dotarem®-enhanced MRA in supra-aortic arteries was assessed in 7 open, non-randomised studies conducted by Guerbet (Table 17).

Table 17: Studies conducted by Guerbet in MRA of supra-aortic arteries

Study ID	**Study location**	**Year**	**Dotarem dosing**	**Number of Patients**	
				AIP	**FAS**
DGD-44-060	Central Re-reading of DGD-44-048	2013-2014	0.1 mmol/kg	222	198*/197**
DGD-44-061	Central Re-reading of DGD-44-049	2013-2014	0.1 mmol/kg	211	187*/187**
DGD-44-048	USA, Colombia, Argentina, Mexico, Korea, Chile	2009-2010	0.1 mmol/kg	222	200*/199**
DGD-44-049	USA, South Africa, Argentina, Mexico, Korea and Chile	2009-2010	0.1 mmol/kg	211	187*/185**
DGD-03-038	Belgium, Switzerland	1997-1998	0.1 mmol/kg	43	40
DGD-44-038	USA	2003-2005	0.1 mmol/kg	12 [a]	11
DGD-44-042 (17)	South Korea	2006-2008	0.1 mmol/kg	11[b]	8
			Total	**932**	**831/827**

M: Multicenter; O: Open; NR: Not Randomised; C: Comparative; AIP: All Included Patients; FAS: Full Analysis Set.
*: FAS population for Technical Failure Rate; **: FAS population for Sensitivity/ Specificity evaluation.
[a]subgroup of patients with investigation of supra-aortic arteries among 100 included patients.
[b] subgroup of patients with investigation of supra-aortic arteries among 92 included patients.

In summary, when compared to TOF MRA, the number of "additional examinations required" dramatically dropped after Dotarem®-enhanced MRA and on a consistent manner for all the readers. This means that patients could more easily and systematically be oriented to an adapted treatment.
The positive predictive values, image quality and diagnostic confidence were also significantly higher with Dotarem®-enhanced MRA as compared to TOF MRA. Dotarem®-enhanced MRA significantly reduced the number of technical failure compared to TOF MRA and allowed detection of stenosis with good level of accuracy and diagnostic confidence.

MRA in Non Supra-Aortic Arteries

Randomized MRA studies sponsored by Guerbet

Four randomised trials were conducted by Guerbet to address the use of Dotarem® in MRA (see Table 18). The first two trials (DGD-03-039; 1994 and DGD-03-037; 1995) compared 0.1 mmol/kg and 0.05 mmol/kg of Dotarem® in two successive injections in lower limbs and pulmonary embolism. In two more recent trials the diagnostic performance of Dotarem® was

compared to that of Gadovist® in peripheral arterial occlusive disease (DGD-44-045 and DGD-44-052).

Table 18: Summary of randomised studies sponsored by Guerbet in MRA indication.

Study Year Study Location	Patients	Primary objective	Efficacy evaluation	Gold standard	Dotarem dose
DGD-3-39 1997-1998 France Austria	Lower limb arterial stenosis. N = 40	Evaluation of Dotarem diagnostic efficacy at 2 doses in detection of arterial stenosis of the lower limbs. Determination of the optimal dose	Sensitivity and specificity of Gd-enhanced MRA. (stenosis > 50 % measured in a centralized MRA reading; arterial segment as a statistical unit).	Conventional X-ray angiography or DSA	2 x 0.05 mmol/kg (20 patients) 2 x 0.1 mmol/kg (20 patients)
DGD-3-37 1997-1998 Netherlands	Pulmonary embolism N = 40	Assessment of Dotarem efficacy at 2 doses for the diagnosis of pulmonary embolism. Determination of the optimal dose	Sensitivity and specificity of contrast-enhanced MRA.	Pulmonary X-ray angiography	2 x 0.05 mmol/kg (20 patients) 2 x 0.1 mmol/kg (20 patients)
DGD-44-052 2009-2010 Germany (25)	Lower limb arterial disease N = 20	Compare the diagnostic performance of Dotarem- and Gadovist-enhanced MRA for Peripheral Arterial Occlusive Disease	Overall image quality of each MRA examination assessed on a 5-point-scale	None	1 x 0.1 mmol/kg
DGD-44-045 2009-2012 France, Germany, Italy, Spain and Austria (26)	Chronic lower limb ischemia N = 189	Assessment of the diagnostic agreement of MRA examinations with Gadovist and Dotarem as compared with the gold standard X-ray angiography. Non-inferiority of Dotarem to Gadovist.	Mean on-site within-patient percent agreement between MRA and gold standard in terms of segment lesion grade in the concerned territory.	Conventional X-ray angiography or DSA	1 x 0.1 mmol/kg

Non-randomised studies sponsored by Guerbet

Six non-randomised studies were conducted by Guerbet with the use of Dotarem® in MRA for other territories than supra-aortic arteries: 3 in renal arteries (DGD-03-036, DGD-44-046, DGD-44-047) including a total of 83 patients, 1 in coronary arteries (DGD-03-042), including 6 patients and 2 in non-coronary arteries (DGD-44-038 and DGD-44-042 (25-28)), including a total of 192 patients (with a subgroup of patients investigated for supra-aortic arteries previously described).

Conclusion of MRA studies in non supra-aortic arteries:
Guerbet-sponsored studies with Dotarem® have proven that contrast-enhanced MRA provides a reliable diagnosis in a shortened timeframe of examination than TOF MRA imaging.

Published studies in MRA
Several studies have been published using Dotarem® in MRA for various arterial territories (29-45).

Conclusion of the published clinical studies in MRA:
The results from published studies investigating Dotarem® injected MRA in different territories showed a high sensitivity (70% to 100%) and specificity (82% to 100%) for detection of stenosis.

In summary, all the results from Guerbet-sponsored studies and non-Guerbet-sponsored studies on supra-aortic arteries and other arterial territories showed that Dotarem®-enhanced MRA can detect with a good accuracy arterial lesions or stenoses whatever the artery location and the disease type. Magnetic resonance angiography with Dotarem® appears to be an effective and reliable non invasive tool as first-line vascular investigation (for renal arteries, pulmonary arteries, or coronary arteries) or as a second-line vascular investigation after Doppler ultrasound (for aorta, lower limbs, and supra-aortic vessels).

3.1.3.2.2 Whole Body Imaging

Both Guerbet-sponsored studies and published studies showed the efficacy of Dotarem®-enhanced MRI in different territories, such as:

- Hepatic and pancreatic imaging (46-49)
- Breast imaging (50-55)
- Cardiac imaging (56-60)

In summary, contrast-enhanced MRI for whole-body imaging – and especially for liver, breast and cardiac imaging – is widely used in clinical practice, both for diagnosis and treatment efficacy follow-up. Clinical studies continuously add new pieces of evidence of the efficacy of Dotarem® in that field.

3.1.4 Overview of safety

Preclinical data have highlighted the very large safety margin of Dotarem® without identifying any particular target organ at risk and no teratogenic, immunotoxic or mutagenic potential nor effects on fertility were observed.

Clinical safety data for Dotarem® as a contrast agent, mostly in single-dose, has been derived from all relevant data available:

- A clinical safety database including 51 phase I to IV clinical studies (including 5 PK studies),
- 9 PMS observational studies,
- Literature data, and
- Post-marketing Pharmacovigilance surveillance from March 8, 1989 to April 15, 2016.

3.1.4.1 Data from clinical trials

The clinical safety of Dotarem® was analysed on a pool of 51 studies including 4 Phase I PK studies, 1 Phase IV PK study in patients<2 years, 1 electrocardiographic safety study and

45 Phase II to IV studies with 3407 patients referred (by physicians) for a CE-MRI based on clinical symptoms or based on a previous imaging procedure.

Among these patients, 2867 received Dotarem®, 371 another GdCA (276 Magnevist® and 95 Gadavist®) and 169 did not receive a contrast agent. Dotarem was used for various indications (Table 19).

To be noted: at the time of the pooled analysis of clinical safety, data from study DGD-44-058 were not available; they are therefore summarised separately. The safety data from this cross-over study that included 268 patients did not show any new signal. Overall, a similar rate of post-injection adverse events (AEs) was reported with both contrast agents: 16.7% with Dotarem® (43 patients) and 17.0% with Gadavist (44 patients). The majority of these AEs were mild or moderate in intensity with only 3 severe AEs that were not related to contrast agents. Post-injection AEs were mainly "medical device pain" (5.8% reported in patients with Dotarem and 6.6% with Gadovist®) and "injection site pain" (4.7% with Dotarem® and 4.6% with Gadavist®). This rate of medical device/injection site pain may be explained by the systematic evaluation of the tolerance at injection site. Among the 109 post-injection AEs recorded, 54 (49.5%) were considered related to contrast agents. A similar percentage of patients with AEs related to contrast agent was observed with Dotarem® (7.8%) and Gadovist® (7.3%), the most frequent related AEs being injection site pain with both contrast agents. For both arms of this cross-over study, fewer AEs related to contrast agents were recorded at the second MRI procedure compared to the first.

Two patients experienced serious adverse events (SAEs), fatal for one patient. All SAEs were assessed by the investigators as not related to contrast agent but related to the progression of the patient's underlying diseases. Regarding vital signs, no clinically significant changes from baseline were observed in systolic blood pressure, diastolic blood pressure and heart rate at both MRI procedures.

Overall Exposure and Characteristics of the Population

Among the 2867 patients who received Dotarem® in the 51 studies conducted by Guerbet, 63.6% received doses between 0.1 and 0.2 mL/kg, essentially as a single injection (91.1%). The mean dose of Dotarem® administered was 0.2 mL/kg (0.1 mmol/kg), with the mean volume of injection being 16.2 mL and mean rate of injection being 1.7 mL/s.

The 2867 patients who received Dotarem® included 54.5% males and 45.5% females and a majority of Caucasian (80.6%). Mean age (±SD) was 52.8 (±19.7) years and 185 pediatric patients (<18 years) were included. Among the medical histories of interest, cardiac disease was the most common underlying disease (n=1033, 36.0%), followed by allergic disease (n=435, 15.2%) and diabetic disease (n=351, 12.2%).

Table 19: Characteristics of the Population included in Clinical Studies.

	Dotarem (N=2867)
Indication studied	
PK or QT (6 studies)	145 (5.1%)
CNS (23 studies)	1328 (46.3%)
MRA (13 studies)	892 (31.1%)
Whole-body (9 studies)	502 (17.5%)
Medical history	
Patient with renal diseases	171 (6.0%)
Patient with hepatic diseases	191 (6.7%)
Patient with cardiac diseases	1033 (36.0%)
Patient with diabetic diseases	351 (12.2%)
Patient with allergic diseases	435 (15.2%)
Patient with past reaction to contrast agents	51 (1.9%)
Age in classes	
< 1 month	5 (0.2%)
1 - <24 months	47 (1.6%)
2 - <6 years	33 (1.2%)
6 - <12 years	57 (2.0%)
12 - <18 years	43 (1.5%)
18 - <65 years	1764 (61.9%)
65 - <75 years	596 (20.9%)
≥75 years	304 (10.7%)
Missing	18
Sex	
Male	1558 (54.5%)
Female	1302 (45.5%)
Missing	7
Dose (ml/kg)	
≤ 0.1 ml/kg	5 (0.2%)
>0.1 - ≤0.2 ml/kg	1819 (63.6%)
> 0.2 ml/kg	1037 (36.2%)
Missing	6

Adverse Events

Of the 2867 patients receiving Dotarem® in the 51 studies, a total of 254 patients (8.9%) experienced at least one post-injection AE (Table 20). Of these patients, 114/254 (44.9%) had AEs that were considered to be related to Dotarem®. Adverse events are summarized per indication in Table 21.

Table 20: Summary of Adverse Events (All Studies)

	Dotarem N=2867		Other GdCA N=371	
	n (%) patients	**n events**	**n (%) patients**	**n events**
Any AE	290 (10.1%)	448	51 (13.7%)	70
Any pre-injection AE	55 (1.9%)	73	5 (1.3%)	9
Any post-injection AE	254 (8.9%)	375	47 (12.7%)	61
Any related AE	114 (4.0%)	154	36 (9.7%)	47
Any SAE[b]	30 (1.0%)	43	1 (0.3%)	1
Any AE resulting in death	8 (0.3%)	12	0 (0.0%)	0

AE: adverse event; GdCA: gadolinium-based contrast agent; SAE: serious adverse event.
Data presented are the number (%) patients who experienced at least one AE ["n (%) patients"] and the total number of events ["n events"]. One patient could have more than 1 event.
[b] One SAE of brain hemorrhage reported in Patient 02012 in Study DGD-03-044 was coded to both CEREBRAL HAEMORRHAGE and HAEMORRHAGE MedDRA preferred terms and reported as 2 separate events. One event should therefore be substracted to the total number of events.
Related adverse events: All events described as "doubtfully, possibly, probably, plausibly or definitely related" to MRI contrast agent.

Table 21: Summary of Adverse Events in Patients Receiving Dotarem® per MR Indication

	PK or QT (N=145)		CNS (N=1328)		Whole-body (N=502)		MRA (N=892)	
	n (%) patients	**n events**	**n (%) patients**	**n events**	**n (%) patients**	**n events**	**n (%) patients**	**n events**
Any AE	46 (31.7%)	117	108 (8.1%)	148	44 (8.8%)	58	92 (10.3%)	125
Any pre-injection AE	19 (13.1%)	26	17 (1.3%)	21	1 (0.2%)	1	18 (2.0%)	25
Any post-injection AE	40 (27.6%)	91	93 (7.0%)	127	43 (8.6%)	57	78 (8.7%)	100
Any related AE	7 (4.8%)	13	8 (0.6%)	12	7 (1.4%)	9	8 (0.9%)	9
Any SAE	14 (9.7%)	21	49 (3.7%)	65	18 (3.6%)	22	33 (3.7%)	46
Any AE resulting in death	0 (0.0%)	0	7 (0.5%)	11	1 (0.2%)	1	0 (0.0%)	0

AE: Adverse event; SAE: Serious adverse event.
Data presented are the number (%) patients who experienced at least one AE ["n (%) patients"] and the total number of events ["n events"]. One patient could have more than 1 event.

The most common AEs that occurred post-injection of Dotarem® were headache (0.9% of patients), nausea (0.8%), and injection site pain (0.7%) (Table 22). The most common related AEs were the same: nausea (0.6%), headache (0.4%) and injection site pain (0.4%).

Table 22: Adverse Events that Occurred Post-Injection in >0.1% of Patients Who Received Dotarem® (All Studies)

System Organ Class Preferred Term	Dotarem N=2867		Other GdCA N=371	
	N (%) patients	n events	N (%) patients	n events
Headache	27 (0.9%)	29	17 (4.6%)	17
Nausea	22 (0.8%)	23	5 (1.3%)	5
Injection site pain	21 (0.7%)	21	4 (1.1%)	4
Feeling hot	6 (0.2%)	6	3 (0.8%)	3
Vomiting	8 (0.3%)	9	1 (0.3%)	1
Dizziness	6 (0.2%)	6	1 (0.3%)	1
Fatigue	5 (0.2%)	5	3 (0.8%)	3
Hypertension	7 (0.2%)	8	0 (0.0%)	0
Hypotension	6 (0.2%)	12	0 (0.0%)	0
Injection site coldness	6 (0.2%)	7	1 (0.3%)	1
Pyrexia	6 (0.2%)	6	0 (0.0%)	0
Rash	5 (0.2%)	5	0 (0.0%)	0
Somnolence	5 (0.2%)	5	0 (0.0%)	0

Data presented are the number (%) patients who experienced at least one AE ["N (%) patients"] and the total number of events ["n events"]. One patient could have more than 1 event.
Post-injection events: All events occurring after injection of the MRI contrast agent or all events with a missing onset for patients who received a dose of MRI contrast agent.

Most post-injection AEs were mild (66.9%) or moderate (20.0%) in intensity, and most resolved without treatment (76.8%). A total of 22 post-injection AEs in 17 patients (0.6%) resolved after treatment and 2 AEs in 2 patients (0.1%) resolved with sequelae. Thirty-three AEs in 24 patients (0.8%) did not resolve or were ongoing and 12 AEs in 8 patients (0.3%) were fatal.

No information concerning overdose, drug abuse, misuse, dependence and withdrawal has been identified, and no event of Nephrogenic Systemic Fibrosis (NSF) has been reported in the 51 clinical studies.

Deaths and Other Non-Fatal Serious Adverse Events

In the 51 clinical studies, events resulted in death in 8 patients (0.3%); none of these events were assessed as related to Dotarem® administration. No deaths were reported in the patients aged <2 years.
Of the 30 patients (1.0%) who received Dotarem® and had an SAE, 22 patients had non-fatal SAEs, including one patient <2 years. None of the SAEs was considered related to Dotarem administration and all resolved.

Safety in Special Groups and Situations
Adverse events were evaluated by subgroups such as age, gender, race, dose, renal function, allergy, hepatic function, cardiac function, diabetes and past reaction to contrast agent for potential safety differences.

Age

Among the 52 patients aged <2 years who received Dotarem® (50.0% males and 50.0% females), the mean age was 0.83 years (approximately 10 months), with 5 patients younger than 1 month; the mean weight was 8.0 kg. MRI indication was CNS imaging in most cases (35, 67.3%). Three patients (5.8%) had history of cardiac disease and two (3.8%) had history of allergic disease. None of the patients had prior reaction to contrast agent. The mean dose of Dotarem® administered was 0.2 mL/kg (0.1 mmol/kg), ranging from 0.15 to 0.22 mL/kg and the mean rate of injection was 1.0 mL/sec.

Among these 52 patients, 14 patients (26.9%) experienced at least one post-injection AE. None of the 5 children under 1 month experienced any post-injection AE. However, only 1 patient (2.1%) experienced a post-injection AE assessed as related to Dotarem® (non-serious rash of moderate intensity). All post-injection AEs were mild or moderate in intensity. The most common AEs that occurred post-injection in patients <2 years who received Dotarem were pyrexia (11.5% of patients), vomiting (3.8%), and leukopenia (3.8%). All the other post-injection AEs occurred in no more than 1 patient. Most post-injection AEs (21/27) occurred between >1 hour to 3 days after the injection of Dotarem®. A total of 14 post-injection AEs lasted less than 3 days, 12 lasted 3 to 30 days and 1 lasted more than 30 days. The only related AE (rash) occurred on the day of Dotarem® administration and resolved within 5 days with medication.

In older pediatric patients (≥2 years to <18 years), the highest incidence of post-injection AEs was reported in patients aged ≥6 to <12 years (n=5/57, 8.8%), followed by patients aged ≥2 to <6 years (n=2/33, 6.1%), and patient aged ≥12 to <18 years (n=1/43, 2.3%). In pediatric patients aged ≥2 to <6 years and in pediatric patients aged ≥12 to <18 years, related were reported in no more than 1 patient. In pediatric patients aged ≥6 to <12 years, the most common related AE was headache (2 patients).

Post-injection SAEs were reported in 1 patient aged 1 to <24 months and 1 patient aged 2 to <6 years and receiving Dotarem®, none of which was considered related to Dotarem® administration.

Among the adults who received Dotarem®, the incidence of post-injection AEs was relatively stable across age groups: 9.0% of patients aged <65 years, 7.2% of patients aged ≥65 to <75 years and 9.9% of patients aged ≥75 years. Serious AEs were reported in 0.9% to 1.2% of adult patients who received Dotarem®, depending on the age group. Nausea was a common related AE in all age group (incidence 0.5% to 1.0%, depending on the age group). Other common related AEs included injection site pain, headache and injection site coldness in adults aged 18 to <65 years, injection site pain, blood creatinine increased, hypotension and hypertension in adults aged 65 to <75 years.

Gender

A total of 147 males (9.4%) and 143 females (11.0%) receiving Dotarem® experienced AEs. The incidence of related AEs was slightly lower in males (50/147, 34.0%) than in females (64/143, 44.8%).

Race
Among the 2867 patients who received Dotarem® in the clinical studies, information on race was missing for 1225 patients (42.7%). Among the remaining patients, the large majority (80.6%) were "Caucasian". The incidence of related post-injection AEs was 4.9% among 1324 "Caucasians", 6.2% among 65 "Black", 2.1% among 189 "Asian" and 6.3% among 64 "Other".

Dotarem Dose
There was no evidence of increased incidence of post-injection AEs with increased dose of Dotarem®. Among patients who received doses ≥0.05 mmol/kg to ≤0.1 mmol/kg, 9.1% had post-injection AEs and 4.0% had related post-injection AEs, vs. 8.4% and 4.1%, respectively, of those who received doses of Dotarem® higher than 0.1 mmol/kg. Only 5 patients (all aged <2 years) received doses <0.05 mmol/kg, 1 of whom had post-injection AEs which were not related to Dotarem®.

Special groups
Considering all 51 clinical studies, the incidence of AEs, related AEs and SAEs was slightly higher in patients with impaired renal function or allergic diseases compared to patients without the disease. However, the incidence of AEs considered related to Dotarem® remained low: 6.4% versus 3.8% for patients with or without renal disease, and 6.7% versus 3.5% for patients with or without allergic disease.

No marked differences in the incidence of related AEs was observed between patients with or without hepatic disease, and between patients with or without cardiac disease. A history of past reaction to contrast agent was associated with a higher incidence of related AEs when considering all 51 clinical studies: 7.8% vs. 3.9% in the patients without any history of past reaction. Generally, the same types of related AEs were reported in the patients with or without the underlying disease.

A phase IV, open-label, non-randomised, multinational study was conducted by Guerbet to prospectively compare the renal safety of Dotarem®-enhanced MRI to a control group (unenhanced MRI) in patients with chronic kidney disease [**Study DGD-44-044**, (61)]. Patients (male or female, aged ≥18 years) with known stable stage 3 or 4 CKD according to the Kidney Disease Improving Global Outcomes (KDIGO) definition (i.e., eGFR >15 ml/min/1.73 m^2 and <60 ml/min/1.73 m^2) scheduled to undergo MRI were included. According to the investigator's judgement (i.e., diagnosis needed) and the hospital's standard practices, patients were assigned to the Dotarem®-enhanced MRI group or the unenhanced MRI group. In each center, MRI procedures were performed according to the hospital's standard protocols. A total of 142 patients were screened in 15 centers in Europe (Belgium, France, Italy, and Spain), 135 were included, and 114 were evaluable for the primary endpoint (70 in the Dotarem-MRI group and 44 in the unenhanced-MRI group). Dotarem® was administered intravenously at a mean dose of 0.1 mmol/kg (range: 0.06–0.29 mmol/kg) and at a mean flow rate of 2 ml/s (range: 0.7–4 ml/s).

The primary endpoint was the percentage of patients with serum creatinine level elevation, determined 72±24 hrs after MRI, of at least 25 % or 44.2 μmol/l (i.e., 0.5 mg/dl) above the baseline value. The non-inferiority margin of the between-group difference was set at −15 %.

Main secondary endpoints were the variation in serum creatinine and eGFR values between baseline and 72±24 h after MRI and the percentage of patients with a decrease in eGFR of at least 25% from baseline. Patients were screened for signs of NSF at 3-month follow-up.

One patient (1.4 %) in the Dotarem® MRI group and no patients in the control group met the criteria of the primary endpoint with a mean difference (unenhanced-MRI – Dotarem-MRI) of −1.4 % [95 %CI: −7.9 %; 6.7 %]. The non-inferiority of Dotarem®-MRI over unenhanced MRI was demonstrated (P=0.001). Consistent results were observed in the PP population (67 patients), with a mean difference of −2.7 % [95%CI: −14.1 %; 8.9 %, P=0.0204]. No clinically significant differences were observed between groups for the secondary endpoints. No serious safety events (including NSF) were noted. This study showed that Dotarem® did not affect renal function and was a safe contrast agent in patients with CKD.

Clinical Laboratory Evaluations
Clinical laboratory evaluations were performed in 23 studies in a total number of 648 patients who received Dotarem. No pooled analysis of laboratory data was performed. No clinically significant variations or abnormal values were observed in most studies. Rare clinically significant abnormal values were mostly attributable to underlying disease and occurred in isolated cases.

In study **DGD-44-063**, blood hematology and biochemistry parameters were measured at screening and one day after Dotarem administration (safety visit) in pediatric patients aged <2 years. Changes from baseline were close to 0 for most hematology parameters and standard biochemistry parameters. Overall, the main changes observed were small mean decreases in erythrocytes, hemoglobin, leukocytes, lymphocytes, platelets, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase and lactate dehydrogenase (LDH). Leukopenia was reported as an AE for 2 patients (who also experienced anemia for one and thrombocytopenia for the other). However, no abnormal laboratory values or changes in renal parameters were reported as AEs related to Dotarem.

Mean (±SD) eGFR was 129.7 (±41.5) mL/min at screening and 135.9 (±51.0) mL/min at safety visit. Changes from baseline ranged from -89 to +92 mL/min, showing variability between patients. Mean (±SD) creatinine level was 23.51 (±6.03) µmol/L at screening visit and 23.95 (±5.43) µmol/L at safety visit with a mean change of 0.35 (±4.35) µmol/L. No abnormal results in urinalysis were reported at the safety visit after Dotarem® administration.

In pediatric study **DGD-03-015**, no clinical relevant changes in mean blood parameters were observed following Dotarem® administration.

Vital Signs, ECG, and EEG Evaluations
Evaluation of vital signs was performed in 21 studies in a total of 1712 patients who received Dotarem®. Electrocardiography was assessed in 5 of these 21 studies in a total of 165 patients who received Dotarem, including 12 pediatric patients. One study in particular evaluated the electrocardiographic safety in 40 subjects receiving a triple dose of Dotarem® (DGD-44-039). In addition, EEG was performed in 1 study (DGD-03-011, in 19 patients who received Dotarem). No clinically significant effect of Dotarem® on vital signs was noted in adults and

pediatric patients older than 2 years. The mean values showed minimal fluctuations from pre-procedure at each time point post-injection. The changes observed in vital signs can be attributed to underlying conditions (hypertension, anxiety).

Regarding ECG safety, no clinically relevant effect of Dotarem® on QT interval was observed. A phase IIb study (DGD-44-039) assessed the effects of the highest cumulative dose of Dotarem® used in clinical practice, i.e. 0.6 mL/kg (0.3 mmol/kg), administered at 0.2 mL/kg (0.1 mmol/kg) as a bolus intravenous at a rate of 1 to 2 mL/sec followed by a second injection of 0.4 mL/kg (0.2 mmol/kg) 20 minutes later. Forty patients were randomised to receive Dotarem® and placebo in either sequence order. Dotarem® had no effect on QT or QTc interval or any other ECG parameter. The good tolerance and safety of Dotarem® was confirmed, as there was no clinically significant abnormality in the laboratory safety and vital sign results. Overall, in the 5 studies that included ECG measurements, no unusual or unexpected AEs with Dotarem® were observed. In particular, there were no clinically relevant cardiovascular side effects with Dotarem®.

No abnormalities in EEG features were observed following Dotarem® injection. There was no clinical evidence of any modification of spontaneous basic rhythm of cerebral electrical activity and no paroxysmal activity (DGD-03-011).

Regarding the population of pediatric patients < 2 years (study DGD-44-063**)**, there was a very small mean decrease in systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate immediately after MRI. There was a mean increase in SBP, DBP and heart rate at time points 2 to 4 hours after injection and 24 hours after injection. However, a great variability was observed between patients and vital signs remained mostly stable overall. The slight changes observed in some patients may be explained by sedation received just before MRI and recovery of normal state after MRI.

Conclusion on the overall safety assessment:
Based on 51 clinical trials conducted with Dotarem®, 4% of the 2867 patients experienced AEs related to the product. The most common related AEs were nausea, headache, and injection site pain. Most AEs were mild or moderate in intensity and a very low incidence of related SAEs was reported, which has no impact on the favourable benefit-risk ratio of Dotarem®.
No clinically relevant abnormality in the laboratory data, vital signs, ECG, and EEG were observed after Dotarem® injection among 648, 1712, 165, and 19 exposed patients, respectively.

3.1.4.2 Data from post-marketing surveillance

Post-Marketing Studies Conducted by Guerbet

Nine post marketing observational studies including 195,481 patients provided additional safety data for both adult and pediatric populations.

- Neiss et al. (14) assessed the efficacy and safety of Dotarem® in MR examinations in 4169 patients including 305 children in 99 centers (France, Switzerland and Belgium). Dotarem® doses ranged from 0.15 to 0.25 mL/kg (i.e. 0.07 to 0.13 mmol/kg). The indications studied were CNS in 77.0% of patients or bone and soft tissues in 11.2% of patients. A total of 35 patients (0.84%) experienced at least one AE. The majority of

the 43 AEs observed were considered of mild or moderate intensity. The most frequently reported AEs were vomiting, nausea and headache. Allergic reactions were very rare (2 cases of rash, one case of respiratory disorders and one case of allergy).

- Briand (15) in France enrolled 402 pediatric patients. MRI was performed for imaging of CNS in 82.4% of patients and bone and soft tissue in 11.4%. A total of 26 patients (6.5%) were aged <2 years. A mean dose of 0.22 mL/kg was injected. There were no AEs reported in children aged below 15 years. One 16-year-old adolescent developed a papule on the inside of the thigh 10 minutes after the injection, but this did not require discontinuation of treatment.
- Ishiguchi (16) in Japan, a total of 3444 patients undergoing imaging of the brain/spinal cord and/or trunk/limbs were included. Among them a total of 40 adverse reactions were recorded in 32 patients, giving an overall incidence of adverse reactions of 0.9%. Gastrointestinal disorders were the most commonly reported adverse reactions (0.5%), mainly nausea (0.4%) and vomiting (0.1%). Most adverse reactions reported were of mild intensity and no serious adverse reactions were reported. No adverse reactions were reported for any of the pediatric patients.
- Emond et al. (17) in France, among 104 neonates and infants <18 months enrolled, no AE was reported.
- In the large post-marketing study by Maurer (18) in Germany, AEs occurred after injection of Dotarem® in 328 out of 104,033 patients (0.3%). AEs were predominantly mild to moderate and uncommon to very rare. The causal relationship was reported in 228 patients. A relationship with Dotarem® was excluded in 2 out of 228 patients (0.9%). The relationship was certain in 69 patients (30.3%), probable in 93 patients (40.8%), possible in 48 patients (21.1%), and unlikely in 16 patients (7.0%). The outcome was reported for 224 patients: 96.9% recovered after the examination, 2 patients (0.9%) had not yet recovered (pruritus, pustular rash and urticaria) and the outcome was unknown in 5 patients (2.2%). In 11 patients (0.01%) at least one SAE was reported. The causal relationship with Dotarem® was rated as possible in 7 patients and doubtful in 3 patients, and was not available in one patient. Ten patients recovered after treatment of the SAE while the outcome was unknown in one patient. There was an increased risk of AEs in patients with allergic predisposition and in patients with a previous reaction to contrast medium. No increased risk of AEs or of SAEs was demonstrated in patients with cardiovascular diseases, renal insufficiency or CNS disorders.
- The international PMS study DGD-55-001, SECURE (19), assessed the general safety profile of Dotarem® in adult and pediatric patients with or without renal insufficiency and undergoing routine contrast-enhanced MR imaging. Imaging was performed for the following indication (multiple indications could be reported for the same patient): CNS (61.0% of patients), Whole body (25.2%), Musculoskeletal (14.3%), Angiography (4.1%), Other (4.8%). The safety population comprised 35474 patients, including 1631 children (106 aged <2 years, 815 between 2 and 12 years, and 710 between 12 and 18 years). A total of 70 post-injection adverse events were reported in 44 patients (0.1%) (mainly urticaria, nausea, vomiting). Most AEs were considered of mild or moderate intensity and 38 AEs (54.3% of all AEs) were considered related to

administration of the contrast agent. When considering children, most of them were included in India (47.8%), Germany (19.8%) and France (19.1%), and CNS examinations accounted for 80.4% of contrast-enhanced procedures. One AE was reported in a pediatric patient (2 years old): mild vomiting, doubtfully related to contrast agent. A total of 515 patients including 3 children (0.2%) were identified with moderate to severe impaired renal function (estimated creatinine clearance <60 mL/min and/or eGFR <60 mL/min/1.73 m²). Follow-up of these patients (≥3 months for 61.5% of the patients) did not show any suspicion of NSF. Five deaths have been reported in the SECURE study. One death was assessed as unlikely related to Dotarem®. The patient experienced a sequence of 6 AEs: candida sepsis, renal failure acute, cardiovascular insufficiency, acidosis, mitral valve incompetence and death. However, the death occurred more than 9 days after GdCA administration.

- The PMS study DGD-55-004 was conducted in Korea to assess the efficacy and safety of Dotarem® and incidence of NSF in the subgroup of patients with renal impairment (moderate to severe and end stage renal impairment). A total of 1862 patients scheduled for a MRI with Dotarem in 16 centers were studied, including 119 children (0-19 years) and 38 patients with renal impairment. Dotarem® doses ranged from 0.01 to 0.26 mmol/kg. No AE or SAE was observed among the 1862 patients enrolled. No suspicion of NSF was observed.
- The PMS study DGD-55-005 was conducted in Germany to gain additional insights into the diagnostic efficacy, reliability and safety of Dotarem® in routine practice. Diagnostic efficacy was assessed by the following endpoints: diagnostic value (yes/no) and imaging quality (5-step scale from excellent to very poor). Safety was evaluated on the basis of the frequency and seriousness of AEs that occurred following Dotarem injection. A total of 44,456 patients (55% female) were included in 52 centers between January 2011 and December 2013. The mean age was 52.3±16.9 years (range: 1 to 98 years). One infant aged <2 years (<0.1%), 81 children from 2 to 11 years old (0.2%) and 617 adolescents from 12 to 17 years old (1.4%) were included. MRI indication was mostly neurological (50.0%). Bones/joints and muscles (MSK system) were examined in 27.8% of patients and internal organs in 13.9% of patients. MR angiography was carried out in 2,044 patients (4.7%). Allergies were reported for 15.5% of patients and hypertension for 5.6%. A total of 225 AEs occurred in 139 patients (0.3%), considered related to contrast agent for 136 patients. The most common AEs were nausea (70 patients, 0.2%), vomiting (22 patients, 0.05%) and urticaria (13 patients, 0.03%). A total of 18 SAEs were observed in 7 patients (0.02%). All patients with AEs fully recovered after the examination. In the pediatric population, no AEs occurred in children below 12 years and 6 adolescents (1.0%) experienced 9 AEs including 3 serious (vomiting, swelling face and urticaria) reported in 2 adolescents. Adverse events occurred in only 1 of the 1416 patients (0.07%) with impaired renal function (eGFR <90 mL/min/1.73 m²).
- The PMS study DGD-55-006 was conducted in Germany to generate additional data on the diagnostic efficacy, reliability and safety of Dotarem® in MR mammography (52). Diagnostic efficacy was assessed on the basis of image quality (5-stage scale from excellent to very poor), diagnosis and cytology test result. Safety was assessed on the basis of the frequency and seriousness of adverse drug reactions (ADRs) observed

following the injection of Dotarem®. A total of 1537 patients were included in 15 centers between January 2012 and October 2013. Patients underwent MR mammography with Dotarem®, most commonly to exclude recurrence (43.4%), screen at-risk patients (27.4%) or clarify an inconclusive finding (16.5%). A total of 54.8% of the examinations were carried out on postmenopausal women, 33.6% on premenopausal and 11.6% on perimenopausal women. Adverse drug reactions occurred in 5 of 1537 patients (0.3%). For one of the 5 patients, ADRs were serious (tachycardia, dysphagia, urticaria, rash). All of the patients with ADRs fully recovered after the examination.

Of these, the 8 PMS observational studies that included patients aged <2 years (n=259) confirmed the good safety profile of Dotarem® in this population, with no AEs reported in that age group.

Conclusion on the safety assessments in post-marketing observational studies:
The studies did not reveal any new findings concerning the safety of Dotarem® among 195,481 exposed patients, and showed that Dotarem® was very well tolerated in routine practice whatever the indication.

Pharmacovigilance Data
After an overview on the general population, the following post-marketing data are therefore presented according to subpopulations based on the patients' profiles: pediatric patients, patients with renal insufficiency, patients of at least 65 years old, patients exposed during pregnancy, and finally patients with NSF.

Overall population
Cumulative post-marketing safety data received by Guerbet Pharmacovigilance Department from worldwide sources beginning with the first European Marketing Authorization for Dotarem® obtained in France on March 8, 1989 and continuing through April 15, 2016 were analysed. A total of 9391 reactions in 4201 cases were reported to Guerbet from 54,378,085 patients exposed in the post-marketing setting during this period, for all Dotarem® dosages and forms. The incidence is estimated to be 17.3 adverse reactions for 100,000 patients and 7.7 cases for 100,000 patients exposed.
In terms of seriousness, 1260 serious cases were reported; the incidence is estimated to be 2.3 serious cases for 100,000 patients exposed. Among all Adverse Drug Reactions (ADRs), the most frequently affected System Organ Classes (SOCs) with at least 5% of all ADRs were:

- Skin and subcutaneous tissue disorders (27.9%) with 2618 ADRs
- Gastrointestinal disorders (19.0%) with 1782 ADRs
- Respiratory thoracic and mediastinal disorders (12.5%) with 1170 ADRs
- General disorders and administration site conditions (10.9%) with 1022 ADRs
- Nervous system disorders (6.9%) with 646 ADRs
- Immune disorders (6.1%) with 570 ADRs

The most frequently reported ADRs were nausea (844 ADRs), urticaria (766 ADRs), vomiting (604 ADRs), erythema (455 ADRs) and pruritus (439 ADRs) with an incidence of 1.6, 1.4,

1.1, 0.8 and 0.8 ADRs for 100,000 patients exposed, respectively. Data are detailed in Table 23.

Fatal cases

As of April 15, 2016, a total of 38 fatal cases have been reported since the first marketing authorization of Dotarem®, i.e., 0.07 fatal cases per 100,000 exposed patients.

The most commonly reported causes of fatal outcomes were anaphylaxis and acute cardiovascular conditions (19 cases), nephrogenic systemic fibrosis (8 cases) followed by other cause of death without obvious signs of hypersensitivity (11 cases).

Among these latter 11 cases, one is not related to Dotarem® but due to erroneous intravenous injection of perflourocarbon derivative, 7 cases are unlikely related to Dotarem®, 2 are possibly related to Dotarem® and the causality could not be assessed for the last one.

The causal relationship between Dotarem and NSF was assessed as unlikely in all 8 cases. Among these cases, 5 are secondary to multiple GdCAs injections and 3 to one unknown GdCA, Dotarem® being not excluded but not confirmed (see section "Nephrogenic Systemic Fibrosis").

Table 23: Cumulative distribution of most frequent Preferred Terms (PTs) (≥50) by SOC in post-marketing Pharmacovigilance cases (estimated incidence for 100 000 patients exposed)

Primary SOC	PT	Number of ADRs	Incidence for 100 000 exposed patients
Cardiac disorders	Tachycardia	58	0.1
Eye disorders	Eyelid oedema	82	0.2
Gastrointestinal disorders	Nausea	844	1.6
	Retching	53	0.1
	Vomiting	604	1.1
General disorders and administration site conditions	Chills	50	0.1
	Feeling hot	109	0.2
	Injection site extravasation	59	0.1
	Injection site pain	57	0.1
	Malaise	105	0.2
Immune system disorders	Anaphylactic reaction	74	0.1
	Anaphylactic shock	77	0.1
	Hypersensitivity	146	0.3
	Type I hypersensitivity	230	0.4
Nervous system disorders	Dizziness	116	0.2
	Headache	86	0.2
	Paraesthesia	95	0.2
	Tremor	52	0.1
	Syringe issue	85	0.2
Respiratory, thoracic and mediastinal disorders	Cough	210	0.4
	Dyspnoea	311	0.6
	Sneezing	99	0.2
	Throat irritation	71	0.1
Skin and subcutaneous tissue disorders	Angioedema	75	0.1
	Erythema	455	0.8
	Hyperhidrosis	72	0.1
	Pruritus	439	0.8
	Rash	287	0.5
	Urticaria	766	1.4
Vascular disorders	Flushing	62	0.1
	Hypotension	77	0.1
	Total ADRs:	**9391**	**17.3**
	Number of cases :	**4201**	**7.7**

Subpopulations

- Pediatric Patients

Comparison of safety data between pediatric patients (age lower than 18 years old) and adults (age of at least 18 years old), shows an identical distribution of the most represented SOCs with at least 5% of ADRs: Skin and subcutaneous tissue disorders (24.1% in children vs. 28.5% in adults), Gastrointestinal disorders (22.7% vs. 19.5%), Respiratory, thoracic and mediastinal disorders (15.1% vs. 12.5%), General disorders and administration site conditions (10.2% vs. 10.7%), Nervous system disorders (6.2% vs. 7.1%) and Immune system disorders (5.6% vs. 6.1%, respectively), see Table 24.

Table 24: Cumulative distribution of ADRs by SOC in pediatric and non-pediatric patients

	<18 years		≥18 years	
Primary SOC	**ADR**	**%[1]**	**ADR**	**%[1]**
Blood and lymphatic system disorders			4	0.0%
Cardiac disorders	10	2.0%	135	1.7%
Congenital, familial and genetic disorders				0.0%
Ear and labyrinth disorders	1	0.2%	34	0.4%
Endocrine disorders			1	0.0%
Eye disorders	13	2.6%	231	2.8%
Gastrointestinal disorders	113	22.7%	1579	19.5%
General disorders and administration site conditions	51	10.2%	871	10.7%
Hepatobiliary disorders	1	0.2%	5	0.1%
Immune system disorders	28	5.6%	496	6.1%
Infections and infestations	5	1.0%	34	0.4%
Injury, poisoning and procedural complications	20	4.0%	207	2.5%
Investigations	7	1.4%	91	1.1%
Metabolism and nutrition disorders			15	0.2%
Musculoskeletal and connective tissue disorders	2	0.4%	85	1.0%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			1	0.0%
Nervous system disorders	31	6.2%	574	7.1%
Pregnancy, puerperium and perinatal conditions	5	1.0%	18	0.2%
Product issues	2	0.4%	51	0.6%
Psychiatric disorders	3	0.6%	58	0.7%
Renal and urinary disorders	1	0.2%	40	0.5%
Reproductive system and breast disorders			8	0.1%
Respiratory, thoracic and mediastinal disorders	75	15.1%	1015	12.5%
Skin and subcutaneous tissue disorders	120	24.1%	2316	28.5%
Social circumstances			1	0.0%
Surgical and medical procedures			8	0.1%
Vascular disorders	10	2.0%	240	3.0%
Total	**498**		**8118**	

[1]: percentage based on the total number of ADRs in the concerned population.

A more detailed analysis based on the 10 most frequent PTs shows a similar safety profile between children and adults, who experienced the same 9 most frequent ADRs: Nausea, Cough, Dyspnoea, Erythema, Hypersensitivity, Pruritus, Rash, Urticaria and Vomiting (Table 25).

Table 25: Cumulative distribution of most frequent PTs in Children and Adults

Primary SOC / PT		<18 years		≥18 years	
		N	%[1]	N	%[1]
Gastrointestinal disorders	Nausea	38	7.63%	760	9.36%
	Vomiting	52	10.44%	523	6.44%
Immune system disorders	Hypersensitivity	11	2.21%	125	1.54%
	Type I hypersensitivity	5	1.00%	197	2.43%
Nervous system disorders	Headache	9	1.81%	70	0.86%
Respiratory, thoracic and mediastinal disorders	Cough	17	3.41%	182	2.24%
	Dyspnoea	20	4.02%	273	3.36%
Skin and subcutaneous tissue disorders	Erythema	28	5.62%	400	4.93%
	Pruritus	20	4.02%	396	4.88%
	Rash	15	3.01%	256	3.15%
	Urticaria	28	5.62%	691	8.51%
	Total :	**498**		**8118**	

N: number of ADRs.; [1]: percentage based on the total number of ADRs in the concerned population .

A specific focus on children ≤2 years old shows that they are most frequently susceptible for overdoses, followed by skin reactions (Table 26). A thorough analysis shows that 5 out of 6 overdoses did not lead to clinical consequences. Overall, due to the low number of cases (n°=°14) and ADRs (n°=°24), no conclusions can be drawn from the other data in this specific class of age.

Table 26: Cumulative distribution of ADRs in children below 2 years old.

Primary SOC	Preferred Term (PT)	Number of ADRs
Cardiac disorders	Tachycardia	1
Eye disorders	Eye swelling	1
General disorders and adm. site conditions	Extravasation	1
	Injection site induration	1
	No adverse event	2
Injury, poisoning and procedural complications	Accidental overdose	2
	Incorrect route of drug adm.	1
	Off label use	1
	Overdose	4
Investigations	Body temperature increased	1
	Heart rate decreased	1
Nervous system disorders	Seizure	1
Respiratory, thoracic and mediastinal disorders	Respiratory arrest	1
	Stridor	1
Skin and subcutaneous tissue disorders	Dermatitis allergic	1
	Erythema	1
	Rash	1
	Urticaria	2
Total		**24**

- Patients with Renal Insufficiency

As of 15 April 2016, a total of 102 cumulative pharmacovigilance cases were reported in the sub-population of patients with renal failure reported as medical history (Table 27). They experienced a total of 213 ADRs, the most representative one being NSF (n=42). It is of importance to note that among the NSF reports, most of them are either multi-products, or Dotarem® could not be excluded due to lack of information about suspected GdCAs (refer to specific section "Nephrogenic Systemic Fibrosis"). Furthermore, patients with NSF but without renal failure reported in medical history are not described in this sub-population. Among NSF patients, symptoms of NSF could also be reported: arthralgia (n=3) or myalgia (n=4). The other most represented ADRs in the sub-population of patients with renal insufficiency were:

- Condition aggravated (n=3) that correspond to 3 cases of aggravated renal failure;
- Renal failure or acute kidney injury (n=11) including 4 cases possibly related to Dotarem® and 7 cases unlikely related to Dotarem;
- 0verdose (n=6) including 3 cases of overdose without adverse drug reactions;
- A series of skin reactions (n=14), excluding NSF, and reported in one publication without more details and assessed as unlikely related to Dotarem®.

- Patients of at least 65 years old

Distribution of ADRs by SOC shows that the most representative SOCs are: Skin and subcutaneous tissue disorders (26.9% of ADRs), Gastrointestinal disorders (15.9% of ADRs), Respiratory, thoracic and mediastinal disorders (13.9% of ADRs), General disorders and administration site conditions (12.5% of ADRs), Nervous system disorders (8.0% of ADRs) and Immune system disorders (6.2% of ADRs). This distribution is the same as for overall population (Table 28).

The most representative PTs (≥50 ADRs) are: nausea (n=100), urticaria (n=91), vomiting (n=74), erythema (n=74), pruritus (n=61) and dyspnoea (n=53) (Table 29). They are the same as in overall population and no specific safety concerns arise from this subpopulation.

Table 27: Cumulative distribution of most frequent PTs (≥ 2) in patients with medical history of renal insufficiency

Primary SOC	**PT**	**Number of ADRs**
Gastrointestinal disorders	Nausea	4
	Vomiting	2
General disorders and administration site conditions	Condition aggravated	3
	No adverse event	3
	Pyrexia	2
Immune system disorders	Type I hypersensitivity	2
Infections and infestations	Onychomycosis	2
Injury, poisoning and procedural complications	Overdose	6
Musculoskeletal and connective tissue disorders	Arthralgia	3
	Myalgia	4
	Pain in extremity	2
Nervous system disorders	Burning sensation	2
	Paraesthesia	2
Renal and urinary disorders	Acute kidney injury	6
	Renal failure	5
Respiratory, thoracic and mediastinal disorders	Dyspnoea	3
Skin and subcutaneous tissue disorders	Eczema	2
	Erythema	4
	Nephrogenic systemic fibrosis	42
	Pruritus	2
	Skin hypertrophy	2
	Skin reaction	14
	Urticaria	2
Vascular disorders	Hypotension	2
Total number of ADRs:		**213**
Number of cases :		**102**

Table 28: Cumulative distribution of ADRs by SOC in patients of at least 65 years old

Primary SOC	Number of ADRs	% of ADRs
Blood and lymphatic system disorders	1	0.1%
Cardiac disorders	40	2.9%
Ear and labyrinth disorders	3	0.2%
Eye disorders	33	2.4%
Gastrointestinal disorders	217	15.9%
General disorders and administration site conditions	171	12.5%
Hepatobiliary disorders	1	0.1%
Immune system disorders	85	6.2%
Infections and infestations	8	0.6%
Injury, poisoning and procedural complications	13	1.0%
Investigations	23	1.7%
Metabolism and nutrition disorders	4	0.3%
Musculoskeletal and connective tissue disorders	13	1.0%
Nervous system disorders	110	8.0%
Product issues	7	0.5%
Psychiatric disorders	10	0.7%
Renal and urinary disorders	18	1.3%
Reproductive system and breast disorders	1	0.1%
Respiratory, thoracic and mediastinal disorders	190	13.9%
Skin and subcutaneous tissue disorders	368	26.9%
Vascular disorders	52	3.8%
Total ADRs	**1368**	

Table 29: Cumulative distribution of most frequent PTs (≥10) by SOC in patients of at least 65 years old

Primary SOC	Preferred Term (PT)	Number of ADRs
Eye Disorders	Eyelid oedema	11
Gastrointestinal disorders	Nausea	100
	Vomiting	74
General disorders and administration site conditions	Feeling hot	18
	Injection site extravasation	17
	Injection site pain	16
	Malaise	19
	No adverse event	13
Immune system disorders	Anaphylactic reaction	15
	Anaphylactic shock	19
	Hypersensitivity	17
	Type I hypersensitivity	25
Nervous system disorders	Dizziness	15
	Headache	12
	Loss of consciousness	11
	Paraesthesia	13
Respiratory, thoracic and mediastinal disorders	Cough	36
	Dysphonia	10
	Dyspnoea	53
	Sneezing	16
	Throat irritation	12
Skin and subcutaneous tissue disorders	Erythema	74
	Hyperhidrosis	17
	Pruritus	61
	Rash	38
	Urticaria	91
Vascular disorders	Flushing	12
	Hypotension	12

- Exposure During Pregnancy

Cumulatively, as of April 15, 2016, there were 159 reports of drug exposure during pregnancy. A cumulative overview of these cases is presented in Table 30.

Out of 159 reports of exposure during pregnancy (several categories are possible):

- 45 pregnancies resulted in birth of normal babies (1 pregnancy resulted in birth of twins); this included 3 pregnancies with preterm delivery of normal healthy babies;
- 2 pregnancies resulted in preterm delivery of premature babies at 31.5 and 36 weeks of amenorrhea;
- 4 pregnancies resulted in delivery of babies with intra-uterine growth retardation in 2 term babies and 2 premature babies;
- 4 pregnancies resulted in miscarriage
- 1 pregnancy resulted in late intrauterine fetal death at 27 weeks of amenorrhea due to vascularization defect;
- 1 pregnancy resulted in live birth at an unspecified term of a baby with severe cardiopathy who died a few days later ;
- 11 pregnancies were terminated voluntarily, one of these concerned a therapeutic pregnancy termination due to congenital malformations;

- In 93 cases of Dotarem® exposure during pregnancy, pregnancy outcome is not known at the time of the report production.

Based on the available information, no new finding regarding exposure during pregnancy has been identified.

Table 30: Cumulative overview of cases of exposure during pregnancy

	Outcome								
Exposure	**Healthy baby**	**Premature baby**	**Intra-uterine growth retardation**	**Mis-carriages**	**Intra-uterine death**	**Post-natal death**	**Mal-formation**	**Voluntary pregnancy termination**	**Outcome unknown**
T_1	37****	5*/****	4*	3	0	1**	2**/***	10***	71
T_2	3	0	0	0	0	0	0	0	5
T_3	5	0	0	0	0	0	0	0	2
Unknown	0	0	0	1	1	0	0	1	15
All	45****	5*/****	4*	4	1	1**	2**/***	11***	93

T: trimester; * premature babies with intrauterine growth retardation included in both columns; **severe cardiopathy with fatal outcome included in both columns; ***voluntary pregnancy termination due to malformation included in both columns; **** preterm delivery with normal healthy baby included in both columns.

Nephrogenic Systemic Fibrosis

As of today, more than 65 million doses of Dotarem® were administered worldwide, with no unconfounded cases of confirmed NSF reported. This included dialysis patients, patients with an eGFR <30 mL/min/1.73 m² and patients with an eGFR ≥ 30 mL/min/1.73 m². This is consistent with nonclinical studies suggesting that Dotarem®'s macrocyclic and ionic structure exhibits the highest kinetic and thermodynamic stabilities among all marketed GdCAs and is thus expected to have a very low propensity to release free Gd.

As of May 31, 2017, a total of 45 medically confirmed cases of suspected NSF in patients having received Dotarem® or an unknown GdCA (Dotarem® not excluded) were identified. The reporting rate was very low and corresponds to 0.70 case per 1 000 000 patients exposed. Forty-two out of 45 cases are European (reported spontaneously, by Authorities or found in the literature). Three cases were reported from Asia (one from Japan under the name of Magnescope, one from Korea and one from China).

Among the 45 reported cases, administration of Dotarem® was confirmed in only 19 cases (17 confounded, 1 non qualifiable and 1 unconfounded), see Figure 4.

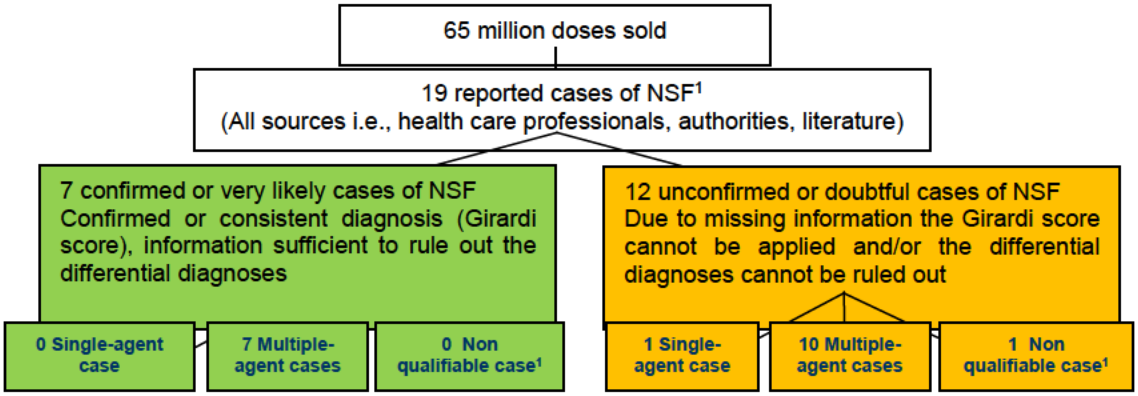
The diagnosis of NSF was confirmed for 7 cases (all confounded) and remained questionable for 12 cases (including the unconfounded case). All cases were considered by Guerbet Pharmacovigilance department as a serious expected case for Dotarem® with an unlikely causal relationship. Most of the cases (n=16) were in patients under dialysis or in patients with an eGFR < 30 mL/min/1.73m² when NSF occurred. Among the 3 other cases:

- One case was in a patient with an eGFR >30 mL/min/1.73m² but the final histology diagnosis according to Cowper analysis was Subtle Dermal Fibrosis, not consistent with the diagnosis of NSF.

- One case was in a patient with an eGFR >30 mL/min/1.73m² who had been exposed to two GdCAs including Dotarem®. The clinical and pathophysiological data are consistent with a diagnosis of NSF, according to the Girardi scoring. However, conditions surrounding the administrations of both GdCAs were not clear (chronology and sequence order); some cofactors such as concomitant treatments and a transplantation status may also have contributed to the occurrence of NSF.
- One case has been reported for which neither the renal status nor an eGFR have been mentioned. However, the NSF diagnosis could not be confirmed and important information on risk factors or past history was lacking to allow a proper assessment of the case.

No cases were reported in the context of a clinical trial.

Figure 4: Summary of NSF cases reported for patients who received Dotarem



[1] Non qualifiable = unspecified agent received in addition to Dotarem

In summary about safety of Dotarem®, based upon the analysis of the cumulative post-marketing experience of over 28 years gathered by Guerbet Pharmacovigilance, with a total exposure of more than 65 million doses, the most commonly reported ADRs with the use of Dotarem® are nausea, vomiting and symptoms of hypersensitivity reactions, the latter being most often cutaneous, respiratory and/or cardiovascular reactions and very rarely leading to death.

The comparison of safety profiles of subpopulations: children, patients with medical history of renal insufficiency, and patients at least 65 years old does not evidence any specificities by subpopulation as compared to the overall population. It seems that children below 2 years old are more susceptible to overdoses but without clinical consequences for most of them. Data obtained from exposure during pregnancy did not show any safety findings in this specific context.

In addition to the low incidence of adverse reactions, there was no single-agent case of confirmed NSF with Dotarem® either from clinical development programs or from post-marketing experience with more than 65 million doses administered. Therefore Guerbet concludes that the benefit-risk ratio of Dotarem® remains favourable.

3.1.4.3 Safety from Published Data

(i) Acute Adverse Reactions

(a) In cardiac MRI

In a large multi-center, multi-national, and multi-ethnical registry with consecutive enrolment of patients, Bruder et al. (62) evaluated the frequency, manifestations, and severity of acute adverse reactions associated with administration of several GdCAs during routine CMR. The EuroCMR registry included 37788 patients from 57 European centers in 15 countries. All data were collected prospectively using online case record forms.

Acute adverse reactions for the following contrast media were evaluated by the EuroCMR Registry; Gadopentetate (e.g. Magnevist®), Gadoteric acid (e.g. Dotarem®), Gadobenate (e.g. MultiHance®), Gadobutrol (e.g. Gadovist®), Gadoteridol (e.g. ProHance®), Gadodiamide (e.g. Omniscan®). All other contrast media were summarized as "others". Eighteen out of the 57 centers exclusively used one single contrast agent for all patients (Gadopentetate: n = 3, Gadoteric acid: n = 3, Gadobenate: n = 0, Gadobutrol: n = 8, Gadoteridol: n = 2, Gadodiamide: n = 2). All other centers used at least two or more different contrast agents in their clinical routine. The mean dose of contrast agent was 24.7 ml (range 5–80 ml), which is equivalent to 0.123 mmol/kg (range 0.01 - 0.3 mmol/kg).

Overall, 45 acute adverse reactions due to contrast administration occurred (0.12%). Wilcoxon rank sum test could not reveal any relations between acute reactions and the dose of gadolinium administered (p = 0.09). The most frequent adverse reactions were rashes and hives (15 of 45), followed by nausea (10 of 45) and flushes (10 of 45). Most reactions were classified as mild (43 of 45) according to the American College of Radiology definition, and 2 were severe (anaphylactic reactions that were graded as severe events due to the combination of bronchospasm and profound hypotension). Those two patients were admitted as inpatients, and were initially treated with adrenaline, steroids and antihistamines. All patients improved during treatment and could be discharged later. There were no deaths due to contrast administration (and no deaths due to CMR imaging), and no accumulation of events in a single center or a cluster of centers.

Between the different contrast agents the rate of adverse events ranged from 0.05% (linear non-ionic agent gadodiamide) to 0.42% (linear ionic agent gadobenate dimeglumine). The rate for gadoteric acid was 0.12% on 4235 examinations,

Table 2 Adverse Reactions Categorized by Severity and Agent

Agent	N° of Examinations	N° of Adverse Reactions			
		Mild	Moderate	Severe	Total
Gadopentetat (e.g. Magnevist)	12810	18 (0.14)	0	2 (0.02)	20 (0.16)
Gadoteracid (e.g. Dotarem)	4235	5 (0.12)	0	0	5 (0.12)
Gadobenat (e.g. Multihance)	706	3 (0.42)	0	0	3 (0.42)
Gadobutrol (e.g. Gadovist)	9378	9 (0.1)	0	0	9 (0.10)
Gadoteridol (e.g. Prohance)	1045	2 (0.19)	0	0	2 (0.19)
Gadodiamide (e.g. Omniscan)	6116	3 (0.05)	0	0	3 (0.05)
Other	3498	3 (0.09)	0	0	3 (0.09)
Total	37788	43 (0.11)	0	2 (0.01)	45 (0.12)

Note - Values in parentheses are percentages

[Table from Bruder et al. 2015 (62)]

The authors did not identify any relation between the rate of acute adverse reactions in the registry population and the specific characteristics of the different contrast agents, including structure or chelate stability ($p = 0.096$). However, the authors mentioned the limitations of the registry regarding the absence of long-term follow-up as parameters like structure and chelate stability may have an effect on long-term complications (e.g. nephrogenic systemic fibrosis). Interestingly, they also found different event rates between the three main indications for CMR ranging from 0.05 % for the group of mostly healthy individuals undergoing stress CMR for risk stratification in suspected coronary artery disease to 0.22 % for patients undergoing non-stress CMR for workup of myocardial viability in the setting of known coronary artery disease and heart failure ($p = 0.001$). They concluded on the basis of this finding, that one may even speculate that in this group some of the often unspecific symptoms such as nausea or anxiety, which had been interpreted as gadolinium-related symptoms, may also be due to the underlying disease (e.g. heart failure). In fact, the reaction rate truly caused by gadolinium itself could be even lower than that currently reported. The updated results from this registry showed that acute gadolinium contrast related complications are rare, and the event rate favourably compares to that reported in the literature in a general radiology setting and the use of GdCA in cardiovascular MR should be regarded as safe concerning the frequency, manifestation and severity of acute events.

In conclusion, these results in a selected population of patients showed a safety profile similar to the one reported for the general population. There was no relation between the rate of acute adverse reactions and the specific characteristics of the different contrast agents, suggesting that the physicochemical properties of the GdCAs (linear/macrocyclic structure of the ligand,

ionicity/non-ionicity of the complex, and osmolality) may not play any role regarding the risk of hypersensitivity.

(b) In various indications

In a recent retrospective analysis on 10,608 examinations, Granata et al. (63) assessed the frequency and severity of adverse reactions associated with IV injection of GdCA in patients who underwent MRI at their cancer institute. From January 2010 to October 2014 they included 10608 Caucasian patients (6.306 men and 4302 women; mean age 61 years; range 21–84 years). There were 7956 in-patients and 2652 out-patients. MR examinations were performed with a 1.5T MR system using an eighteen-channel body surface phased-array coil.

Five different types of GdCA were used: Gd-DOTA (Dotarem®) in 3501 cases, Gd-BTDO3A (Gadavist®) in 3002 cases, Gd-BOPTA (MultiHance®) in 1812 cases, Gd-EOBDTPA (Eovist® / Primovist®) in 1487 cases and Gd-DTPA (Magnevist®) in 806 cases. Choice of GdCAs was made in relation to the type of examination and to the clinical question.

The contrast agent was administered IV as a bolus, with a power injector at the standard recommended dosage (0.1mL/kg* for Eovist® and Gadavist®, 0.2mL/kg* for MultiHance®, Dotarem®, and Magnevist®) followed by a 20 mL saline flush. No patient received a double dose or a repeatinjection. The injection rate was 2 mL/s. According to the institute procedure, all patients who underwent contrast-enhanced MRI were monitored up to two hours after the end of the examination. The adverse reactions were regarded as acute if the symptoms occurred during the first hour after CM administration.

**erroneously written "mmol/kg" in the publication, which is not corresponding to standard recommended dose*

Table 2: Population distribution for each GBCA.

	Gd-BT-DO3A	Gd-DOTA	Gd-BOPTA	Gd-DTPA	Gd-EOB-DTPA	*p* value
Age (mean ± range)	59 (22–79)	62 (29–78)	56 (22–82)	60 (22–84)	61 (29–86)	0.21
Gender (number of men/women)	1771/1231	2106/1395	1051/761	483/323	895/592	0.59
No patients	3002	3501	1812	806	1487	
Patient type (number of inpatients/outpatients)	2350/652	2766/735	1409/403	624/182	1159/328	0.76
No patients premedicated	510	596	299	136	244	0.89
No patients using concomitant drugs	1350	1610	779	378	661	0.24
Iodinated CM hypersensitivity	158	201	74	40	70	0.14
MRI examination type (abdomen/brain/head & neck/breast)	1377/1405/0/220	3501/0/0/0	230/0/0/1582	726/0/80/0	1487/0/0/0	<0.001

[Table from Granata et al. 2016 (63)]

Overall, 32 (0.3%) acute adverse reactions to all GdCAs were reported. The reactions occurred in 6 men and 26 women (mean age 53 years; range 32–78 years); in 22 women the CM was administrated for breast study, in 2 for rectal cancer, and in 2 for liver study. Among the men, 4 patients had rectal cancer, one sarcoma, and one pancreatic cancer.

Twenty four patients developed a mild reaction (75.0%), 4 moderate reactions (12.5%), and 4 severe reactions (12.5%). Seven of these subjects had a seasonal allergic rhinitis history but

no one had history of drug or CM allergies/hypersensitivity, so no one was premedicated. No patient had liver or kidney failure.

The most common adverse reactions were mild skin rash and hives. The 4 moderate reactions were: bronchospasm using gadobutrol in a patient with pancreatic cancer (man; 51 years), dyspnea with gadoterate in a 38-year-old woman with rectal cancer, symptomatic tachycardia with gadopentetate in a 48-year-old man with sarcoma, and mild laryngeal oedema with gadobenate in a 76-year-old woman with breast cancer. Among the four severe reactions, 3 occurred with gadobenate (one severe respiratory distress, an episode of progressive angioedema, and one of arrhythmia, consisting in supraventricular tachycardia) in women (mean age 63) with breast cancer and another one manifested by using gadoterate (severe respiratory distress) in a 32-year-old man affected by rectal cancer. Nevertheless, no lethal acute reaction was observed. Although the patients were transferred to the Intensive Care Unit (ICU), all of those were discharged after 24 hours of observation.

When analyzing the rate of adverse reactions according to the GdCA used, an adverse reaction was found in 0.34% of the patients receiving gadoterate, 0.5% of the patients receiving gadobutrol, 0.2% of the patients receiving gadobutrol, 0.2% of the patients receiving gadoxetate, and 0.25% of the patients receiving gadopentetate. The higher percentage of adverse reactions, including the most severe reactions, occurred with gadobutrol, which caused three out of the four severe reactions. However, there was no statistically significant difference between various contrast media used neither was there a prevalence of adverse reaction significantly higher or lower related to patients age or the use of drugs as aspirin or chemotherapeutic agents.

Table 4: Overall and percontrast medium prevalence and severity of adverse reactions.

	Gd-BT-DO3A Number (%)	Gd-DOTA Number (%)	Gd-BOPTA Number (%)	Gd-DTPA Number (%)	Gd-EOB-DTPA Number (%)	*Total*	*p value*[a]
Mild reactions	5 (0.17)	10 (0.29)	5 (0.28)	1 (0.12)	3 (0.20)	24 (0.75)	0.053
Moderate reactions	1 (0.03)	1 (0.029)	1 (0.055)	1 (0.12)	0 (0)	4 (0.125)	0.91
Severe reactions	0 (0)	1 (0.029)	3 (0.17)	0 (0)	0 (0)	4 (0.125)	0.07
Total	6 (0.2)	12 (0.34)	9 (0.5)	2 (0.25)	3 (0.20)	32 (0.3)	
p value	0.03	0.001	0.26	0.61	0.05		0.038

[a] χ^2.

[Table from Granata et al.2016 (63)]

In conclusion, this retrospective study showed a low rate of acute adverse reaction to GdCAs of 0.3%, in a time period of about five years. Most of the acute adverse reactions occurring in the study were mild reactions, represented mainly by skin reactions, such as hives or rash. The higher percentage of adverse reactions (0.5% versus 0.2–0.3%) and the most severe reactions occurred with Gd-BOPTA; however there was no statistically significant difference between various GdCAs used. Like in Bruder's article, the authors concluded that thermodynamic/kinetic stability data do not play any role regarding the risk of hypersensitivity, whereas stability of GdCAs is more involved in the development of NSF and in the Gd deposition in neural structures, such as the dentate nucleus and globus pallidus.

Jung et al. (64) conducted a retrospective study of patients who had been given GdCAs at Seoul National University Hospital between August 2004 and July 2010. Demographics, comorbid

disease, and prescribed medication data were extracted from the electronic medical record. To retrieve data on immediate hypersensitivity reactions, all medical records written by physicians, nurses, and radiology technicians were searched with terms possibly related to immediate hypersensitivity reactions, such as pruritus, skin rash, and urticarial, and with terms for respiratory symptoms. The following GdCAs were utilized: *(a)* macrocyclic agents including ionic gadoteric acid (Dotarem®) and nonionic gadobutrol (Gadovist®) and *(b)* linear agents including ionic agents gadopentetate dimeglumine (Magnevist®), gadobenate dimeglumine (MultiHance®), and gadoxetic acid (Primovist®) and the nonionic agent gadodiamide (Omniscan®).

A total of 141 623 MR examinations with MR contrast media were performed in 84367 patients during the 6-year period. Most patients (72.2%) were exposed to gadolinium-based contrast media only one time. The numbers of exposures to MR contrast media varied from one to 54, with a mean of 1.7 exposures per person. There were 148 acute reactions, of which 36 cases of vomiting, nausea, and pain at the injection site were excluded. The incidence of immediate hypersensitivity reactions was 0.079% (112 of 141 623). These occurred in 0.121% (102 of 84 367) of patients. Among the 112 hypersensitivity reactions, the most frequent symptom was urticaria (102 cases, 91.1%). Respiratory symptoms occurred in 17 cases (15.2%); hypotension in 11 cases (9.8%), and angioedema in 6 cases (5.4%). Nineteen cases (17.0%) had multiple symptoms. Eleven severe hypersensitivity reactions occurred in 10 patients, and all of them met the diagnostic criteria for anaphylaxis.

Gadobenate dimeglumine had the highest incidence of immediate hypersensitivity reactions (14 [0.22%] of 6361), followed by gadoxetic acid (six [0.116%] of 5152), gadobutrol (33 [0.099%] of 33 242), gadoteric acid (31 [0.080%] of 38 580), gadopentetate (26 [0.061%] of 42 323), and gadodiamide (two [0.013%] of 15 959) (*P*=0.0001). There was no significant difference in the incidence of reactions according to the molecular structure of the contrast agents (64 [0.089%] of 71 822 in macrocyclic agents and 48 [0.069%] of 69 801 in linear agents) or the ionicity (77 [0.083%] of 92 345 in ionic agents and 35 [0.071%] of 49 201 in nonionic agents). Among the linear agents, ionic agents had a higher incidence of immediate hypersensitivity reactions than nonionic agents (0.085% vs 0.013%, *P*= .0004), but the presence or absence of ionicity did not affect the incidence rate among the macrocyclic agents.

Figure 2

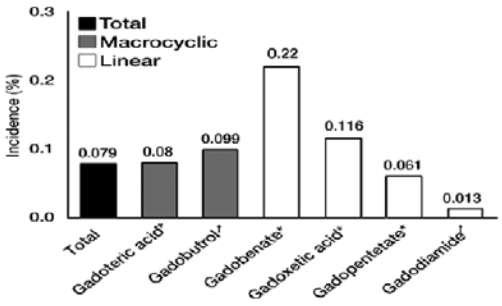


Figure 2: Graph shows incidence of immediate hypersensitivity reactions to MR contrast media, which was 0.079% of the total doses administered. Gadobenate dimeglumine had the highest rate of incidence (0.22%), and gadodiamide had the lowest (0.013%). * = ionic agent, † = nonionic agent.

[Table from Jung et al. 2012 (64)]

The rate for immediate hypersensitivity reactions was significantly higher in female patients (odds ratio = 1.687; 95% confidence interval: 1.143, 2.491) and in patients with allergies and asthma (odds ratio = 2.829; 95% confidence interval: 1.427, 5.610). Patients with a previous history of immediate hypersensitivity reactions had a higher rate of recurrence after reexposure to MR contrast media (30%) compared with the incidence rate in total patients (*P*=0.0001).

In conclusion, this paper showed a low incidence rate of 0.079% for MR contrast media induced immediate hypersensitivity reactions. There was no significant difference in the incidence of reactions according to the molecular structure or the ionicity of the contrast agents. A high recurrence rate of immediate hypersensitivity reactions of 30% was reported in patients who previously experienced hypersensitivity reactions.

In the paper from Heshmatzadeh Behzadi and Prince (65), the authors discuss the choice of GdCA related to risk of severe anaphylactoid reactions. They indicate that anaphylactoid reactions have been reported with both macrocyclic and linear-type GdCAs, with an incidence of severe anaphylactoid reaction of only 0.001% to 0.01%. The authors suggested based on results from several studies that the nonionic linear agent gadodiamide may have a lower rate of severe reactions than ionic linear or macrocyclic agents. However, these are older retrospective studies, which did not use all current GdCAs. The retrospective analysis of databases (where several GdCAs such as gadobutrol or gadoterate meglumine may not be taken into account) can be subjected to many potential biases and should be performed with extreme caution. The currently published prospective, controlled, double-blind clinical trials confirm that all marketed GdCAs cannot be differentiated with respect to hypersensitivity reactions and no rigorous data support any structure-activity relationship concerning GdCA-induced hypersensitivity reactions so far.

3.2 OPTIMARK®

3.2.1 Regulatory history

Optimark is a gadolinium-based, non-ionic magnetic resonance contrast medium indicated for cranial, spinal, and liver magnetic resonance imaging (MRI). To date, Optimark is authorized in 33 countries worldwide.

Optimark was added to the product portfolio of Guerbet following the acquisition of the “contrast media and delivery systems” business of Mallinckrodt in November 2015.

The very first marketing authorization for Optimark was granted on 08 December 1999 in the USA. The European Commission granted a centralized marketing authorisation valid throughout the European Union for Optimark on 23 July 2007.

In June 2016, Guerbet informed the EMA on the intention not to submit a renewal application for Optimark authorised for the European Union (+Iceland and Norway). This company decision has been made for commercial reasons and product portfolio rationalization. The marketing authorisation for the EU, Iceland and Norway expired on 25 July 2017.

Guerbet is currently phasing out Optimark progressively from the different markets.

3.2.2 Approved indications

The current US approved indication are as follows:
Optimark is a gadolinium-based paramagnetic contrast agent for diagnostic magnetic resonance imaging (MRI) indicated for intravenous use:

- In patients with abnormal blood-brain barrier or abnormal vascularity of the brain, spine and associated tissues ;
- To provide contrast enhancement and facilitate visualization of lesions with abnormal vascularity in the liver in patients who are highly suspect for liver structural abnormalities on computed tomography.

Outside US, Optimark is also indicated for use with magnetic resonance imaging (MRI) of:

- Central Nervous System (CNS) ;
- Liver.

3.2.3 Overview of efficacy data

Optimark was evaluated in 4 controlled clinical trials (two liver and two CNS studies). Out of 461 patients who received Optimark, there were 252 men and 209 women with a mean age of 49 years (range 12 to 82 years); 83% were Caucasian, 9% Black, 3% Asian, and 5% other racial or ethnic groups. The trials were designed to compare combined non-contrast and Optimark 0.1 mmol/kg contrast MR images to non-contrast MR images, based on pre-specified imaging characteristics (endpoints).

In the two CNS studies, MR images were analyzed from 262 patients who were highly suspect for CNS disorders and received Optimark. Pre-contrast and pre-plus-post-contrast (combined) images were independently evaluated by three blinded readers (each reader examined approximately 1/3 of the images). The images were evaluated by the blinded readers for the following endpoints using a scale from 1 to 10: the level of conspicuity of all lesions, the ability to delineate lesion borders from parenchyma/structures, the number of lesions, and the confidence in the number of lesions. As shown in Table 5, the first row of each endpoint group represents the difference in the mean score of the combined pre- and post-contrast MRI from the mean score of the pre-contrast MRI alone. Also, the table shows the number of patients whose paired MRI images were better, worse or the same as the pre-contrast MRI. Results from the contrast image alone were not evaluated. In Table 31 for these endpoints, when read in combination with the non-contrast images, Optimark provided a statistically significant improvement over baseline. In addition to these measures, the images were evaluated for the blinded reader's confidence in the diagnosis. Although improvement over baseline was noted, the diagnosis was not rigorously confirmed.

Table 31: Results of MRI Central Nervous System Studies with 0.1 mmol/kg Optimark

Endpoints	Study A	Study B
	Optimark N = 132†	**Optimark N = 129**
Conspicuity: Difference of Means [(a)]	0.39*	0.66*
Worse	24 (18%)	24 (19%)
Same	69 (52%)	52 (40%)
Better	39 (30%)	53 (41%)
Border Delineation: Difference of Means	0.70*	0.86*
Worse	23 (17%)	25 (19%)
Same	55 (42%)	51 (40%)
Better	54 (41%)	53 (41%)
Number of Lesions: Difference of Means		
Pre	1.8	3.0
Pair [(b)]	2.0◊	3.3*
Worse	9 (7%)	16 (12%)
Same	101 (77%)	86 (67%)
Better	22 (16%)	27 (21%)
Confidence in Number of Lesions: Difference of Means	0.11*	0.56*
Worse	19 (14%)	18 (14%)
Same	86 (65%)	60 (47%)
Better	27 (20%)	51 (40%)

[(a)] Difference of means = (Side-by-side pre- and post-Optimark mean) - (pre-mean)
[(b)] Pair = Side-by-side pre- and post-Optimark
* Statistically significant for both the median (Wilcoxon test) and mean (paired t test)
◊ Statistically significant for median (Wilcoxon test)
† 1 patient was excluded from this analysis because a non-contrast image was not obtained for that patient

In the two liver studies, MR images were analyzed from 199 patients with a suspected liver abnormality on a contrast CT who received Optimark. Patients had both pre-contrast and post-contrast MRI scans covering the entire liver. In each study, the images were read by 3 blinded readers (each reader examined approximately 1/3 of the images). Using a scale of 1 to 10, the images were evaluated by the blinded readers for the level of conspicuity of all lesions, the ability to delineate lesion borders from parenchyma/structures, the number of lesions and confidence in the number of lesions. The results are shown in Table 6. The first row of each endpoint group represents the difference in the mean score of the combined pre- and post-contrast MRI from the mean score of the pre-contrast MRI alone. Also, the table shows the number of patients whose paired MRI images were better, worse or the same as the pre-contrast MRI. Results from the contrast image alone were not evaluated. As shown in Table 32 for these endpoints, when read in combination with the non-contrast image, Optimark provided a statistically significant improvement over non-contrast images. In addition to these measures, the images were evaluated for the blinded reader's confidence in the diagnosis. Although improvement over baseline was noted, the trial was not designed to rigorously confirm the diagnosis.

Table 32: Results of MRI Liver Studies with 0.1 mmol/kg Optimark

Endpoints	Study C Optimark N = 99	Study D Optimark N = 100
Conspicuity: Difference of Means [(a)]	0.77*	0.75*
Worse	21 (21%)	14 (14%)
Same	37 (37%)	50 (50%)
Better	41 (41%)	36 (36%)
Border Delineation: Difference of Means	0.77*	0.69*
Worse	21 (21%)	15 (15%)
Same	38 (38%)	45 (45%)
Better	40 (40%)	40 (40%)
Number of Lesions: Difference of Means Pre Pair [(b)]	 2.4 3.0*	 3.5 3.8†
Worse	13 (13%)	16 (16%)
Same	50 (51%)	58 (58%)
Better	36 (36%)	26 (26%)
Confidence in Number of Lesions: Difference of Means	1.6*	1.0*
Worse	39 (39%)	38 (38%)
Same	2 (2%)	8 (8%)
Better	58 (59%)	54 (54%)

[(a)] Difference of means = (Side-by-side pre- and post-Optimark mean) - (pre-mean)
[(b)] Pair = Side-by-side pre- and post-Optimark
* Statistically significant for both the median (Wilcoxon test) and mean (paired t test)
† Borderline statistical significance in paired t test

3.2.4 Overview of safety

3.2.4.1 Data from clinical trials

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The adverse reactions described in this section were observed in a total of 1,309 subjects (24 healthy volunteers and 1,285 patients in clinical trials). Patients ranged in age from 12 to 85 years (mean age of 50 years) and 680 subjects (52%) were men. The ethnic distribution was 84% White, 9% Black, 3% Asian, and 4% other.

Overall, 460 subjects (35%) reported at least one adverse reaction. Most adverse reactions were mild or moderate in severity. The most commonly noted adverse reactions were: injection associated discomfort (26%), headache (9.4%), vasodilatation (6.4%), taste perversion (6.2%), dizziness (3.7%), nausea (3.2%), and paresthesia (2.2%). Table 33 lists adverse reactions reported in 1% or greater of patients.

Table 33: Adverse Reactions Experienced by ≥1% of Patients

Body System or Event	Optimark (N = 1309)
Injection associated discomfort	26.4%
Headache	9.4%
Vasodilatation	6.4%
Taste Perversion	6.2%
Dizziness	3.7%
Nausea	3.2%
Paresthesia	2.2%
Diarrhea	1.9%
Pain Abdomen	1.8%
Asthenia	1.5%
Injection Site Reaction	1.5%
Rhinitis	1.5%
Dyspepsia	1.2%
Pain Back	1.2%
Pain	1.0%

The following adverse reactions occurred in less than 1% of the patients:

Body as a Whole: allergic reaction, facial edema, fever, malaise, neck rigidity, neck pain, pelvic pain, increased sweating

Cardiovascular: arrhythmia, chest pain, hypertension, hypotension, pallor, palpitation, syncope, tachycardia, vasospasm

Digestive: anorexia, constipation, dry mouth, dysphagia, eructation, increased salivation, thirst, vomiting

Metabolic and Nutritional: increased creatinine, edema, hypercalcemia

Musculoskeletal: arthralgia, leg cramps, myalgia, spasm

Nervous System: agitation, anxiety, confusion, diplopia, dystonia, hypertonia, hypesthesia, somnolence, tremor, vertigo

Respiratory System: cough, dyspnea, laryngismus, pharyngitis, sinusitis, voice alteration

Skin and Appendages: erythema multiforme, pruritus, rash, thrombophlebitis, urticaria

Special Senses: parosmia, tinnitus

Urogenital: oliguria

A subsequent study of 140 normal volunteers evaluated the safety of Optimark 0.1 mmol/kg delivered by power injector. Imaging results were not studied. The normal volunteers were randomized to receive Optimark injected manually, or Optimark or saline injected at 3 different power injector rates. At 2 mL/sec, the adverse event rates were comparable in the Optimark and saline controls when delivered manually and by power injector. In these small sample sizes, there was a trend towards increasing adverse events with increasing rates of power injection. Patients with abnormal vascularity were not evaluated. The safety and efficacy of power injector rates higher than 2 mL/sec has not been established.

3.2.4.2 Data from post-marketing surveillance

The following adverse reactions have been identified during post-approval use of Optimark:

- Nephrogenic Systemic Fibrosis (NSF)
- Hypersensitivity reactions including bronchospasm and laryngeal/pharyngeal edema
- Seizures

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to Optimark.

4 REGULATORY ACTIONS TAKEN/ON GOING IN LINK WITH BRAIN GADOLINIUM DEPOSITION

4.1 AT THE INITIATIVE OF THE AUTHORITIES

Several regulatory actions were taken or are on-going at the initiative of the authorities. These actions are presented below in chronological order.

1. European Union
   a. Request for cumulative review of gadolinium brain accumulation – OPTIMARK® and DOTAREM®

   In June 2015, the EMA requested for Optimark® and Dotarem® a cumulative review on data referring to the accumulation of free gadolinium, intact gadolinium-contain contrast agent, or other gadolinium compounds in the brain. A cumulative review of the relevant literature references and any other relevant data sources were submitted on 31 July 2015. In the conclusion of this procedure, received at the end of January 2016, the CHMP requested to update the Risk Management Plan of Optimark®. An updated Risk Management Plan (RMP) of Optimark® was submitted on 30 June 2016. Concerning Dotarem, the conclusions (update of RMP and update of the product information) were part of the outcome of a separate PSUR assessment.

   b. Update of SmPC according to the outcome of Periodic Safety Update Single Assessment (PSUSA) - DOTAREM®

   Following an EU periodic safety update reports (PSUR) single assessment procedure for gadoteric acid which ended on 27 January 2016, the Co-ordination group for Mutual recognition and Decentralised procedures – human (CMDh), taking into account the Pharmacovigilance Risk Assessment Committee (PRAC) Assessment Report, issued the following scientific conclusions:

   "The current SmPC states that the product does not cross the intact blood-brain barrier. There are no specific studies that support this statement, which is not consistent with the published studies that have shown increased signal hyperintensity on MRI and the presence of gadolinium in post-mortem tissue samples. This statement is therefore misleading and not consistent with current scientific knowledge. A mechanism for gadolinium crossing the blood-brain barrier, and the form in which gadolinium is present in the brain are not yet established, and research into the issue of gadolinium deposition in the brain continues to be published. It is therefore difficult to make a definitive statement on what information on the potential for gadolinium to cross the blood-brain barrier and accumulate in brain tissue

would be appropriate, or on meaning clinical guidance and recommendations for use of the product. The MAH is therefore requested to remove the statement from the SmPC."

As per CMDh conclusion, a variation to update the SmPC of Dotarem® according to the outcome of PSUSA was submitted and approved in all EU countries in June 2016.

c. Update of the Risk Management Plan (RMP) according to the outcome of PSUSA - DOTAREM®

In accordance with the PRAC PSUR Assessment Report dated 14 January 2016, the proposed RMP was amended to include:
Addition of important potential risks:
- Gadolinium accumulation in organs and tissues other than brain tissues.
- Accumulation and retention of gadolinium in the brain.
Addition of missing information:
- Clinical significance of gadolinium accumulation in organs and tissues other than brain tissues.
- Clinical significance of gadolinium retention in the brain.

The updated RMP of Dotarem® was approved in all EU countries on 11 December 2016.

d. EMA referral on gadolinium retention in brain - DOTAREM® and OPTIMARK®

On 18 March 2016, the EMA initiated a review of the risk of gadolinium deposition in brain tissue following the repeatuse of GdCAs in patients undergoing MRI scans. A referral procedure under article 31 of Directive 2001/83/EC resulting from pharmacovigilance started in March 2016 with a first list of questions on gadolinium accumulation, sent to the marketing authorization holders (MAHs) of GdCAs authorized on the European market. This first series of questions was supplemented by three lists of outstanding issues received in June, September and December 2016.

On 10 March 2017, after carrying out an in-depth review of the risk of gadolinium deposition in brain and of the overall benefit-risk balance of these products, the EMA's PRAC recommended the suspension of the marketing authorizations of four intravenous linear GdCAs (gadodiamide, gadopentetate, gadoversetamide and gadobenate), because of a higher propensity of releasing Gd which can accumulate in various organs, including the brain. The PRAC also confirmed the favorable risk/benefits balance for macrocyclic products (gadoterate, gadoteridol and gadobutrol) as well as the linear hepato-specific agent gadoxetate. The PRAC recommended an update of the product information for macrocyclic GdCAs, to recommend the use at the lowest dose that enhances images sufficiently to make diagnoses and only when unenhanced MRI scans are not suitable.

Two MAHs (GE Healthcare and Bracco) requested a re-examination of the PRAC recommendations. Therefore, the procedure re-started and updated final recommendations from PRAC were issued on 6 July 2017 with the same outcome as on March 2017 except for gadobenate which was not anymore suspended but its use restricted to liver imaging indication **(which is not an approved indication for gadobenate in the US)**. The Committee for Medicinal Products for Human Use (CHMP) adopted this last opinion on

July 21st. Final decision will be taken by the European Commission and is awaited end September 2017.

2. United States - DOTAREM®
   a. Information request on Gadolinium retention - DOTAREM® (*note : at the date of this request, Optimark® was not part of Guerbet product portfolio, yet*)

   An Information Request was received on 16 September 2014 to review Guerbet's pharmacovigilance data for cases of possible gadolinium retention in the brain and other organs. The response was submitted on 23 December 2014. As a follow-up to this request, Guerbet submitted additional information on 16 April 2015.
   On 27 July 2015, FDA published a first Drug Safety Communication to announce that they will study the possible safety risks of brain deposits following repeatadministration of GdCAs.

   b. Summary analysis performed by FDA - DOTAREM® and OPTIMARK®

   In quarter 4 2016, the summary analysis performed by the FDA was posted on the FDA website stating that "no new safety issues were identified" and "no regulatory actions are required at this time.

   c. Drug Safety Communication - DOTAREM® and OPTIMARK®

   On 22 May 2017, the FDA issued a n update of the drug safety communication dated 27 July 2015 to announce that *"the FDA review to date has not identified adverse health effects from gadolinium retained in the brain after the use of gadolinium-based contrast agents (GBCAs) for magnetic resonance imaging (MRI). All GBCAs may be associated with some gadolinium retention in the brain and other body tissues. However, because we identified no evidence to date that gadolinium retention in the brain from any of the GBCAs, including GBCAs associated with higher retention of gadolinium, is harmful, restricting GBCA use is not warranted at this time. We will continue to assess the safety of GBCAs and plan to have a public meeting to discuss this issue in the future."* and no change to FDA recommendations was made.

3. New Zealand - Request from Medsafe on gadolinium in brain tissue - DOTAREM®

   On 20 February 2017 Medsafe (New Zealand Medicines and Medical Devices Safety Authority) requested Guerbet to provide with any of the safety reviews provided to other regulators on gadolinium accumulation in brain tissue. The answer was provided on 22 February 2017. New Zealand authority is currently assessing the possibility of a Product Information update in order to address the gadolinium accumulation in brain tissue.

4. Kuwait – Suspension of the Marketing Authorization of Optimark by Health Authorities - OPTIMARK®

   Further to the publication of the PRAC recommendations (dated 10 March 2017), the Ministry of Health in Kuwait decided to suspend the Marketing Authorization of Optimark, on 20 March 2017.

5. Canada - Request from Health Canada on gadolinium in brain - DOTAREM® and OPTIMARK®

On 31 March 2017, Health Canada imposed a class labeling change leading to a change to the labeling information of all GdCAs (linear and macrocyclics) with respect to the risk of gadolinium deposits in brain with repeat administration of these contrast agents. The following text was added to the product monograph of all GdCAs:

Creation of a subheading titled **'Accumulation of Gadolinium in Brain'** in PART I under **'Warnings and Precautions'** and insertion the following text:
"*The current evidence suggests that gadolinium may accumulate in the brain after multiple administration of GBCAs. Increased signal intensity on non-contrast T1-weighted images of the brain has been observed after multiple administrations of GBCAs in patients with normal renal function. Gadolinium has been detected in brain tissue after multiple exposures to GBCAs, particularly in the dentate nucleus and globus pallidus. The evidence suggests that the risk of gadolinium accumulation is higher after repeat administration of linear than after repeat administration of macrocyclic agents.*

The clinical significance of gadolinium accumulation in the brain is presently unknown; however, gadolinium accumulation may potentially interfere with the interpretation of MRI scans of the brain. In order to minimize potential risks associated with gadolinium accumulation in the brain, it is recommended to use the lowest effective dose and perform a careful benefit risk assessment before administering repeatdoses."

Addition of the following statement under **"Dosage and administration**" in PART I:
"The lowest effective dose should be used."

Addition of the following statement under **"Action and Clinical Pharmacology"** in PART I:
"The current evidence suggests that gadolinium may accumulate in the brain after repeatadministration of GBCAs although the exact mechanism of gadolinium passage into the brain has not been established."

Addition of the following statement under **"TOXICOLOGY"** in PART II:
"Recent studies conducted in healthy rats injected repeatedly with linear macrocyclic GBCAs demonstrated that linear agents were associated with progressive and persistent T1-weighed hyperintensity on MRI in the deep cerebellar nuclei (DCN). Signal enhancement in the globus pallidus (GP) could not be seen in the animals. No changes in signal intensities in either DCN or GP were observed for the macrocyclic GBCAs.

Quantitative results using mass spectrometry demonstrated that the total gadolinium concentrations were significantly higher with the linear GBCAs than with the macrocyclic GBCAs. These studies reported no abnormal behavioural changes suggestive of neurological toxicity."

Addition of the following heading and text, suing exactly the same text ad format below to meet plain language requirements, under **"Warnings and Precautions"** in **PART III: Consumer Information**:

"Accumulation of gadolinium in the brain:
Recent information shows that gadolinium (as in Optimark/Dotarem) may build up in the brain after multiple uses and:

- *The effect on the brain is unknown right now.*
- *Your doctor will:*
  - *Carefully consider whether to use repeatdoses*
  - *Use the lowest doses"*

The variation to change the Product monograph of Optimark and Dotarem according to this request was submitted on April 28, 2017 and approved respectively by Health Canada on June 15, 2017 and June 16, 2017.

In addition, on 30 May 2017, Health Canada requested the submission of a PSUR including the most up-to-date worldwide specific exposure information and all relevant information from nonclinical/clinical studies and scientific literature regarding gadolinium deposition in the brain.

6. Australia – Request from the TGA on gadolinium in brain – DOTAREM and OPTIMARK
A request from the TGA (Therapeutic Goods Administration) was received on July 27, 2017 to amend the Dotarem and Optimark PI (Pharmacology, Precautions and Dosage and Administration sections) as indicated here below:

PHARMACOLOGY:
Under the heading 'Pharmacokinetics', change to the wording as follows:

"After intravenous injection, gadoteric acid is distributed in the extracellular fluid of the body. It does not bind with plasma albumin ***~~and does not cross the normal blood brain barrier~~.***
Current evidence suggests that gadolinium accumulates in the brain after repeat administration of Gadolinium-based contrast agents (GBCAs) although the exact mechanism of gadolinium passage into the brain has not been established. "

PRECAUTIONS:
Under a new heading 'Accumulation of gadolinium in the brain', the following wording is to be inserted:

*"**The current evidence suggests that gadolinium accumulates in the brain after multiple administrations of GBCAs. Increased signal intensity on non-contrast Tl weighted images of the brain has been observed after multiple administrations of GBCAs in patients with normal renal function. Gadolinium has been detected in brain tissue after multiple exposures to GBCAs, particularly in the dentate nucleus and globus pallidus.***

The evidence suggests that gadolinium accumulation is higher after repeat administration of linear than after repeat administration of macrocyclic agents.
The clinical significance of gadolinium accumulation in the brain is presently unknown.
In order to minimize potential risks associated with gadolinium accumulation in the brain, it is recommended to use the lowest effective dose and perform a careful benefit risk assessment before administering repeatdoses. *"*

DOSAGE AND ADMINISTRATION
The wording is to be amended as follows:

"The maximum recommended dose is 0.1 mmol/kg, i.e. 0.2 mL/kg for adults, children and infants. ***The lowest effective dose should be used****."*

7. Request from several authorities following PRAC's recommendation on gadolinium retention in brain - DOTAREM and OPTIMARK
   After the issuance of the PRAC's recommendation, Guerbet was contacted by several Health Agencies to provide information in relation with this matter: Australia, Singapore, Japan, China and South Korea. Since then, no further regulatory actions were taken.

4.2 AT THE INITIATIVE OF GUERBET

In July of 2016, Guerbet submitted a CBE-30 Safety Label Supplement for NDAs 020937, 020976, and 020975 to add gadolinium deposits in the brain to the US labeling for Optimark (gadoversedamide injection).

On August 23, 2016, Guerbet reached agreement with the Agency on the following statement added to Section 12.3 of the Optimark labeling.

Deposition with repeatdosing
Increased signal intensity on non-contrast T1-weighted images within the brain, mainly the globus pallidus and the dentate nucleus, has been observed after multiple administrations of linear (ionic and nonionic) gadolinium-based contrast agents due to gadolinium deposition. Following repeat GBCA administration, gadolinium deposits may be present for months or years in bone, liver, skin, brain, and other organs. Deposition depends on multiple factors and may be greater following administration of gadoversetamide and other linear GBCAs than following administration of macrocyclic GBCAs. GBCAs have been associated with the development of NSF in patients with renal impairment [see Boxed Warning]. The clinical significance of gadolinium retention in the body and brain is otherwise unknown.

5 REVIEW OF SCIENTIFIC DATA AVAILABLE

5.1 NONCLINICAL STUDIES

Guerbet Research and Innovation department did not conduct any study with gadoversetamide (Optimark®). Therefore, no information regarding this compound is included in this section.

Summary of information presented hereafter
1) Evidence of Gadolinium Retention in the brain : - Nonclinical results are translational to human results; studies have been performed in healthy and renally impaired rats - GdCA entrance into the brain through the CSF route (plexus choroids) has been demonstrated - Based on analytical measurement methods, Gd was detected in brain regions with all GdCA tested, with a 4 to 30 fold increase for linear agents compared to macrocyclic agents. Furthermore, the Gd clearance from brain tissue of macrocyclic agents occurred at a much faster rate ➢ A 30-fold higher total Gd concentration in the cerebellum is observed 5 months after the last injection of gadodiamide as compared to gadoterate (healthy rat model). ➢ In cerebellum, for gadoterate, 91±5% of Gd found just after the last injection was cleared 5 months after, unlike gadodiamide where only 29±11% of the Gd was cleared. ➢ Total Gd elimination half-life from the cerebellum after gadodiamide is longer than 400 days (healthy rat model).

- Dose-effect is demonstrated: the higher the cumulated dose, the greater the Gd retention in the case of of linear GdCA.

- Based on MRI, T1 enhancement in the cerebellum including dentate nucleus was observed only with linear agents
- Based on speciation analysis, it has been evidenced that different chemical forms of Gd were detected after linear agents (insoluble form, soluble form associated to macromolecules, small molecule soluble form attributed to intact GdCA,) whereas with the current methods, only small molecule soluble form attributed to intact GdCA was observed after macrocyclic agents
  - Most of the Gd detected in the cerebellum of rats treated with the linear GdCA gadodiamide is no longer under intact chelated form (bound to macromolecule) and to a large extent in insoluble form
  - Insoluble Gd deposits are found after administration of gadodiamide and gadobenate. It is localized in basal membrane around DCN microvessels, interstitium (ie. beyond the blood brain barrier (BBB)), and sometimes intracellular (astrocytes, macrophages) where they are associated to a pigment, likely lipofuscin (intracellular). Intact chelated form is the only form found in cerebellum of rats treated with gadoterate
- Data on kinetic and thermodynamic stability, as well as in vitro and nonclinical studies, strongly suggest that L-GdCAs release gadolinium from the ligand molecules.

2) Retention in the skin, bones, and other tissues

- Based on analytical measurement methods, Gd retention in tissues such as skin, bone have been observed with a similar behavior but in higher quantity than in the brain
- The higher the stability, (macrocyclic agents) the lower is the Gd retention in all organs and tissues
- Brain, skin and bone retention of linear GdCAs is potentiated by renal impairment, as well as in juvenile rats (immature renal function)
- Strong evidence of retention of dechelated Gd after L-GdCA
- Hypothesis of deep long-term storage compartment (e.g. bone) is highly probable. So far, there is no experimental evidence of a direct link with brain accumulation.

3) Toxicological risk

- Toxicity of Gd^{3+} release by low stability GdCA has been demonstrated (skin lesion, etc)
- Increased morbidity is found in animals after repeat administration of the less stable GdCA gadodiamide (weight loss, severe adverse events)
- So far, no neuro-histological consequences of Gd brain uptake have been reported in published nonclinical studies.

5.1.1 Toxic effects of gadolinium

Gadolinium (Gd^{3+}), as other lanthanide, has well-known acute and chronic toxic properties. Its ionic radius (107.8 pm) is close to that of Ca2+ (114 pm). Consequently, it is a potent blocker of many types of Ca-dependent biological pathways. Furthermore, metal exchange between endogenous metals and Gadolinium ion inhibit molecular processes. As examples, Gadolinium ions increases the expression of certain cytokines and growth factors. Major lesions related to single or multiple dose administrations of gadolinium chloride to rats consisted of mineral deposition in capillary beds, phagocytosis of mineral by macrophage-like cells, hepatocellular and splenic necrosis followed by dystrophic mineralization, decreased platelet numbers and increased coagulation times. Gadolinium ion is a potent inhibitor of the mononuclear phagocyte system (MPS). Lastly, it is noteworthy that Gd^{3+} has a proliferative effect on fibroblasts in vitro and may promote their migration (66).

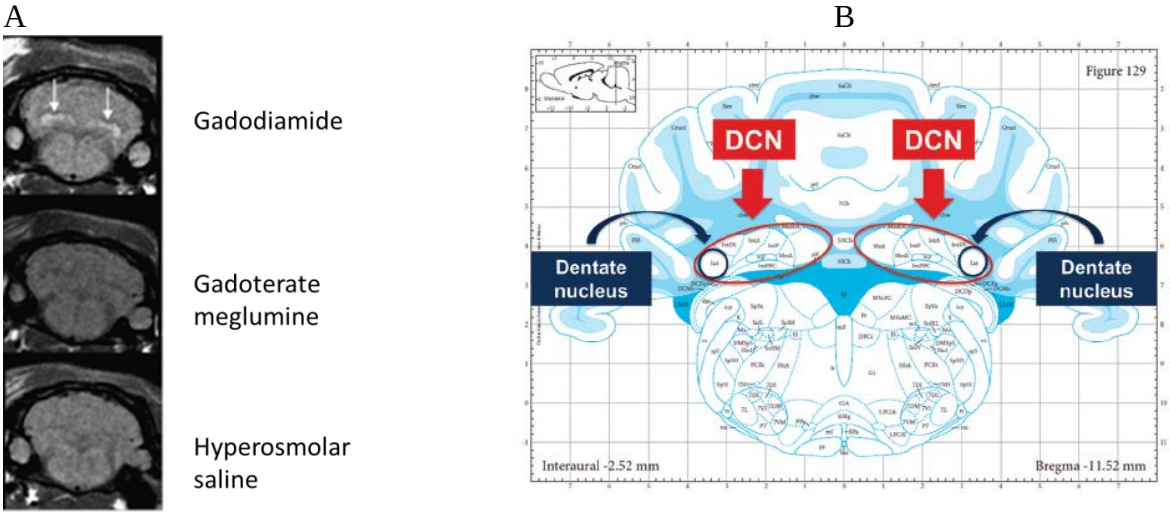
Gadolinium ion release from GdCA is dependent of their kinetic stability and thermodynamic stability parameters; thus, a close attention is devoted to these parameters to limit the risk of Gadolinium ion toxicity.

5.1.2 Long-term Gd retention in the brain: recent findings in healthy rats

When in 2015 it came to light that gadolinium could accumulate in the brain after repeat admnistration of GdCAs in patients with normal kidney function, some GdCAs NDA holders and academic groups initiated nonclinical models in order to try to better characterize the general safety risks.

Recently published nonclinical studies in rats following repeat exposure with GdCAs demonstrated persistent T1-weighted signal hyperintensity in MRI scans and total gadolinium presence in the brain (66-74). In these studies, significant and persistent T1 signal hyperintensity (SI) in deep cerebellar nuclei (DCN) which includes the dentate nucleus, was observed after repeat high-dose administration of linear GdCAs (gadodiamide, gadopentate, gadobenate). Such finding was never shown in the case of macrocyclic agents (gadoteridol, gadobutrol and gadoterate) (see Figure 5).

Figure 5: A) Example of T1w MRI at week 10 (completion of the 5 week treatment-free period). B) Anatomy of rat brain: localization of the deep cerebellar nuclei (DCN) and dentate nucleus



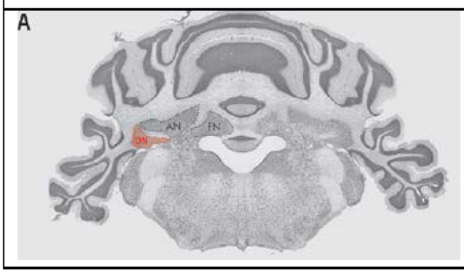
(Reproduced and adapted from Robert et al. 2015 (66))

Only one study from McDonald et al. suggested recently that macrocyclic agents induce a T1 hypersignal in the dentate nucleus (72). However, we have one concern regarding the MRI part of this study, the rest of the study being of high quality. Careful observation of images presented in this paper and comparison to the reference rat brain atlas (75) led us to conclude that, although the axial slice of cerebellum shown in box A is indeed Dentate Nucleus, the region of interest that appear in box C refer to the fourth ventricle (filled with choroid plexus) and maybe also the dorsal cochlear nucleus, but not dentate nucleus (see Figure 6).

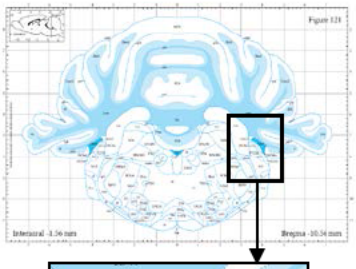
In our experience (on nonclinical 2.35 and 4.7T magnets), it is very difficult to distinguish deep cerebellar nuclei (DCN) one from another. McDonald selected a slice thickness of 2 mm. That of DCN is only 1 mm maximum in rats (75). Our data (73) and those from Jost et al. (76) clearly indicate that all categories of GBCAs easily access the 4th ventricle and, 3 days after the last of 20 administrations (cumulated dose 12 mmolGd/kg), in our hands, choroid plexus were still enhanced in the fourth ventricle (73). We therefore have serious doubts about the relevance of the T1 enhancement data presented by McDonald et al. Because of an MRI protocol with a too low spatial resolution and an error in the localization of the region of interest positioning, authors have misinterpreted the MRI images. In our opinion, the data presented in this paper do not support the conclusion that macrocyclic contrast agent induce a T1 hypersignal in the dentate nucleus.

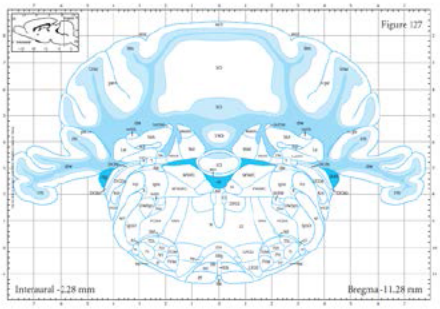
Figure 6: Concern about the conclusions of McDonald et al. on T1 hypersignal observed in dentate nucleus (72). DN is indeed shown in box A but not in box C which corresponds to 4th ventricle which contains choroid plexus

Figures extracted from Mc Donald *et al.*(72)



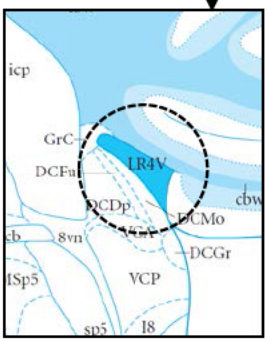
Rat Brain Atlas
corresponding to the box C of the McDonald paper





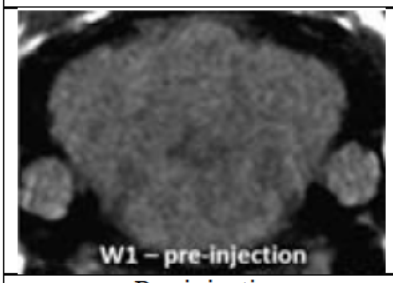
← Level in the brain atlas corresponding to box A of the McDonald paper is DN

LR4V: lateral recess of the 4th ventricle, including choroid plexus (box C)At this level of the cerebellum, dentate nucleus is not visible →

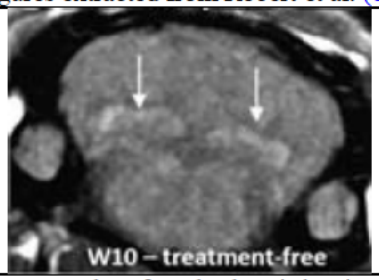


As compared to Guerbet data:

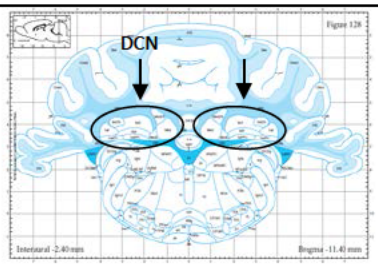
Figures extracted from Robert et al. (67)



Pre-injection



1 months after the last injection of gadodiamide



Corresponding location in the Atlas

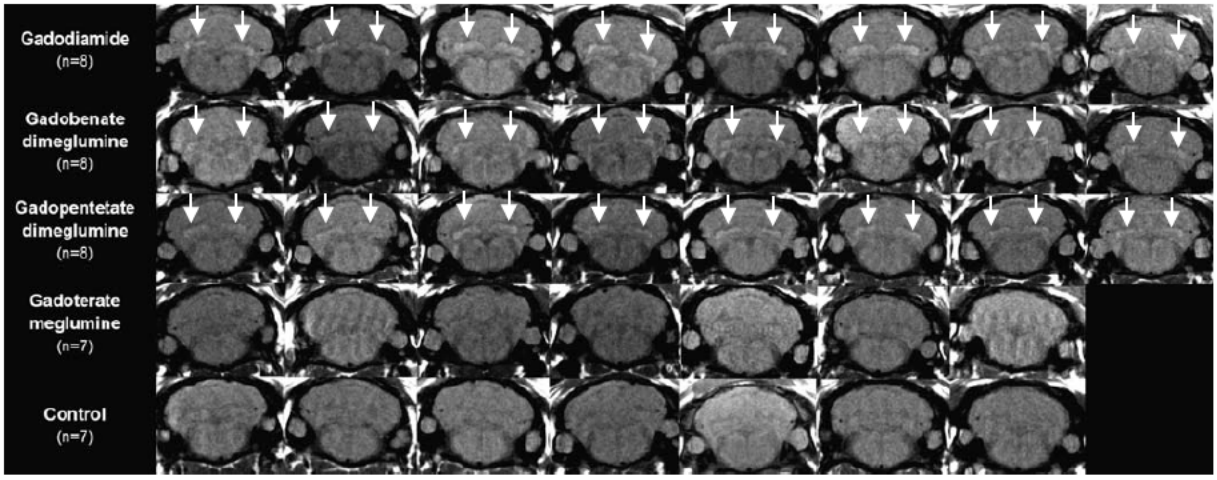
Data from ongoing nonclinical studies, extending these published findings, are provided in this section:

- the pathway(s) by which Gd enters the brain;
- the extent, location and time course of Gd deposition in the brain;
- the molecular form(s) of Gd present is the brain;
- the potential for GdCA deposition resulting in neurological or histopathological changes after repeat administration of linear and macrocyclic contrast agents.

5.1.2.1 MRI hypersignal and Gd dosage data

Rapid T1 hyperintensity between DCN and the surrounding cerebellum was observed after gadodiamide administration (66). Enhancement after gadobenate dimeglumine or gadopentetate dimeglumine appeared more progressively during the 10 weeks of imaging compared with gadodiamide (67). No such enhancement was observed with gadoterate or isotonic saline, which remained at baseline levels: (see Figure 7).

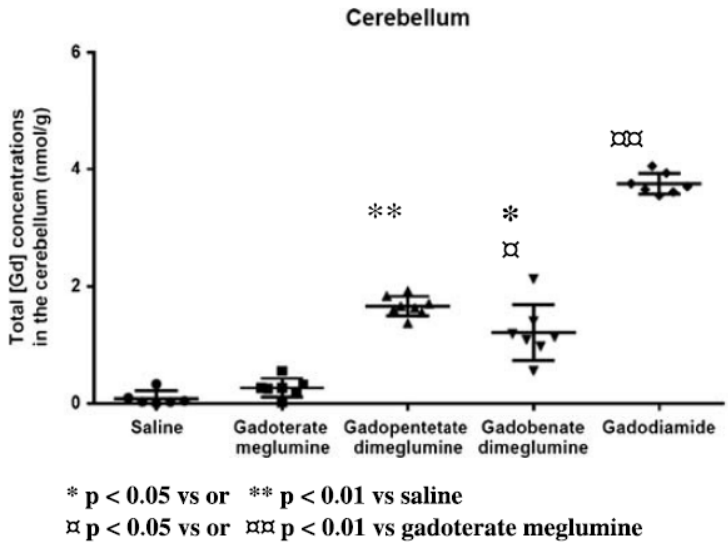
Figure 7: T1w MRI (2.35 T) performed 1 month after the last injection: DCN are visible only for linear GdCA gadodiamide, gadobenate and gadopentetate, all animals included in the study



[reproduced from Robert et al. 2016 (67)]

Total Gd (i.e. under its elemental form) measured by inductively coupled plasma-mass spectrometry (ICP-MS) was detected in all brain tissue (brain cortex, subcortical brain, brain stem), not just the DCN, with all GdCAs tested. In contrast to gadoterate, the presence of total Gd was statistically detected with gadodiamide, gadobenate and gadopentetate compared to saline ($p<0.05$, Figure 8). The highest Gd levels found in the brain of rats exposed to 20 repeat doses of 0.6 mmol/kg of gadodiamide was 3.75±0.18 nmol/g (cerebellum).

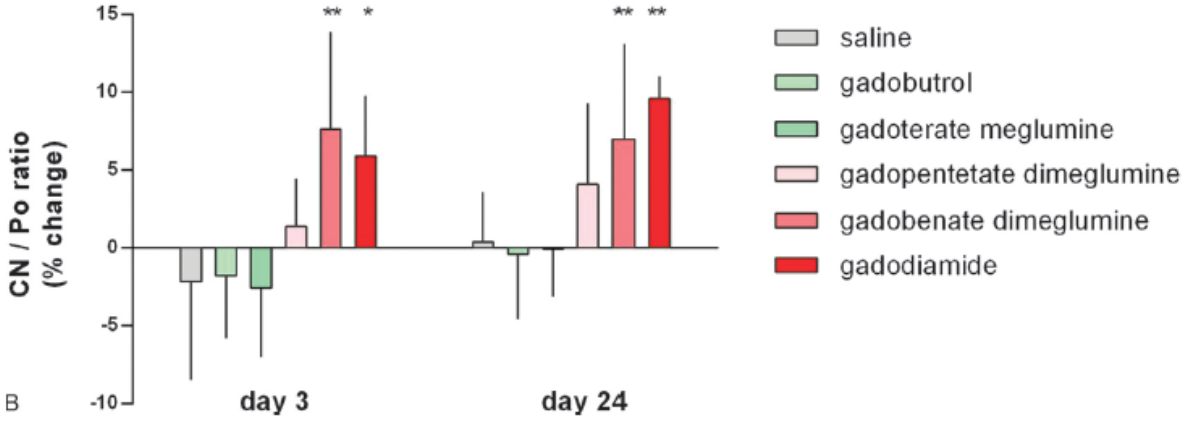
Figure 8: Total gadolinium concentration in nanomole Gd per gram of tissue for cerebellum Individual values, mean, and SD are given



[reproduced directly from Robert et al. 2016]

In a further study by Bayer (68), increased SI in the deep cerebellar nuclei was found up to 24 days after multiple, extended doses of linear GdCAs, thus confirming both the clinical data and others rat studies (66, 67). The signal enhancement in the globus pallidus (GP) could not be seen in rats (Figure 9).

Figure 9: Percent change of CN/Po for day 3 and day 24 post-injection compared with baseline after injection of saline, gadobutrol, gadoterate meglumine, gadopentetate dimeglumine, gadobenate dimeglumine, and gadodiamide



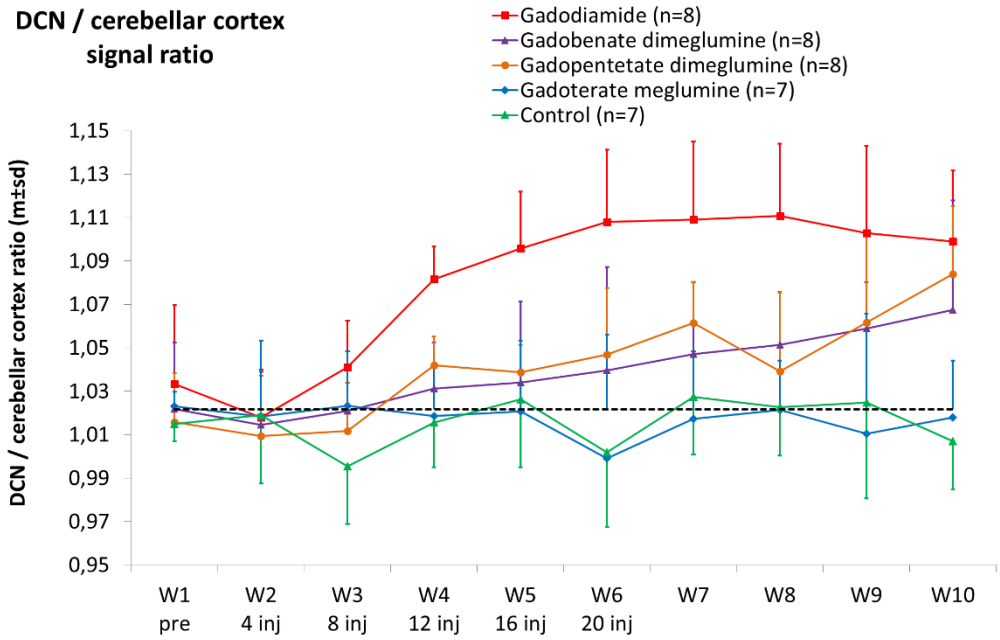
*P < 0.05 and **P < 0.01 indicate significance of GdCA group compared with saline
[reproduced directly from Jost et al. 2016 (68)]

Similar results have been subsequently published by GE in the same rat model (74) and, more recently, by Bayer (71) and an US academic team (72).

5.1.2.2 Dose-dependent Gd accumulation

Studies have shown a dose-dependent T1 hypersignal in the brain for linear agents. The hypersignal increases progressively during the injection phase for linear GdCA, whereas no change were observed for gadoterate and saline groups: Figure 10.

Figure 10: Quantitative changes of DCN/cerebellum signal ratio according time and number of injections.



The dash line corresponds to the mean ratio pre-injection for all rats (n=38). W corresponds to weeks.

This is likely related to cumulative dosing rather than single large or repeat small dose regimens (67).

In term of total Gd concentration, Smith et al. (74) have shown a dose-dependent increase of total Gd in the brain: 1.39±0.20 nmol/g 1 week after 6 mmol/kg of gadodiamide and 2.49±0.29 nmol/g at after 12 mmol/kg cumulated.

5.1.2.3 Long-term brain wash-out kinetics

A major discrepancy between clinical and pre-clinical studies concerns the time scale of subjects follow up. In the clinical field, retrospective studies are mainly conducted on a time scale of 5 to 15 years.

In the nonclinical field, however, prospective studies are focused on the early first weeks following the last injection (66-68, 73). In a recent study, Smith et al. (74) investigated the Gd

wash-out in rat brains on a longer period from 1 to 20 weeks. They reported a Gd level of 2.5±0.3 nmol/g of brain tissue at week 6 (one week after the last injection of gadodiamide) and 1.4±0.1 nmol/g at week 20 (5 months after the last injection). They concluded that "Low levels of gadolinium are present in the brain after repeat dosing with gadodiamide, which is partially cleared over 20 weeks." However, no information was given about the chemical form of gadolinium and furthermore it was only a 40% decrease at 5 months post-dose, indicating more Gd retention than wash-out. From these data, we might assume that the amount of gadolinium retained in the brain reflects gadolinium dissociation (77).

In a mouse model, Kartamihardja et al. 2016 have shown only a 33% decrease in the total Gd concentration in 6 weeks in the cerebellum after repeat gadodiamide administration(69). In comparison, concentration started with a 4.5-fold lower level after gadoterate at day 3 and decrease to 92% in the same period**:** Table 34.

Table 34: Gd clearance in normal mouse model: comparison between the linear gadodiamide and the macrocyclic GdCA gadoterate: (adapted from Kartamihardja et al. in 2016)

Gd concentration in the cerebellum (nmol/g)	3 days after the last injection	45 days after the last injection	**Delta day 45 vs day 3 (%)**
Linear Gadodiamide	28.6±7.6	19.1±3.8	**-33%**
Macrocyclic Gadoterate	6.4±0.6	0.5±0.1	**-92%**
Ratio Linear/Macrocyclic	**4.5**	**38.2**	

In the study by Frenzel et al. 2017, total brain gadolinium concentrations showed a clear decrease in the tissue concentrations between day 3 and day 24 post-injection for the macrocyclic agents (−62% to −72%) compared to the linear agents (−23% to −47%) with a also a huge difference in the overall quantity of Gd between these 2 families of compounds (70). This is consistent with the results from Kartamihardja et al. (69).

Three studies in rats were launched by Guerbet Research to document this issue:

- Study ER-15-00019 focusing on the persistence of the MRI T1 signal of gadodiamide over 12 months after the last injection,
- Study ER-16-00011 comparing the signal persistence for gadodiamide, gadobenate and gadoterate over 3 months
- Study ER-16-0005 comparing the long-term kinetics and the form of Gd accumulated in the brain during 5 months after repeat administration of gadodiamide or gadoterate.

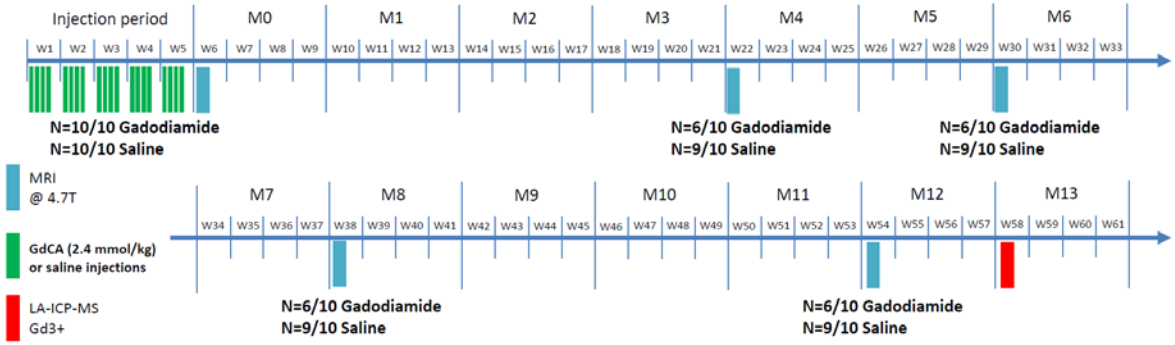
In Guerbet study ER-15-00019 (ongoing, unpublished), two groups of 10 rats each were included in this study. All the injections were performed according to the injection protocol described previously (66). Healthy female Sprague-Dawley rats received 20 intravenous injections of 0.6 mmol of Gd per kilogram over a period of 5 weeks (4 injections per week). The daily dose of 0.6 mmol Gd per kilogram is equivalent to the usual human dose of GdCAs, after adjustment for body surface area. The first group received gadodiamide for total dose of 12 mmol/kg and the second group isotonic saline with the same injection protocol.

MRI follow-up examinations were performed in blinded conditions at 5 time points using a T1w gradient echo sequence (4.7T):

- M0: at week 6, i.e. one week after the last injection → 0 month of washout period.
- M4: at week 22 → 4 months of washout period.
- M6: at week 30 → 6 months of washout period.
- M8: at week 38 → 8 months of washout period.
- M12: at week 54 → 12 months of washout period.

Region of interest (ROI) positioning was performed blindly for the groups and time points. The signal intensity ratio was calculated as the ratio of the maximum DCN signal intensity to the brain stem signal intensity: DCN/brain stem ratio. Injection and MRI schedules are summarized in Figure 11.

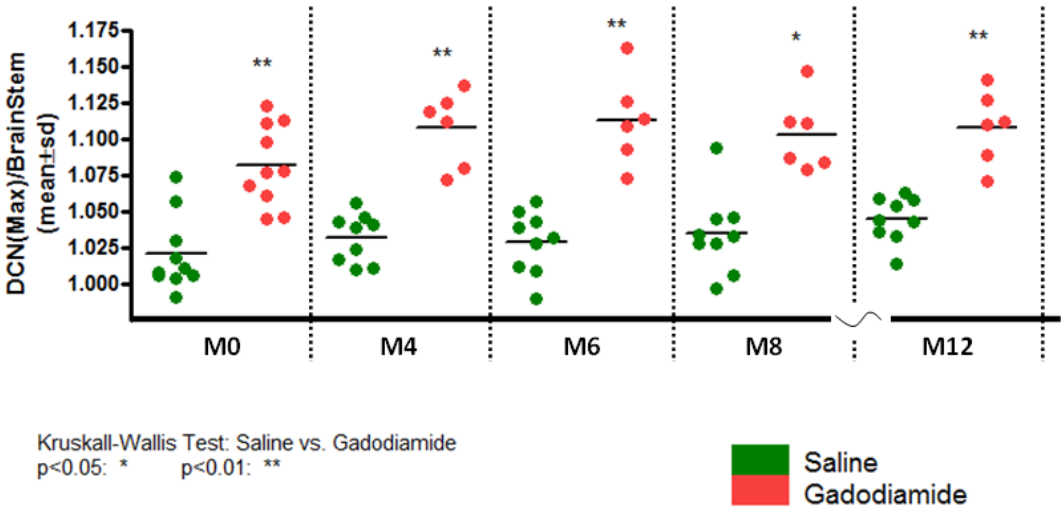
Figure 11: Injection and MRI schedules, Unpublished Guerbet study ER-15-00019



LA-ICP-MS : Laser-Ablation ICP-MS → Elemental high resolution imaging technic

Results: There was a significant and persistent increase in the DCN/brainstem MR signal ratio on T1w gradient echo images that lasted 12 months after the last injection of gadodiamide. No significant increase in the DCN/brainstem MR ratio was observed after multiple saline injections (Figure 12).

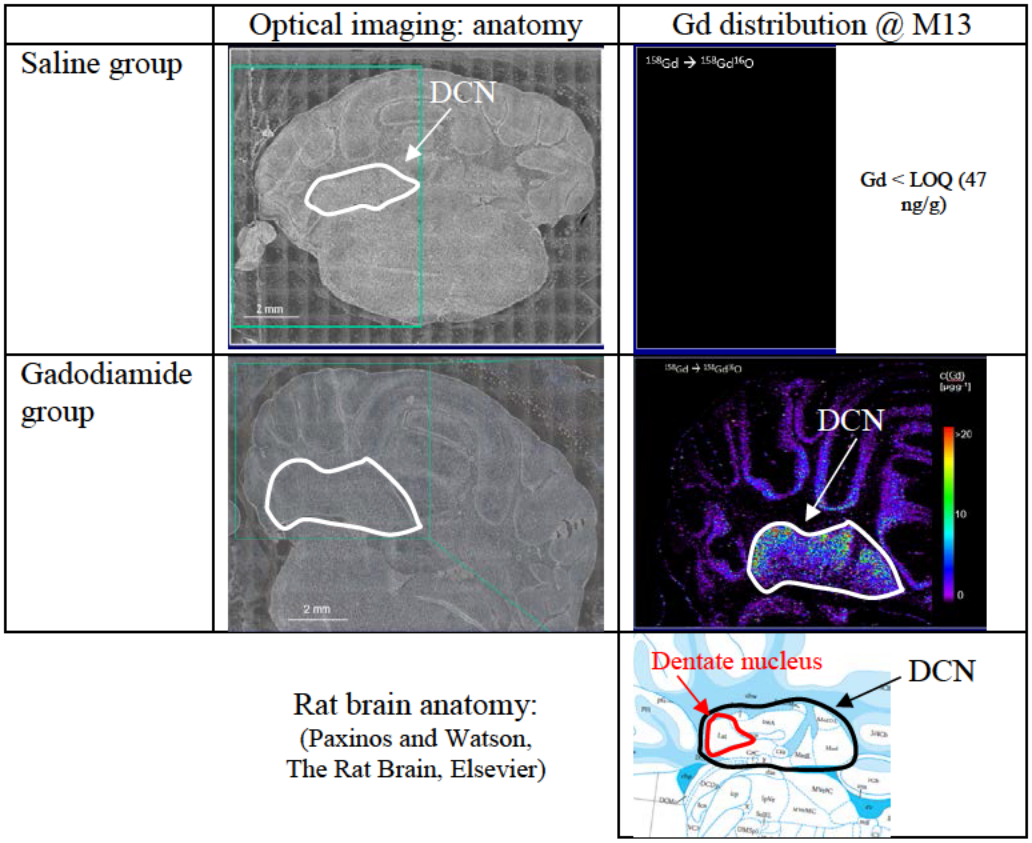
Figure 12: 12-month follow-up of DCN/brain stem signal ratio after repeat administration of gadodiamide



This study shoxed a persistent T1 signal enhancement of the DCN in healthy rats, lasting at least 1 year following the last injection of gadodiamide.

This hyper-enhancement can be attributed to Gadolinium deposition as demonstrated by Laser-Ablation ICP-MS: Figure 13 Interestingly, Gd deposits are observed in all the cerebellar nuclei, not only in the dentate nucleus.

Figure 13: Spatial distribution of Gd in cerebellum by LA-ICP-MS 13 months after the last injection



Example of one rat in the saline group and one rat in the gadodiamide group. Courtesy of Pr. Uwe Karst.

In Guerbet study ER-16-00011 (ongoing, unpublished), four groups of rats treated with gadoterate meglumine, gadobenate dimeglumine, gadodiamide or with no injection (n=10 rats/groups) were included in this study. All the injections were performed according to the injection protocol described in Robert et al. 2016 (67). Healthy female Sprague-Dawley rats received 5 intravenous injections of 2.4 mmol of Gd per kilogram over a period of 5 weeks (1 injection per week). The daily dose of 2.4 mmol Gd per kilogram is equivalent to 4-fold the usual human dose of GdCAs, after adjustment for body surface area.

The three injected groups were submitted to MRI follow-up examinations performed in blinded conditions at 3 time-points using a T1w gradient echo MR sequence (4.7T):

- M0 → 1 week after the last injection.
- M1 → 1 month of wash-out period.
- M2 → 2 months of wash-out period.

- M3 → 3 months of wash-out period.

A non-injected group was also imaged with the same MR sequence.

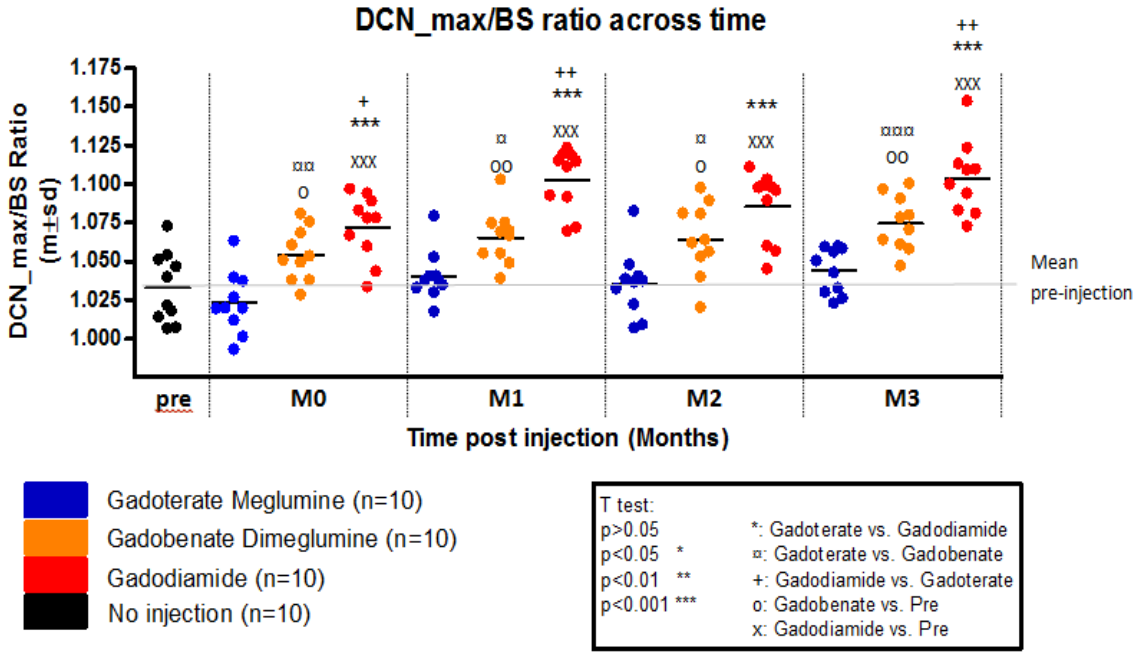
The injection and MRI schedules are summarized in Figure 14.

Figure 14: Injection and MRI schedule

The ROI positioning was adjusted at each time-point. The signal intensity ratio was calculated as the ratio of the DCN signal to the brain stem signal intensities.

Results: The MRI follow-up shows a significant and persistent increase in the DCN/brain stem MR signal ratio on T1w gradient echo images in the DCN that lasted at least 3 months after the last injection for the gadobenate dimeglumine and the gadodiamide groups. No significant increase was observed after multiple gadoterate meglumine injections (Figure 15).

Figure 15: Changes in the DCN/brain stem ratio on T1w gradient echo images for up to 3 months of wash out in rats treated with 3 different GdCAs

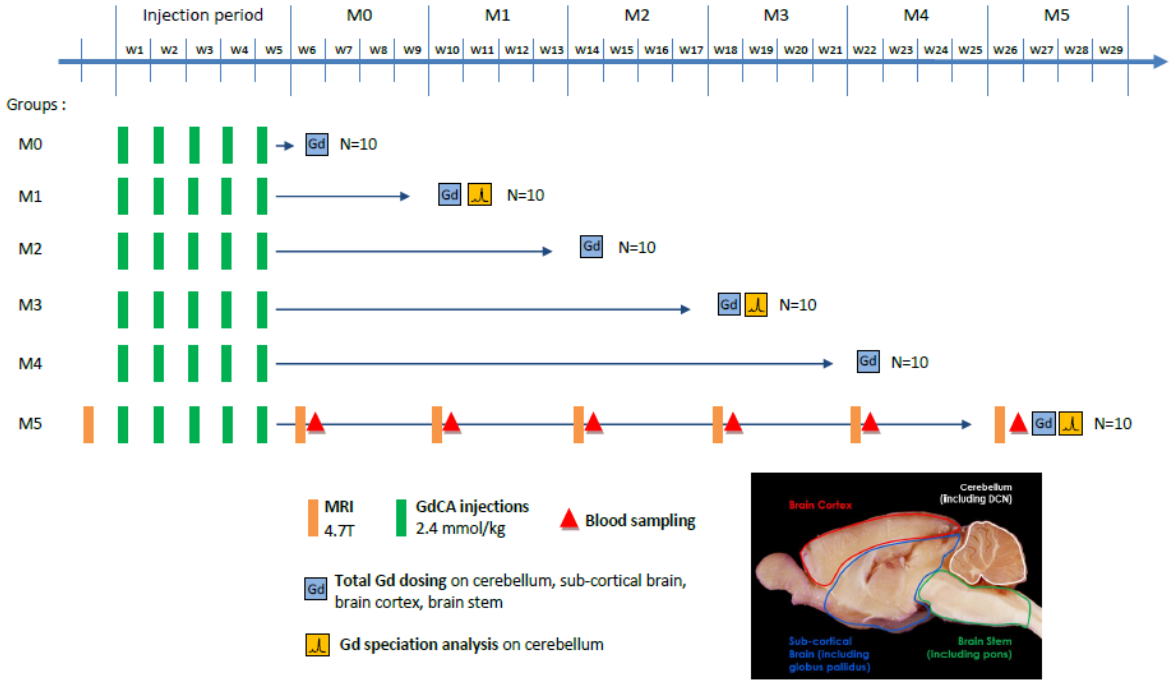


In Guerbet study ER-16-00005 (ongoing, unpublished), the long-term kinetics and the form of Gd accumulated in the brain were compared during 5 months after repeat administration of gadodiamide or gadoterate meglumine.

In this study, healthy rats received five intravenous injections of 2.4 mmol/kg of gadodiamide or gadoterate over a period of five weeks (1 injection per week, N=120). Rats were divided in 6 groups with 0, 1, 2, 3, 4 and 5 months of reversibility period (N=10/agent, groups M0 to M5). T1w-MRI of cerebellum was performed at 4.7 T each month for group M5. At each time-point, animals were sacrificed and cerebellum was sampled and separated longitudinally in two parts: Figure 16.

Total Gd concentration was measured by ICP-MS in the left cerebellum part, the sub-cortical brain, the brain cortex and the brain stem and the plasma.

Figure 16: Injection, sampling and MRI schedules. One injection of 2.4 mmolGd/kg per week was performed for 5 weeks (cumulated total Gd dose was 12 mmol/kg)



Results: 5 months after the last injection, all the rat were positive for DCN T1 hypersignal after gadodiamide, unlike gadoterate: (Figure 17).

This is confirmed by quantitative analysis of DCN/Brainstem signal: (Figure 18).

Figure 17 : MR Images five months after the last injection, all rats from the group M5

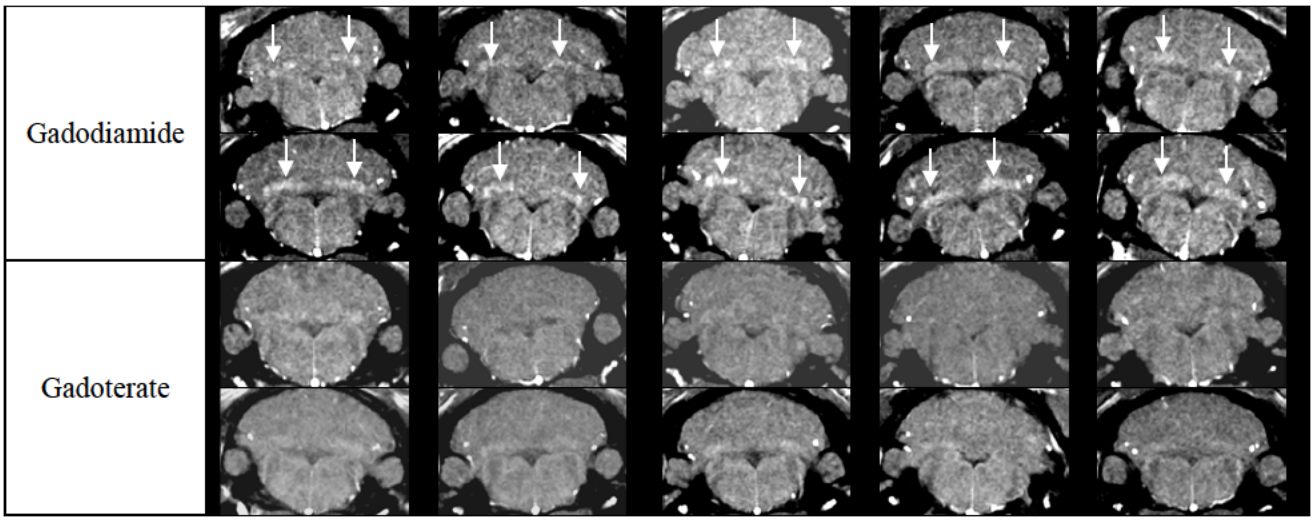
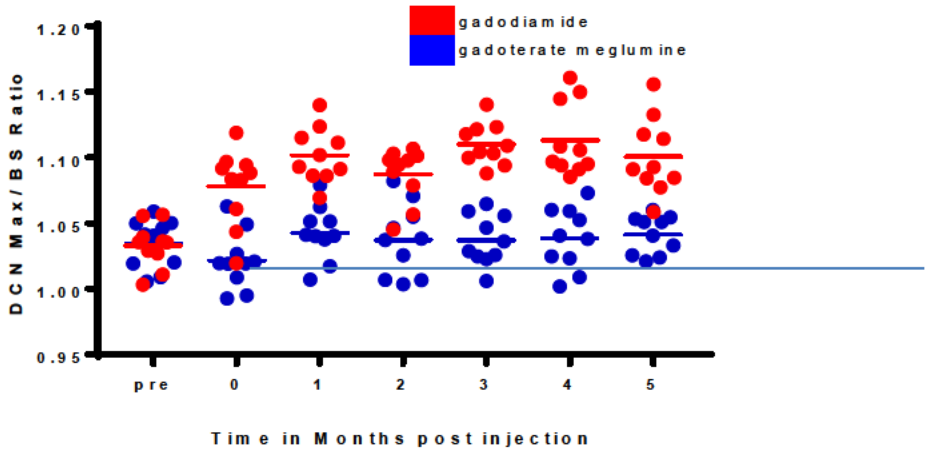


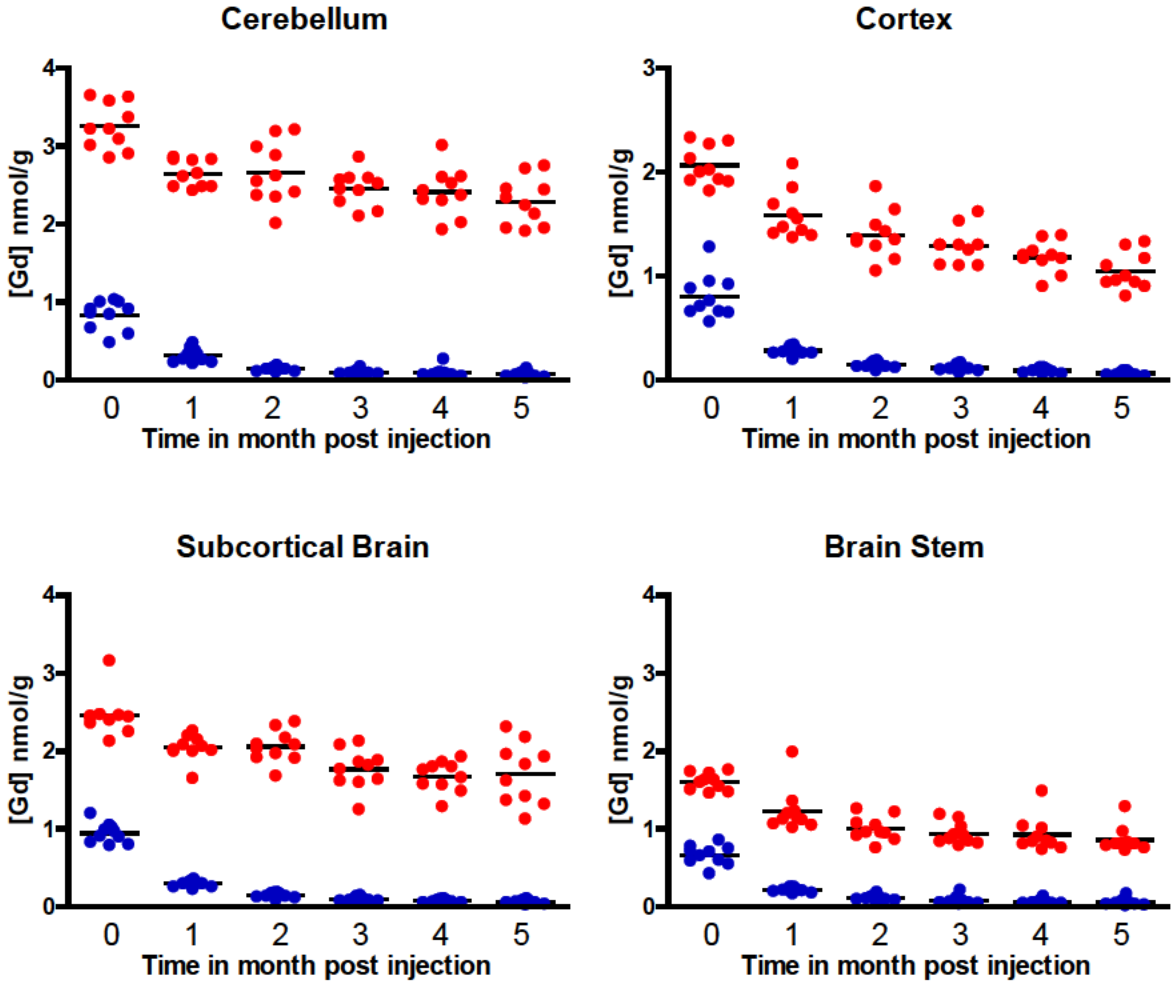
Figure 18 : Blinded quantitative MRI evaluation → DCN/Brain stem signal ratio was still increased at 5 months in the gadodiamide group



N=10 rats/time-point and GdCA.

Follow-up data of total Gd levels in the brain following the administration of macrocyclic agents are represented in Figure 19.

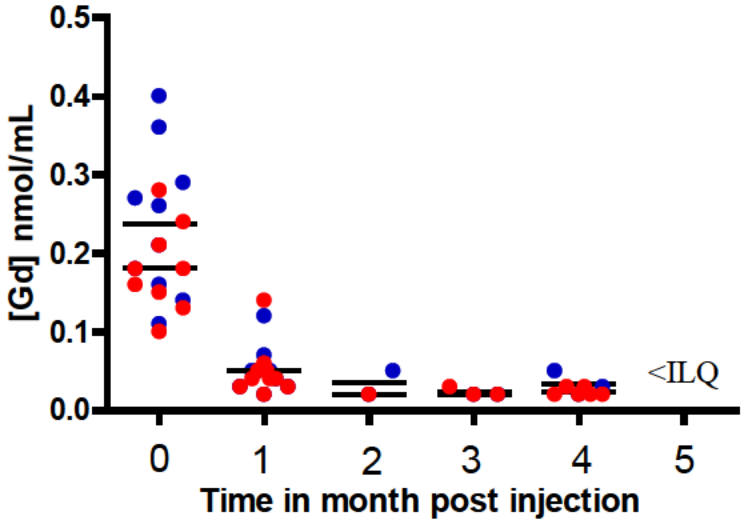
Figure 19: Evolution of total Gd concentration in Brain after repeat injection of gadodiamide (red dots) or gadoterate meglumine (blue dots)



For both GdCAs, total Gd was detectable within the complete studied period, i.e., 5 months after the last injection.

A higher clearance rate from the brain was observed with gadoterate compared to gadodiamide: at M5, 30-fold more Gd was measured in the cerebellum in the gadodiamide group (2.29±0.30nmol/g) versus gadoterate (0.075±0.037nmol/g, $p<0.001$) but no remaining Gd was detected in the blood for both products: Figure 20.

Figure 20: Evolution of total Gd concentration in plasma after repeat injection of gadodiamide or gadoterate méglumine (blue dots).



ILQ: Inferior Limit of Quantification

In cerebellum, for gadoterate, 91±5% of Gd found at M0 was cleared at M5, unlike gadodiamide where only 29±11% of the Gd was cleared ($p<0.001$). By fitting the exponential decrease in cerebellum, the half-life of elimination of total Gd after gadodiamide is higher than 400 days.

From the time-follow-up curves (Figure 21), area under the curve (AUC) representing the total gadolinium exposure within the brain during the 5 months of washout period, were calculated for each brain area, showing a 6.2- to 11.5-fold higher total Gd concentration retained in the brain for gadodiamide compared to gadoterate: (Figure 22).

Figure 21: Time course of the Gd concentration ratio over time in the cerebellum following repeat administration of Omniscan and Dotarem

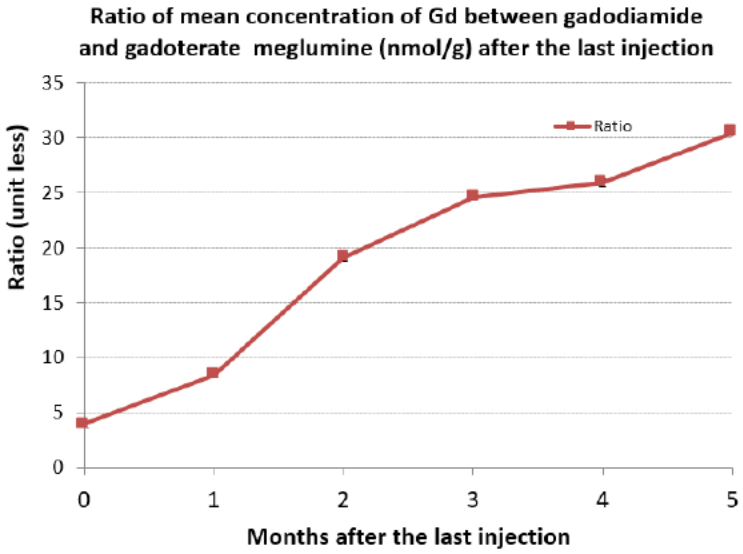
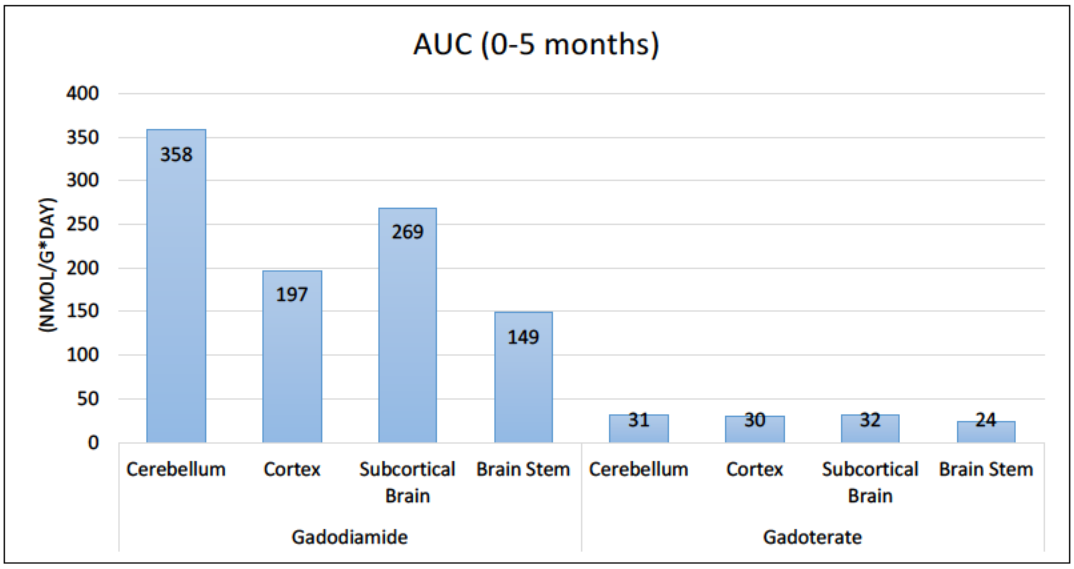


Figure 22: AUC among the 5 months of follow-up, study ER-16-00005

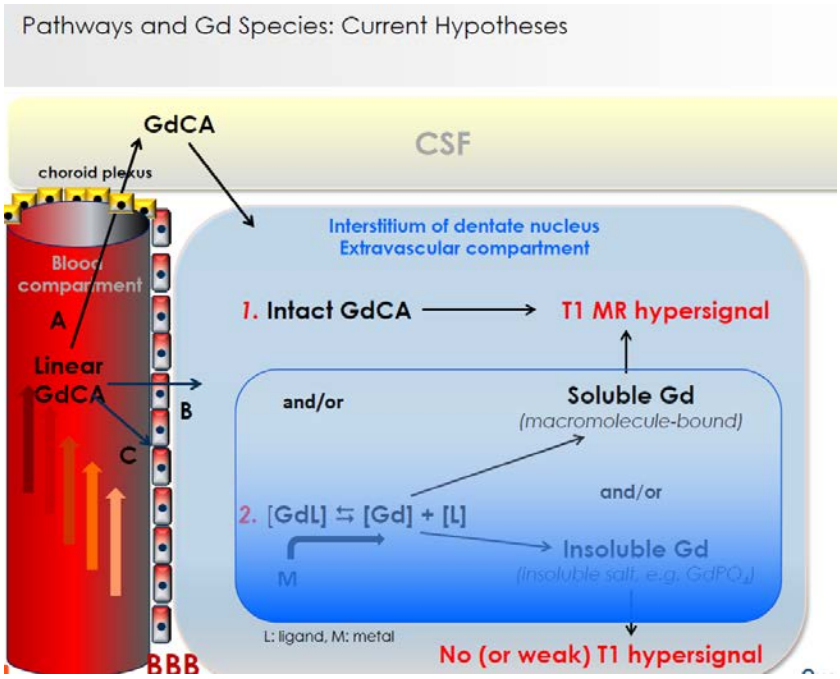


5.1.2.4 Mechanism of entry of GdCAs to the brain

Basically, several hypotheses can be raised as regards the mechanism of entry of GdCAs and the subsequent changes the complex may undergo. They are summarized below.

The GdCA may A) enter the ventricles through the choroid plexus, then enter the CNS interstitium; B) cross the BBB, C) stick to intact BBB. Once in the CNS interstitium (e.g. into the dentate nucleus). Evidence of mechanism of entry via A is described in the following studies. The GdCA can remain intact or dissociate into a soluble (and macromolecule-bond)

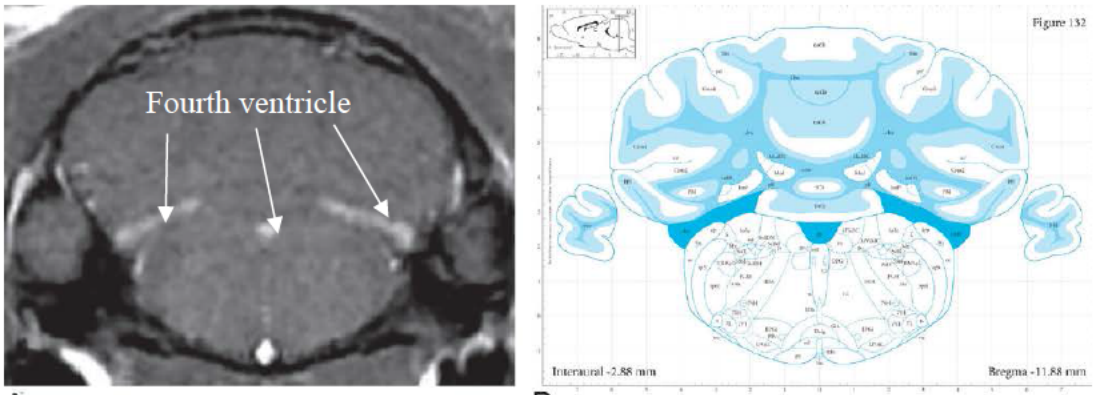
form (thus inducing a T1 effect) and/or precipitate under an insoluble form. Speciation studies based on analytical methods showed that these 3 forms are detected for linear GdCA only.



Jost et al. 2016 and 2017 demonstrated that all GdCAs tested may circumvent the blood brain barrier (BBB) and enter the brain as parent compound (68, 76). A possible route of entry for GdCAs into brain tissue is via the choroid plexus (76). Appearance in the CSF occurs at an early time point (within 10 minutes) and clearance from the CSF was found 4 hours later. The retained Gd concentration was found to be higher in the olfactory bulbs of mouse after repeat injection of gadodiamide or gadoterate, which supports the hypothesis that Gd enters the brain via CSF (69).

In a study published by Guerbet (73), repeat administration of gadodiamide in rats with moderate renal failure was associated with an increase of a T1 hypersignal in the choroid plexus of the fourth ventricle at 6 weeks. This is consistent with the hypothesis of entry of GdCAs via the blood/CSF barrier in the choroid plexus and subsequently in the CNS interstitium through the ependymal layer. This effect was persistent 6 days after the last administration. Typical images of this specific enhancement are shown in Figure 23.

Figure 23: (A) Hypersignal in the choroid plexus (3 distinct areas) in the fourth ventricle of gadodiamide + SNx rats, on T1wMRI scans obtained on week 6, and (B) darkest blue areas are referred as choroid plexus ("chp") of the fourth ventricle ("4 V") in the Paxinos and Watson atlas, 2007



A B

This suggest that CSF route may be involved in brain deposits of Gd.

5.1.2.5 Molecular form of Gd in the brain, speciation studies

Initial findings demonstrate major differences between the two classes of GdCAs in the residual Gd found in the rat brain after repeat administration as shown in Figure 24 below. It is suggest that with linear GdCAs, Gd is present in at least 3 distinctive forms:

- soluble small molecular weight form, including the intact GdCA;
- soluble macromolecules (the nature of which remains unknown);
- and to a large extent in an insoluble form (70).

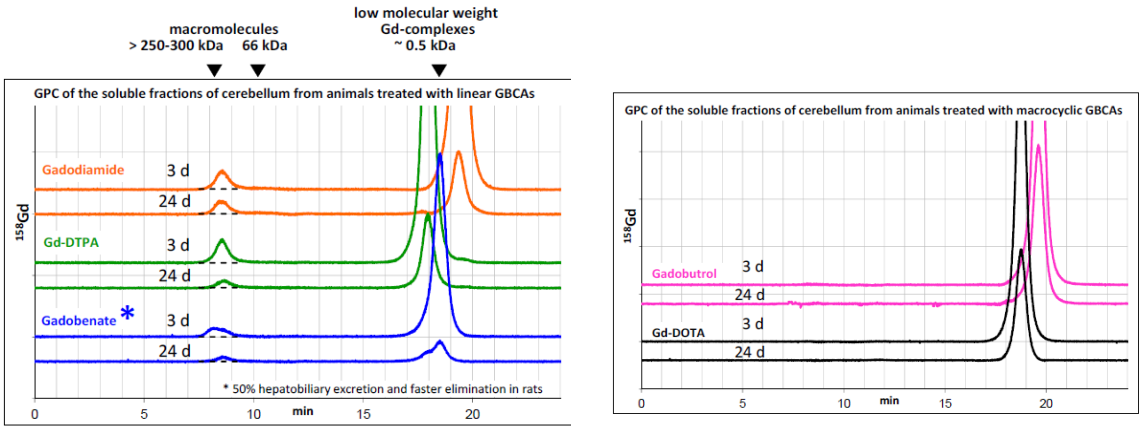
As opposite, in the case of macrocyclic GdCAs, Gd is exclusively detected in the intact soluble form with no interaction with macromolecules. The following additional observations were made in the study from Frenzel et al.:

- After tissue fractionation, the soluble fractions from animals receiving macrocyclic GdCAs contained only small Gd-containing molecules, which the authors considered as the intact macrocyclic GdCA itself.
- The Gd concentration of the soluble fractions from all agents (linear and macrocyclic agents) decreased from Day 3 to Day 24 post-administration indicating that the elimination from the brain was still ongoing, but occurred at a much slower rate than from other tissues. The washout of the soluble fraction from day 3 to day 24 was in the range −60% to −73%, which was similar for all investigated GBCAs and for the 3 brain sections.
- The Gd concentrations in the insoluble fractions of the cerebellum (pellet) were considerably lower for the macrocyclic GdCAs (0.3–0.5 nmol Gd/g tissue) than for linear GdCAs (2.5 to 4.4 nmol Gd/g tissue).

- The nature of the insoluble forms has not been determined.
- The chromatographic separation did not allow identification of the chemical nature of the macromolecule and whether it had bound the intact GdCA or the transmetallated Gd^{3+} ion. The authors considered that it is very unlikely that the intact GdCA were bound to a macromolecule as their binding to plasma proteins is very low or negligible.

Figure 24: Examples of Gd-specific GPC chromatograms of cerebellum homogenates from animals, 3 and 24 days after injection with (A) linear GdCAs Omniscan, Magnevist and MultiHance and (B) macrocyclic GdCAs Dotarem and Gadovist. The chromatograms show the intensity * Smaller peak area likely due to faster elimination of MultiHance because of relevant hepatobiliary excretion which is about 50% in rats but only 3-5% in humans.

SEC-ICP-MS on samples from in vivo study (Bayer Study, Frenzel et al., 2017)



From Frenzel et al. (70)

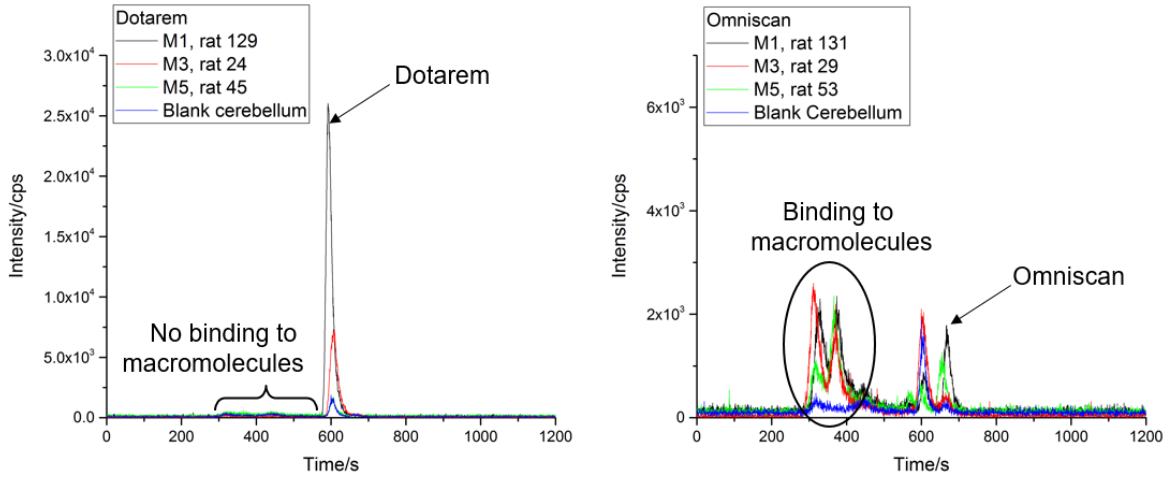
In the Guerbet study ER-16-00005 (Figure 25, chemical form of residual gadolinium in the cerebellum has been assessed for M1, M3 and M5 groups is from 1 to 5 months after the last injection. Soluble and insoluble fractions were separated by centrifugation and the soluble fraction was further analyzed by liquid chromatography methods coupled to an ICP-MS instrument. Size exclusion chromatography (SEC) was applied to provide information on Gd species bound to macromolecules and hydrophilic-interaction-chromatography (HILIC) was used to detect the intact contrast agents and their potential metabolites.

Results: after injection of gadoterate, according to the method applied, Gd is detected only as intact GdCA, with decreasing of the amount overtime. After injection of gadodiamide only, a large fraction of the Gd remained in the pellet and most of the soluble Gd is bound to macromolecules, with no significant changing in levels with time, as depicted in the Figure 26. Only traces of intact GdCA were detected, with decreasing amount over the time.

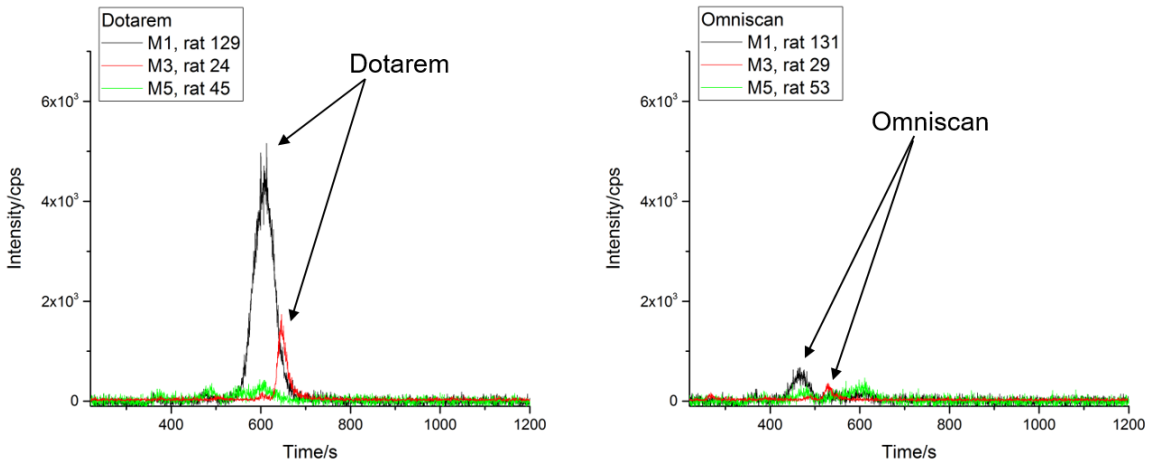
Figure 25: Examples of Gd specific SEC-ICP-MS (top) and HILIC-ICP-MS (bottom) chromatograms of the soluble fractions of rat cerebellum homogenates 1 (M1), 3 (M3) and 5 (M5) months after the last injection of GdCA (study ER-16-00005). For HILIC, a new column was used for the analysis of group M3, resulting in slight different retention times for both GdCA.

Guerbet Study (ref. ER-16-00005, unpublished)

SEC-ICP-MS: detection of bound-soluble form and low molecular weight soluble form (including intact chelate)

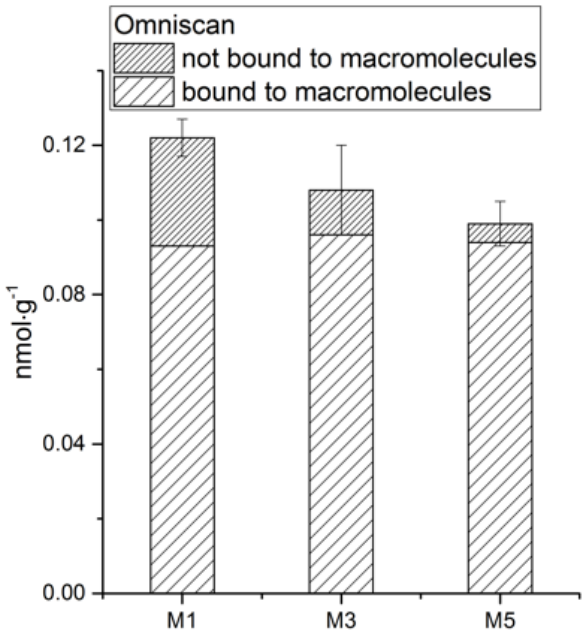


HILIC-ICP-MS: detection of the intact Gd-Chelate



(Courtesy of Pr. Uwe Karst)

Figure 26: Determination by SEC-ICP-MS analysis the concentration of gadolinium that is not bound and bound to macromolecules in the soluble fractions of rat cerebellum homogenates 1, 3 and 5 months after the last injection of gadodiamide (study ER-16-00005, unpublished). For gadoterate, no binding to macromolecules was found.



These results are consistent with previous studies from Bayer at M1 (70), confirming the major differences between linear and macrocyclic GdCA in term of accumulation and potential interaction with endogenous species.

Also, these gadodiamide results demonstrate that the decrease of total Gd over the time from the soluble fraction of rat cerebellum homogenates can be linked to the wash out of the intact GdCA, the fraction bound to macromolecules remaining stable. These findings strongly support the fact that the T1 hypersignal could result, in the case of gadodiamide, from the binding of soluble Gd to macromolecules, and that this T1 signal persists over the time because this fraction of Gd is not eliminated from the brain tissue. As yet, the nature of the interactions between the macromolecules (the nature of which remains unknown) and the gadolinium remains unclear and needs to be investigated.

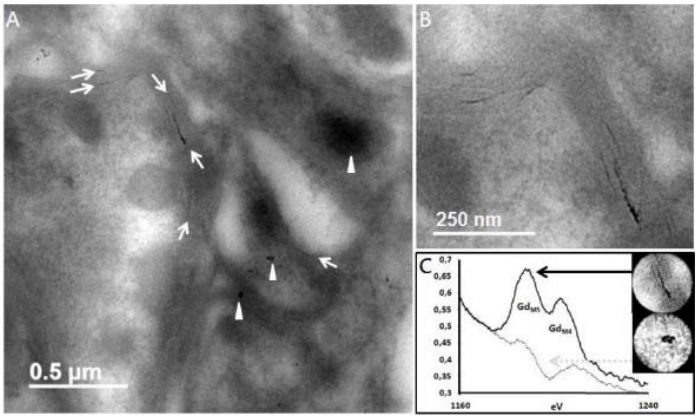
5.1.2.6 Neurological or histopathological findings after repeat administration of linear and macrocyclic GdCAs

Thus far, no published nonclinical studies have reported clinical signs of neurotoxicity associated with retained Gd up to 50 weeks post-dosing. Furthermore, no histopathology findings have been reported in brain tissues associated with Gd levels up to approximately 4-13 nmol/g in one study (74). In another study, histopathological sections were made from the brain tissue of treated animals (H&E staining, cresyl violet stains for Nissl bodies, immunohistochemistry for glial fibrillary acidic protein (GFAP) and ionized calcium-binding adapter molecule 1 (Iba-1) to study respectively resident astrocytes and early activation of microglia (71). No abnormalities were found in the brain detected by light microscopy

examination in animals treated with any of the GdCAs. However, in 4 gadodiamide treated animals, macroscopic and microscopic pathologies were observed in the skin and reported to be similar in many aspects to lesions of human nephrogenic systemic fibrosis (NSF).

In one unpublished Guerbet study (ER-15-00002), deep cerebellar nuclei of one gadodiamide-treated rat were analysed by TEM/EELS. Tissue samples were not stained with uranyle and/or osmium, in order to avoid potential overlap of Gd deposits with stained membranes: Figure 27.

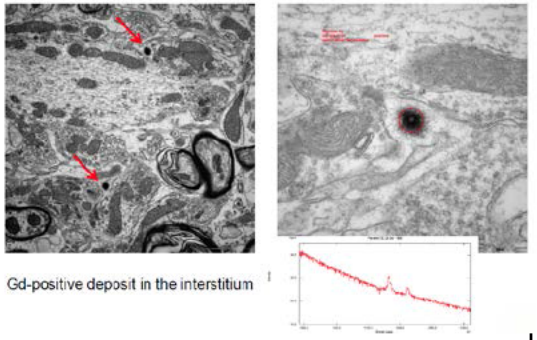
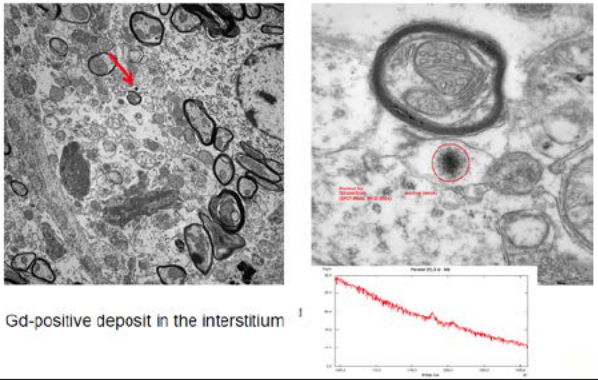
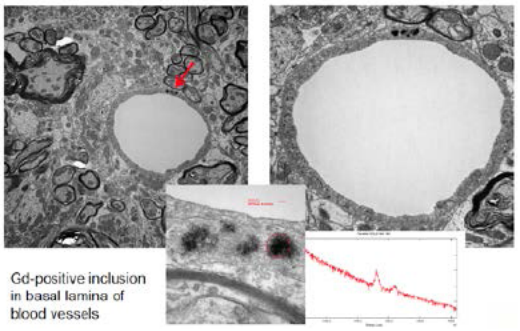
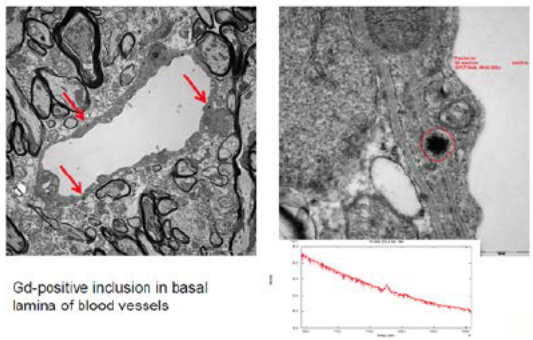
Figure 27: Transmission electron microscopy of deep cerebellar nuclei in a gadodiamide-treated rat, and EELS spectrum. Presence of filamentous electron-dense Gd deposits interest in one hemisphere



An ongoing Guerbet study (ER-16-00030) is currently investigating the cerebellar Gd deposition in the brain of rats after repeat administration of gadodiamide by electron microscopy, and X-Ray Fluorescence. In this study, renally-impaired rats received 20 injections of the L-GdCAs gadodiamide (Omniscan®), gadobenate (Multihance®), and the macrocyclic GdCA gadoterate (Dotarem®), (cumulated dose: 12mmol Gd/kg), or saline over 5 weeks . After four weeks of wash-out, the animals (one per group) were euthanized and the cerebellums collected. The granular layer of the cerebellar cortex and the deep cerebellar nuclei were dissected and embedded in epon-resin. The comparative transmission electron microscopy (TEM) analysis was performed blindly in Regensburg University (Institut für Pathologie, Regensburg, Germany, Profs Schroeder and Brochhausen). Gd deposits were characterized by electron energy loss spectroscopy (EELS). Furthermore, one healthy rat received the same cumulated dosis of gadodiamide over 5 weeks (7-week wash-out period). In all studies, MRI examinations were performed blindly at 4.7 T.

In this study, T1 hypersignal was systematically observed in the DCNs of rats treated with both L-GdCAs but not with gadoterate. Numerous dark inclusions with characteristic “sea urchin” shape were found in the basal membrane of vessels and the extracellular space of the interstitium in the area of the DCN and granular layer of cerebellar cortex in groups treated with gadodiamide and gadobenate, but not in the gadoterate and saline groups. Some of these deposits, of ~300nm in diameter, revealed positivity for Gd, by EELS analysis. Sometimes, intracellular (in glial cells or macrophages) were observed. In such case, they were associated with a pigment (likely lipofuscin) Figure 28.

Figure 28: Transmission electron microscopy & characterization of Gd deposits by electron energy loss spectroscopy (EELS)

Deep cerebellar nuclei Compartment:	Gadodiamide (Omniscan®)	Gadobenate (Multihance®)	Gadoterate (Dotarem®)
Interstitium	Group 4: Omniscan - animal#28 (EM#:17-040) and animal#36 (EM#:17-041) localisation: DCN  Gd-positive deposit in the interstitium	Group 3: Multihance - animal#23 (EM#:17-038) and animal#29 (EM#:17-039) localisation: DCN  Gd-positive deposit in the interstitium	No Gd deposits found
Perivascular basal lamina	Group 4: Omniscan - animal#28 (EM#:17-040) and animal#36 (EM#:17-041) localisation: DCN  Gd-positive inclusion in basal lamina of blood vessels	Group 3: Multihance - animal#23 (EM#:17-038) and animal#29 (EM#:17-039) localisation: DCN  Gd-positive inclusion in basal lamina of blood vessels	No Gd deposits found

Studies performed (blinded) at Zentrum für Elektronenmikroskopie, Institut für Pathologie, Universitätklinikum Regensburg, Regensburg, Germany (Dr Josef Schroeder & Dr Christoph Brochhausen).
Guerbet study ER-16-00030. Renally-impaired rats (2/group) received 20 injections of the GdCAs gadodiamide (Omniscan®), gadobenate (Multihance®), and the macrocyclic GdCA gadoterate (Dotarem®), (cumulated dose: 12mmol Gd/kg), or saline over 5 weeks. After four weeks of wash-out, the animals (were euthanized and the cerebellums collected. The deep cerebellar nuclei were dissected and embedded in epon-resin.

5.1.2.7 At risk population: impact of renal impairment on brain accumulation

Renal impairment is known to increase the long-term retention of Gd in rats in line with the propensity of L-GdCAs to release Gd *in vivo* (78). It has been shown, in renally-impaired rats that gadodiamide gradually dissociates and thus releases soluble Gd (79). As previously published, patients with renal impairment and/or NSF present brain T1 hyperintensities (80).

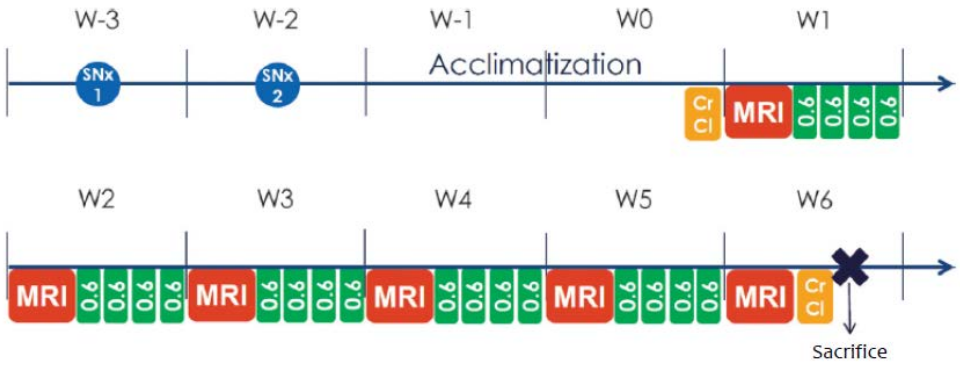
A study published by Kartamihardja et al. in 2016 recently evaluated in mice models the impact of impaired renal function on Gd deposition in various organs of mice after repeat intravenous administrations (69). They found that long-term Gd retention for GdCAs was almost unaffected by renal function, suggesting that the chemical structures of retained Gd may not be consistent and some Gd is slowly eliminated after initially being retained. However, authors observed that "in the gadoterate group, Gd was eliminated from the brain in both mouse models, while in the gadodiamide group, the Gd clearance of the Gd present in high concentration was very slow"

In a recent published Guerbet study, it has been found that reiterated administrations of gadodiamide in rats with renal failure was associated with an increase in the T1 hypersignal in the DCN relative to gadodiamide-treated rats compared with normal renal function (73). Moreover, this study demonstrated that that renal failure increased the concentration of circulating free gadolinium after gadodiamide (dissociated form from the ligand).

Hereafter we describe the complete results concerning the impact of renal impairment on the previously published pre-clinical rat model (66, 67).

Subtotal nephrectomy (SNx) Sprague Dawley rats were compared to rats with normal renal function (sham-operated). The animals (10/group) received 4 daily injections of 0.6 mmol Gd/kg a week for 5 weeks (cumulative dose of 12 mmol Gd/kg) of gadodiamide (Omniscan®) or saline solution, and were followed 1 week after the last injection: Figure 29.

Figure 29: Schedule of Guerbet ER-15-00020 study. Protocol scheme of the study. SNx, subtotal nephrectomy of the 5/6 or shamoperation; SNx 1 indicates first part of the surgery; SNx 2, second part of the surgery; CrCl, creatinine clearance. MRI was performed before the first injection, and then once a week (W). Twenty injections of gadodiamide, 0.6 mmol Gd/kg/injection, were distributed over 5 weeks, leading to a cumulative dose of 12 mmol Gd/kg. Killing was performed 6 days after the last injection.



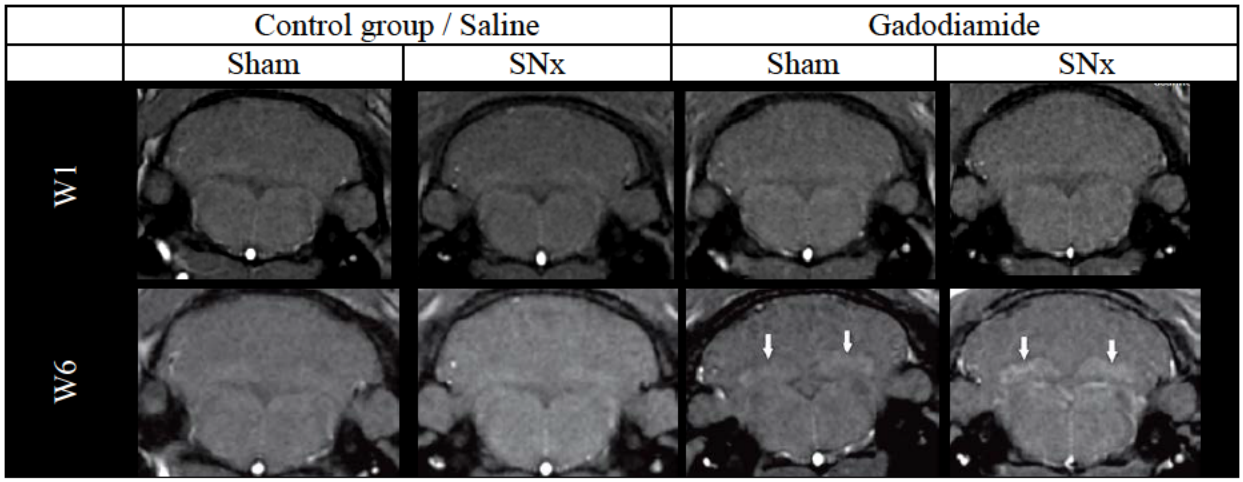
The MR signal enhancement in different areas, such as the deep cerebellar nuclei (DCN), was monitored by weekly magnetic resonance imaging examinations (4.7T). One week after the final injection, the total Gd concentration was measured by ICP-MS in different regions of the brain including the cerebellum, plasma and cerebrospinal fluid. To differentiate the form of the gadolinium, an additional measurement in plasma was added by coupling high-pressure liquid chromatography (LC) to ICP-MS.

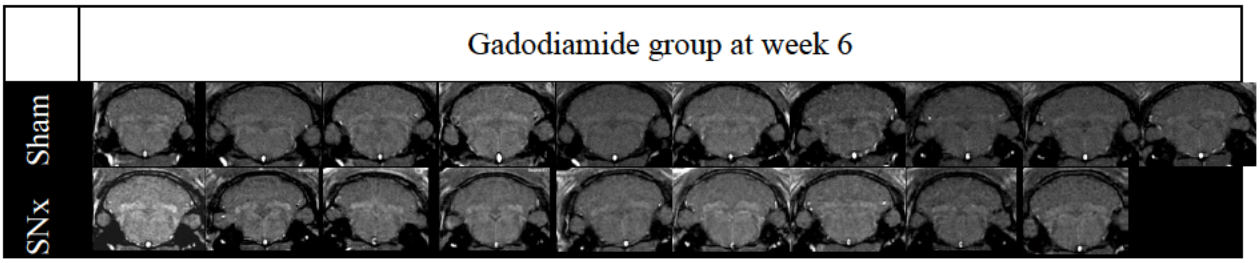
Results are shown below:

- Qualitative assessment of deep cerebellar nuclei T1 hyperintensities

As presented below, (Figure 30) no T1 hyperintensities were observed on week 1 for all groups and on week 6 for the control/saline group. In contrast, clear T1 hyperintensities were seen in the DCN on week 6 in the gadodiamide group. These T1 hyperintensities were clearly more pronounced in the case of renal impairment.

Figure 30: MR images of cerebellums of renally-impaired rat repeatedly treated with gadodiamide

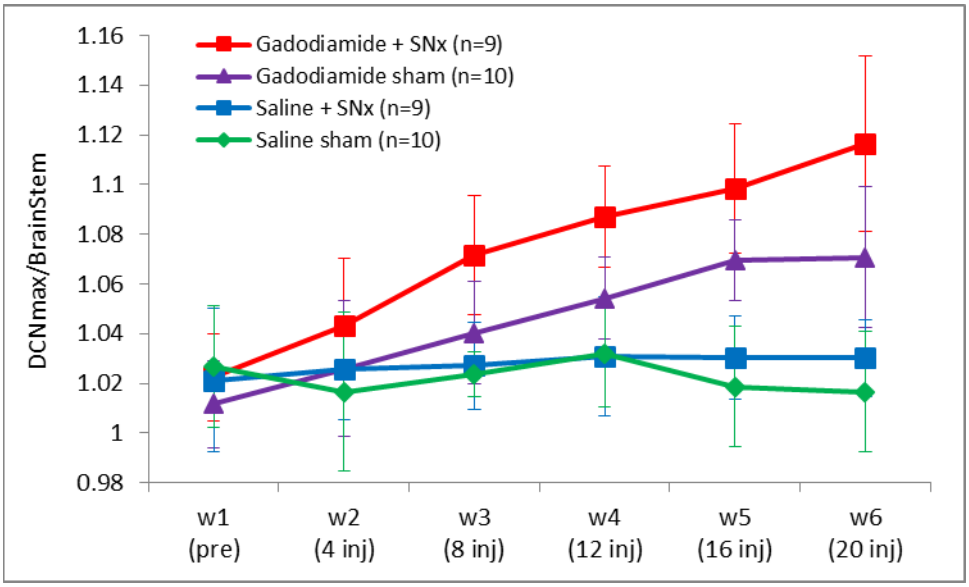




- Quantitative assessment of deep cerebellar nuclei T1 hyperintensities and cerebral gadolinium concentrations and form

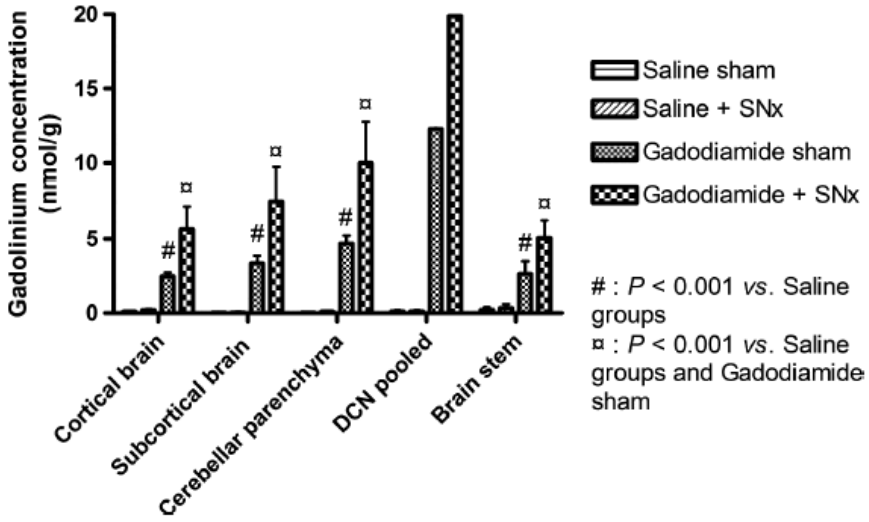
The quantitative measurements confirmed the previous results. After administration of gadodiamide, the subtotal nephrectomy (SNx) group presented a significantly higher T1 signal enhancement in the DCN and a major and significant increase in the total Gd concentration in all the studied structures, compared with the normal renal function group receiving gadodiamide. The analysis is shown below in Figure 31.

Figure 31: Quantitative analyses of T1 signal in the DCN. Evolution of DCN/brain stem T1w signal intensity ratios over the course of the injections.



Renal failure was associated with an increased total Gd concentration in all brain areas, with a maximal concentration of 12.3 nmol/g of total Gd found in DCN: (Figure 32).

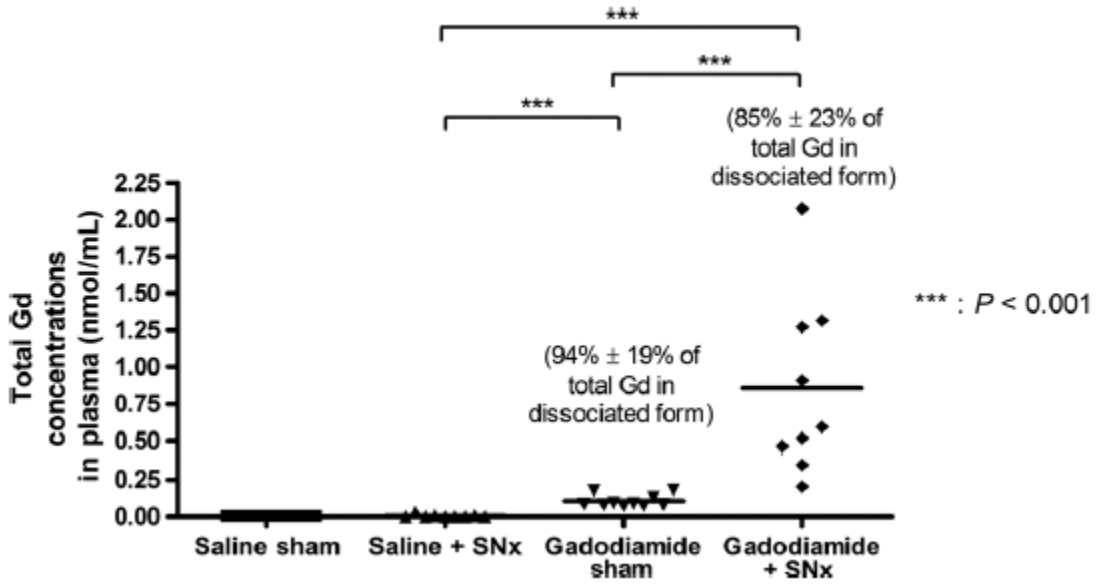
Figure 32: Total gadolinium concentration in the cortical and subcortical brain, cerebellar parenchyma, DCN (pooled), and brain stem.



However, the relevant question is not only the tissue concentration of total gadolinium but also its chemical form, as underlined by Frenzel *et al.* (70). In renally-impaired rats receiving gadodiamide, plasma total Gd concentration (measured 6 days after completion of intravenous administrations), was around 1 µmol/L. Interestingly, in these animals as well as in the sham-operated rats, plasma Gd was found to be predominantly in a dissociated and soluble form

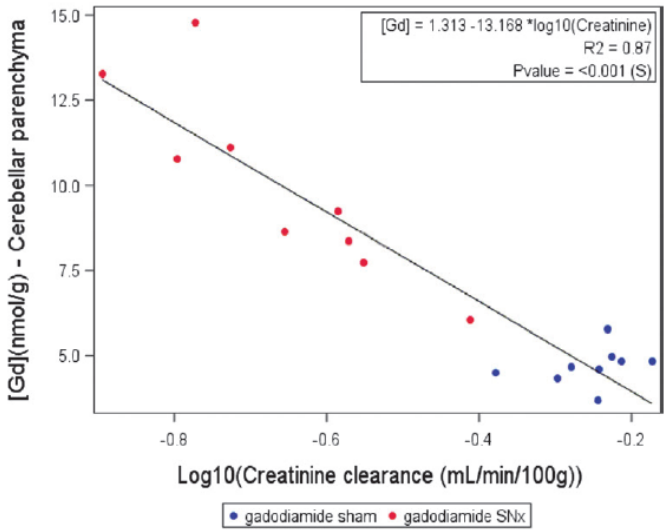
(around 90% of total Gd) in this latter case (Figure 33). This result strongly supports the hypothesis of an *in vivo* gradual dissociation of gadodiamide.

Figure 33: Total gadolinium concentration determined by ICP-MS in plasma collected 6 days after the last injection. Percentages (± SD) represent the proportion of dissociated Gd, determined by LC-ICP-MS.



Total Gd concentrations in the brain, cerebellum, plasma, and bones correlated with creatinine clearance in both gadodiamide-treated groups: example in the cerebellum in Figure 34.

Figure 34 : Logarithmic correlations between total Gd concentration in the cerebellar parenchyma and Creatine Clearance.



(From Rasschaert, 2017, (73))

New data (unpublished Guerbet study ER-16-00030) including gadobenate and gadoterate has completed this study, demonstrating that accumulation of Gd into DCN is observed for gadobenate, unlike gadoterate. (see Figure 35 and Figure 36)

Figure 35 : Hypersignal of deep cerebellar nuclei in renally impaired rats after repeat administration of gadobenate, gadodiamide or gadoterate (Study ER-16-00030). Qualitative (0-2) analysis of T1 images: W1 = pre-injection, W2-W6 = injection weeks, W7-W10 = wash-out period, Blinded qualitative quotation of 4.7T T1w MR images (randomized per time-point and treatment, as described in Robert et al. (2015)

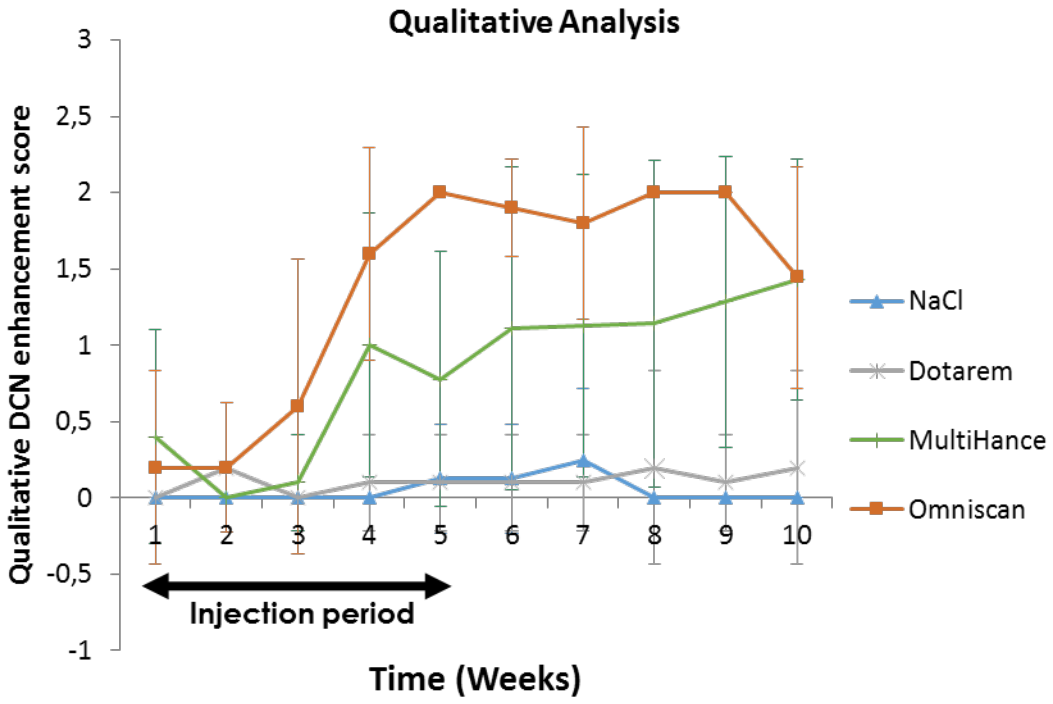
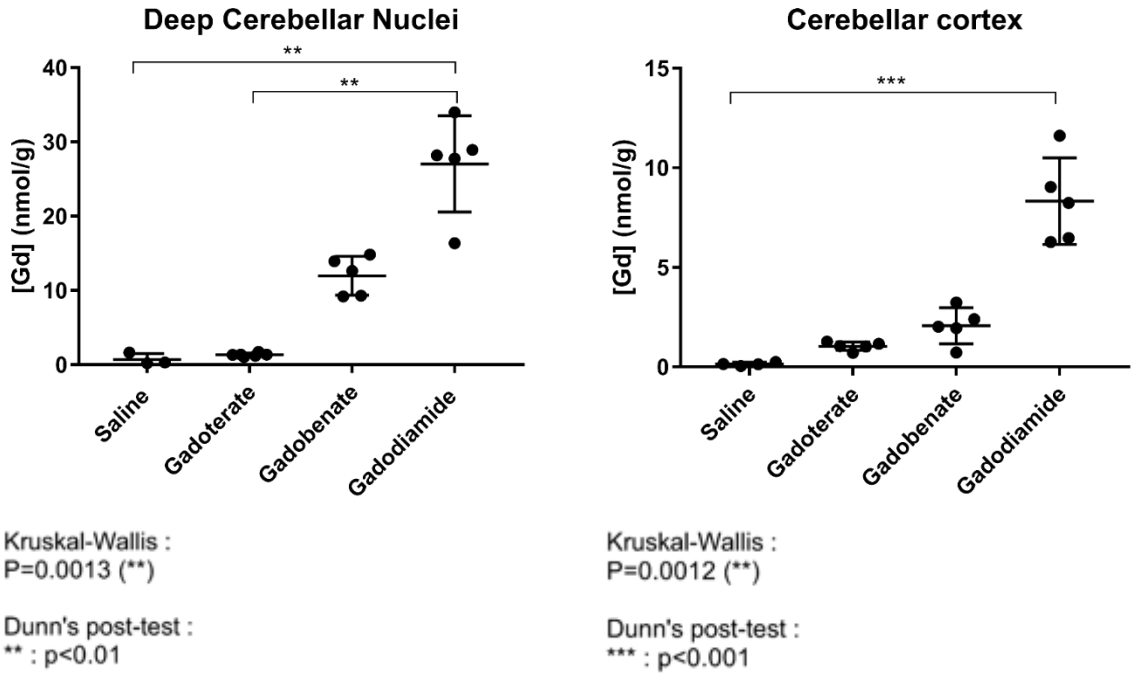


Figure 36 : Total Gd concentration in dissected deep cerebellar nuclei and cerebellar cortex in renally impaired rats after repeat administration of gadobenate, gadodiamide or gadoterate (Study ER-16-00030)



In conclusion, these results indicate that renal impairment substantially potentiates the T1 signal enhancement in the DCN and total Gd concentrations in various brain structures of gadodiamide treated rats. These data suggest first that underlying moderately impaired renal function may increase the risk of brain uptake of Gd in a dissociated form, and secondly that, regardless of the renal function, Gd is predominantly dissociated from the gadodiamide chelate.

These results are consistent with the study of Barbieri et al. demonstrating T1 hyperintensities in patient with impaired renal function (80).

5.1.3 Gd retention in skin, bones and other tissues: background from NSF nonclinical research in naive and renally-impaired animal models

From 2006 to 2014, extensive nonclinical research studies have been performed at Guerbet to understand the mechanism and the role of GdCA injection in the Nephrogenic Systemic Fibrosis (NSF). From these studies, “It rapidly appeared that the occurrence of NSF was associated with prior administration of gadolinium chelates with lower thermodynamic stability. Although a role for the chelated form of the less stable GdCAs has been proposed, the most commonly accepted hypothesis involves the gradual release of dissociated gadolinium in the body, leading to systemic fibrosis” (81).

All these studies have shown that, contrary to what was commonly thought, high content of Gd may be retained in some tissues after repeat administration of linear GdCA, in a dose-dependent relationship.

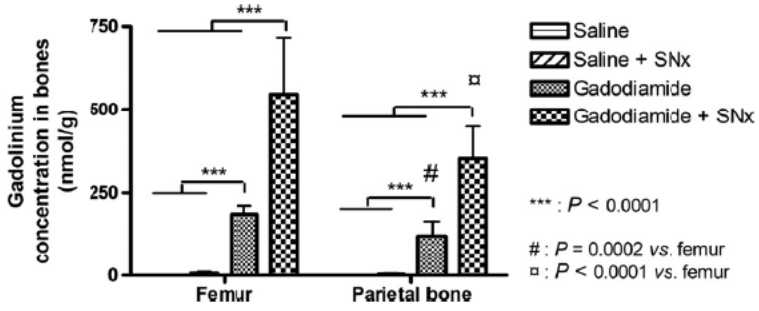
Sieber et al.demonstrated after a cumulated dose of 50 mmol/kg in a naïve rat model a skin, bone and liver retention of Gd in the following order (82):

Linear GdCA			Macrocyclic GdCA
gadodiamide > (Omniscan®)	gadoversetamide > (Optimark®)	gadopentetate = gadobenate > (Magnevist®, MultiHance®)	gadobutrol, gadoterate (Gadavist®, Dotarem®)

This retention is potentiated in case of renal impairment:

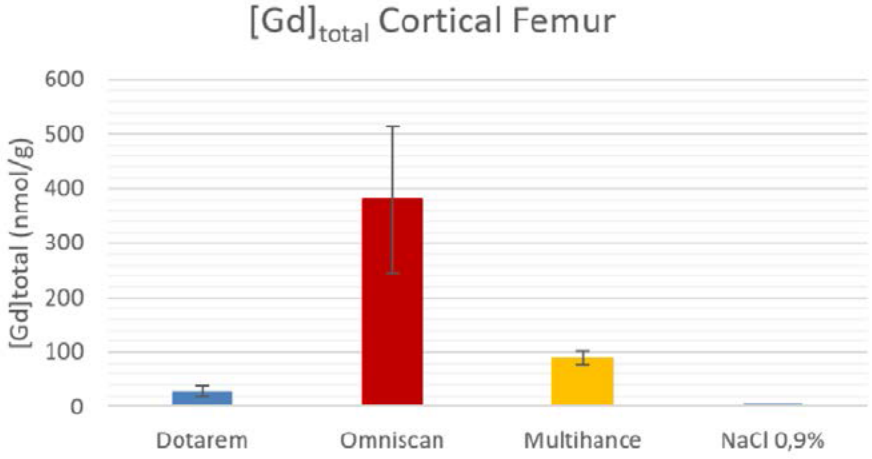
- In bone, a recent study have shown that the Gd retention of gadodiamide is more than 2-fold higher in case of moderate renal impairment: (Figure 37).

Figure 37: Increase bone retention of Gd renally-impaired rats (SNx) as compared to in normal rats (73). Cumulated dose of 12 mmol/kg, Gd dosage performed 1 week after the last injection.



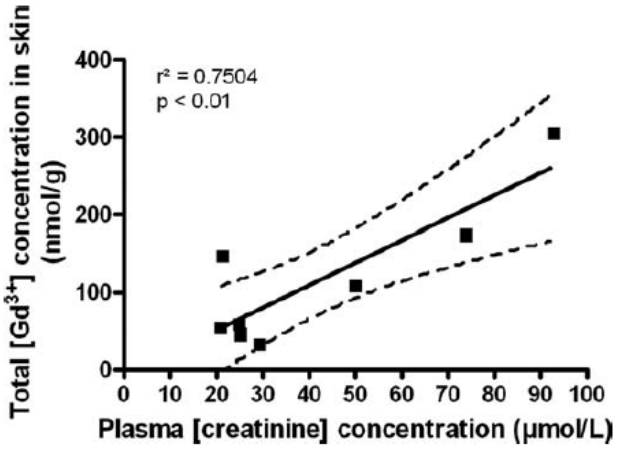
In this model of impaired renal function, it has been shown the difference of Gd retention in the bone between the macrocyclic GdCA gadoterate and the linear GdCA gadodiamide and gadobenate (Guerbet on going study ER-16-00030) (Figure 38).

Figure 38: Bone retention in renally-impaired rats 5 weeks after the last injection of 4 daily injections of 0.6 mmol Gd/kg a week for 5 weeks.



- In skin as well, total Gd concentration is dependent on the renal clearance, as shown by Fretellier et al (83): (see Figure 39)

Figure 39: Positive linear correlation between plasma creatinine and skin gadolinium concentration at sacrifice in rats receiving five consecutive daily injections of gadodiamide (2.5 mmol/kg) following adenine diet for either 8 days (study 1) or 14 days (study 2). Dotted lines indicate 95% confidence limits.



- Tissue retention and other effects in juvenile rats

Juvenile animals are a model of interest because of the immaturity of the kidney function in the early stage of life.

Gadoterate meglumine was tested in neonatal and juvenile (pre- and post-weaning) rats following a single intravenous (i.v.) administration at 10 days of age (PND 10) or repeat i.v. administration every four days from 10 days to 4 weeks of age (PND 30). The dose levels were 0.6, 1.25 and 2.5 mmol/kg/day. The animals were sacrificed either after the single or last treatment or after a 60 day-treatment-free period [study DGD-33-041 and published by Giorgi et al. (84)].

Based on plasma area under the curve (AUC) measurements, there was no accumulation of gadoterate observed after 6 administrations and a decrease in exposure was even observed on PND 30 in comparison with PND 10. Gadoterate being excreted by urinary route, this difference in AUC between PND 10 and PND 30 is attributed to the maturation of the kidney function and the consequential accelerated urinary excretion.

Assays of total gadolinium in liver, bone, kidneys and skin showed that only traces of gadolinium were quantifiable almost exclusively in the kidneys (excretory organ) two months after a single or repeat administration. By comparing organ gadolinium concentrations after single or repeat dosing, no accumulation of gadolinium was observed in any of the assessed organs and at any dose (see Table 35 - Table 36 - Table 37 - Table 38). Precisely about organ gadolinium concentrations, the following observations can be made:
- At the end of the treatment period, total gadolinium concentrations in tissues increased proportionally with increasing dose, which is completely normal and expected.

- The gadolinium concentrations were similar after single (subgroup D) and repeat dosing (subgroup B), suggesting no accumulation of gadolinium in any tissue (most concentrations after repeat dosing are even lower than after single dose).
- At the end of the treatment-free period in almost all animals, only kidney (excretory organ) gadolinium concentrations were quantifiable.
- At the end of the dosing period, comparable gadolinium concentrations (nmol Gd/g) were found in the kidneys between single and repeat doses (subgroup D versus subgroup B – see Table 38): 278 ± 225 vs. 448 ± 71 at low dose, 1014 ± 458 vs. 915 ± 138 at intermediate dose and 1595 ± 1013 versus 1805 ± 300 at high dose.
- At the end of the treatment-free period (comparing subgroup A and subgroup C), it is the same observation (1.4 ± 1.6 vs. 0.3 ± 0.5 at the low dose and 2.7 ± 1.8 vs. 0.4 ± 0.6 at the intermediate dose). Only at the high dose, a marginally higher concentration was observed after repeat dose (9.8 ± 6.2 vs. 1.0 ± 0.6 after single dose) but this is in the same order of magnitude and knowing the standard deviation, we cannot conclude at a significant difference.

Gadolinium was not measured in the brain in this study as it was done before the brain Gd deposition issue arose, but as we do not observe gadolinium accumulation in organs like skin, liver, bone and kidneys, there is no reason to believe in any risk of accumulation in brain with gadoterate based on this study.

Table 35: Total gadolinium in bone (juvenile rats)

Bone (concentration, nmol Gd/g)	**Subgroup A** (single dose – sacrifice after a 60-day treatment-free period)	**Subgroup B** (repeated doses – sacrifice after the last treatment)	**Subgroup C** (repeated doses – sacrifice after a 60-day treatment-free period)	**Subgroup D** (single dose – sacrifice 24 hours after treatment)
Control	< LOQ (1)	< LOQ (1)	< LOQ (1)	< LOQ (1)
Low dose (0.6 mmol/kg)	< LOQ (1 or 2)	4.5 to 8 **5.89 (±1.18)**	< LOQ (2)	2.3 to 12 **6.14 (±4.06)**
Mid dose (1.25 mmol/kg)	< LOQ (1 or 2)	9 to 15 **13.3 (±1.85)**	< LOQ (2)	7.2 to 42 (7.2 to 26.3 but 42) **20.9 (±9.59)**
High dose (2.5 mmol/kg)	< LOQ (1 or 2)	25 to 39 **30.2 (±4.67)**	< LOQ (2) except 4 values from 1.1 to 1.3 **0.401 (±0.593)**	1.1 to 65 **35.7 (±21.4)**

(1): LOQ = 0.509 nmol/g (2): LOQ = 1.02 nmol/g.
Mean ± SD values are indicated in bold.

Table 36: Total gadolinium in skin (juvenile rats)

Skin (concentration, nmol Gd/g)	**Subgroup A** (single dose – sacrifice after a 60-day treatment-free period)	**Subgroup B** (repeated doses – sacrifice after the last treatment)	**Subgroup C** (repeated doses – sacrifice after a 60-day treatment-free period)	**Subgroup D** (single dose – sacrifice 24 hours after treatment)
Control	< LOQ (1)	< LOQ (1)	< LOQ (1)	< LOQ (1)
Low dose (0.6 mmol/kg)	< LOQ (1)	7 to 14 **9.79 (±1.76)**	< LOQ (1)	6 to 69 **34.3 (±36.7)**
Mid dose (1.25 mmol/kg)	< LOQ (1)	15 to 25 **21.2 (±3.19)**	< LOQ (1)	18.5 to 380 (most values around 40 to 60) **95.7 (±101)**
High dose (2.5 mmol/kg)	< LOQ (1)	35 to 69 **48.3 (±9.15)**	< LOQ (1)	61 to 198 **109 (±43.2)**

(1): LOQ = 0.509 nmol/g.

Mean ± SD values are indicated in bold.

Table 37: Total gadolinium in liver (juvenile rats)

Liver (concentration, nmol Gd/g)	**Subgroup A** (single dose – sacrifice after a 60-day treatment-free period)	**Subgroup B** (repeated doses – sacrifice after the last treatment)	**Subgroup C** (repeated doses – sacrifice after a 60-day treatment-free period)	**Subgroup D** (single dose – sacrifice 24 hours after treatment)
Control	< LOQ (1)	< LOQ (1)	< LOQ (1)	< LOQ (1) except 1 value at 0.62
Low dose (0.6 mmol/kg)	< LOQ (1)	10 to 19 **15.7 (±3.06)**	< LOQ (1)	1 to 34 **16.7 (±11.7)**
Mid dose (1.25 mmol/kg)	< LOQ (1)	20 to 41 **35.0 (±6.10)**	< LOQ (1)	26 to 141 **72.4 (±33.8)**
High dose (2.5 mmol/kg)	< LOQ (1)	63 to 99 **78.3 (±10.4)**	< LOQ (1) except 2 values 0.6 and 1.7 **0.196 (±0.515)**	3.7 to 220 **114 (±76.3)**

(1): LOQ = 0.509 nmol/g.

Mean ± SD values are indicated in bold.

Table 38: Total gadolinium in kidneys (juvenile rats)

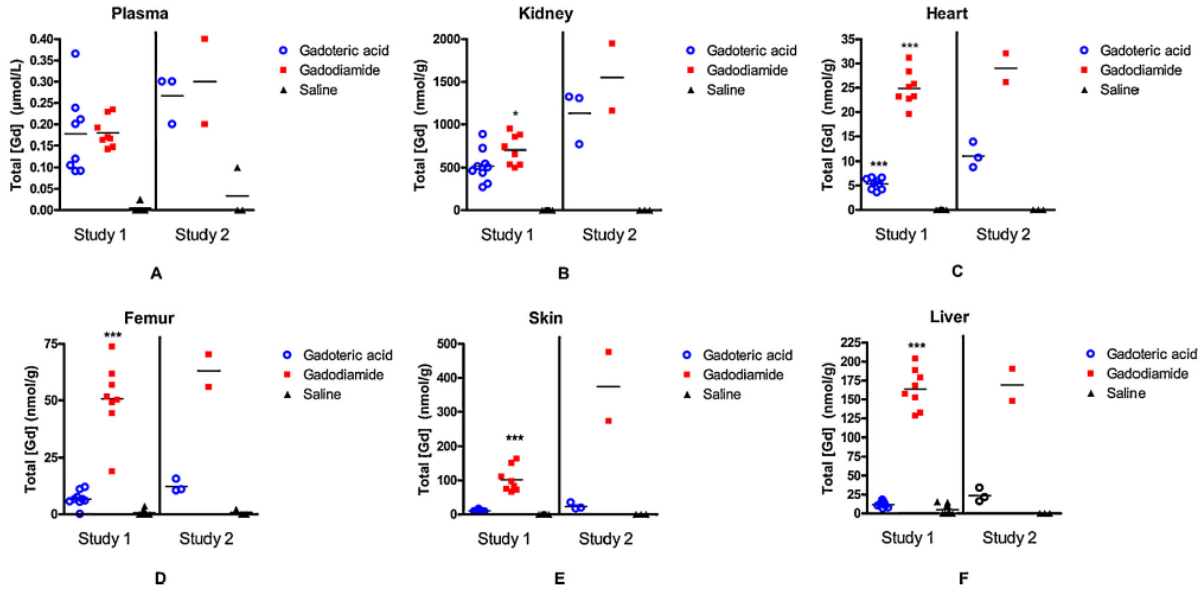
Kidneys (concentration, nmol Gd/g)	**Subgroup A** (single dose – sacrifice after a 60-day treatment-free period)	**Subgroup B** (repeated doses – sacrifice after the last treatment)	**Subgroup C** (repeated doses – sacrifice after a 60-day treatment-free period)	**Subgroup D** (single dose – sacrifice 24 hours after treatment)
Control	< LOQ (1)	< LOQ (1)	< LOQ (1)	< LOQ (2)
Low dose (0.6 mmol/kg)	Most values < LOQ (1) but few values from 0.5 to 1.2 **0.28 (±0.449)**	307 to 566 **448 (±71)**	0.6 to 5.7 and few values < LOQ (1) **1.37 (±1.57)**	1.4 to 803 **278 (±225)**
Mid dose (1.25 mmol/kg)	Most values < LOQ (1) but few values from 0.5 to 1.9 **0.415 (±0.602)**	685 to 1110 **915 (±138)**	0.6 to 6.7 One value < LOQ (1) **2.74 (±1.85)**	360 to 1740 **1014 (±458)**
High dose (2.5 mmol/kg)	0.7 to 2.2 and few values < LOQ (1) **1.05 (±0.641)**	1440 to 2300 **1805 (±300)**	3 to 22 **9.76 (±6.18)**	50 to 2810 **1595 (±1013)**

(1): LOQ = 0.509 nmol/g (2): LOQ = 1.02 nmol/g.
Mean ± SD values are indicated in bold.

Furthermore, in this study, there was no treatment-related death. Eye opening occurred in all rats between PND 13 and PND 17. The gripping reflex and papillary and auditory reflexes were not affected by treatment (following single or repeat dosing). No abnormalities of behavioral tests (watermaze and open field tests) were observed in pups following repeat doses of gadoterate meglumine. No effect on sexual maturation was observed in male and female pups.

The tissue retention differences between linear and macrocyclic GdCA has been also investigated in another juvenile rats study (85). In heart, femur, skin, liver and kidney, totale Gd concentration were significantly higher (10-fold higher in some tissues) in animals that received gadodiamide compared to those who received gadoterate ($p<0.05$): Figure 40.

Figure 40: Total Gd concentration measured in different tissue of Juvenil Rats treated with 5*2.5 mmol/kg of gadodiamide (85).



In this study, gadodiamide induced mortality, alopecia and hyperpigmentation of dorsal skin.

In the review article by Idee *et al* (81), based on the analysis of more than 40 nonclinical studies, authors concluded that the potential presence of free Gd3+may lead to toxic effects extending well beyond NSF.

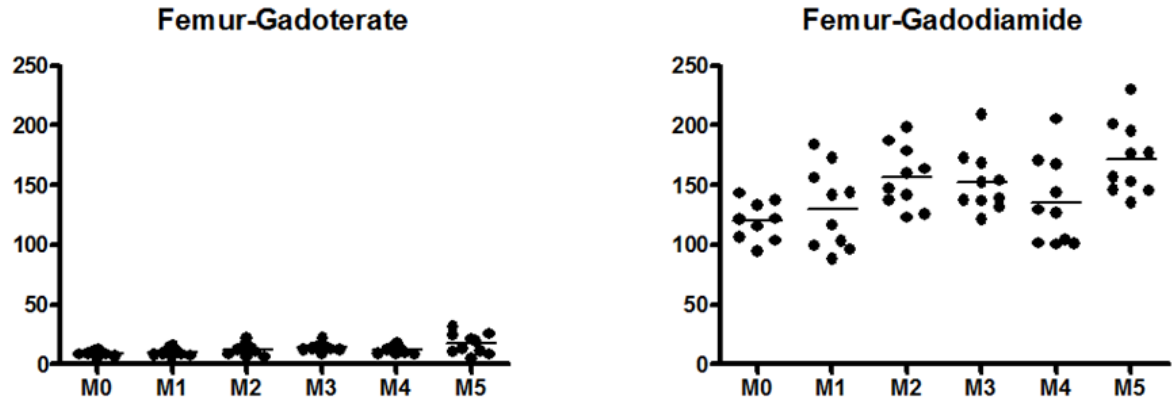
5.1.4 Hypothesis of deep long-term storage compartment

Gd levels found in the brain of the treated animals were found to be much lower compared to Gd levels found in other organs, such as skin. In these studies, laser ablation coupled with ICP-MS was used to visualize the tissue distribution pattern of gadolinium. Measurements made in the brain revealed a local presence of Gd in the DCN (including the dentate nucleus in humans) only for gadopentetate dimeglumine but not for gadobutrol. These studies also indicated that the Gd concentrations in the skin correlated with concentrations found in the brain but Gd concentrations in the skin were found to be higher.

In the Guerbet study ER-16-00005 (on going, not published), Gd concentrations found in the bones of normal rats exposed to repeat administration of gadodiamide or gadoterate, were approximately 50-fold higher as compared to those measured in the brain: in the range of 15 nmol/g after repeat injection of gadoterate and in the range of 150 nmol/g after repeat injection of gadodiamide.

In the femur, total Gd is 10-fold higher after gadodiamide as compared to gadoterate: Figure 41.

Figure 41: Evolution of total Gd concentration (n=10 animals/ delay) in femur (nmol/g) during 5 months after repeat injection of Gadodiamide or Gadoterate dimeglumine (unpublished). M0: just after the last injection to M5: 5 months after the last injection



As proposed by Lancelot (77), this suggests the bone as a deep storage compartment for the less stable GdCA: "Using a nonconventional pharmacokinetic approach, it was shown that gadoterate meglumine undergoes a much faster residual excretion from the body than the linear GBCAs, a process that seems related to the thermodynamic stability of the different chelates. Gadolinium dissociation occurs in vivo for some linear chelates, a mechanism that may explain their long-term retention and slow release from bone."

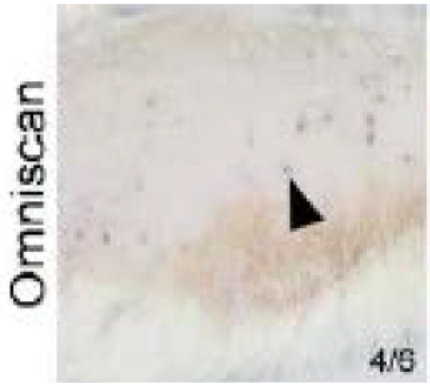
5.1.5 Impact on general health status of the animals: skin lesions, weight loss, increase morbidity/mortality

Early studies investigating the toxicity of gadolinium (Gd) showed that when injected directly into the CNS, GdCA have a neurotoxic potential (86, 87) associated with dose-dependent morphologic and behavioural changes. Ray *et al.* showed that gadodiamide, when administered into the lateral ventricle of rats at high doses produced predominately acute cerebellar changes (87).

Gadolinium has also been shown to be toxic in nonclinical studies, with effect including cellular necrosis, fibrosis, and lesions related to mineral deposition (88, 89), and in one *in vitro* study in rat neurons, gadolinium-induced cytotoxicity via oxidative injury was reported (90).

In a study in healthy rats (82), macroscopic and histological skin changes similar to those seen in NSF patients were observed in rats receiving gadodiamide: Figure 42.

Figure 42 : Skin lesions after gadodiamide injection



(from Sieber *et al*, (82))

In renally-impaired rats, the linear GdCAs gadodiamide, gadopentetate and gadobenate were associated with an increase in the r_1 relaxivity value, unlike the macrocyclic GdCAs gadobutrol and gadoterate. This effect was found both in the skin and the femur. The increase in the r_1 relaxivity value is likely the consequence of a gradual dissociation of linear GdCAs in tissues with release of dissociated and soluble Gd, while the macrocyclic agents had no effects (83). As describe in section 5.1.1, this release of dissociated Gd is prone to induce toxicity.

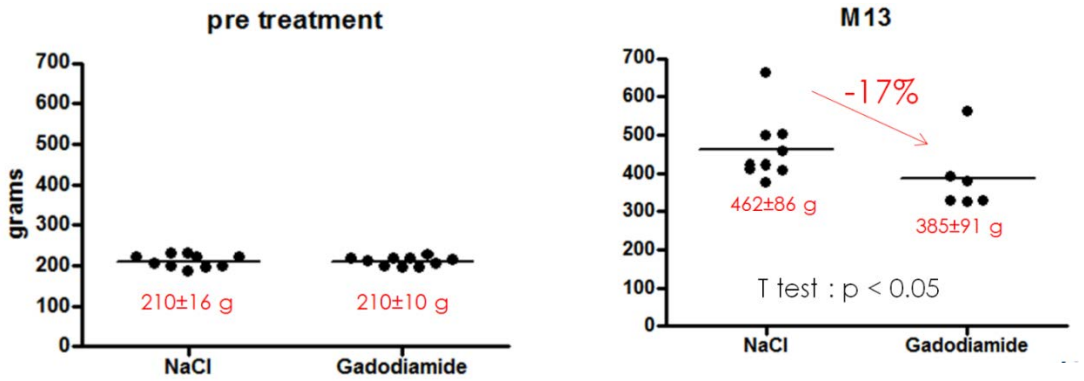
In the Guerbet study ER-15-00019 (unpublished), general health status has been followed during 1-year after the last injection of linear Gadodiamide. In this study, four deaths over ten rats including in this group occurred during the follow-up period:

- In the saline group, 1 death at M0 due to anaesthesia overdosing.
- In the gadodiamide group, 1 unexplained death (M0), 3 ethically sacrificed (1M0, 2M1) because of pain with visible skin lesions: Figure 43

Figure 43: Skin lesion in a rat with no kidney impairment treated with repeat administration of gadodiamide (total dose of 12 mmol/kg over 5 weeks of injection)

Moreover, the rats treated with gadodiamide had a 17% decrease in body weight compared with saline-treated rats ($p<0.005$, t-test): Figure 44

Figure 44: Evolution of the weights of the animals in the saline (NaCl 0.9%) and gadodiamide groups at the start (week 1 = pre-treatment) and at the end of the study (M13 = 14 months after the start).



As a last example, in juvenile rats received 5 intravenous administrations (between postnatal day [PND] 4 and 18) of gadoterate, gadodiamide (both GdCAs: 5 x 2.5 mmol/kg) or saline, and were sacrificed at PND 25, it has been shown that Gadodiamide induced mortality, alopecia and hyperpigmentation of dorsal skin. Two gadodiamide-treated rats presented severe epidermal and dermal lesions. No abnormal signs were detected following administration of gadoterate.

5.1.6 Nonclinical studies conclusion

From 2006 and 2014, a large amount of preclinical data has been produced by some GdCA NDA holders and academic teams to investigate the underlying conditions of NSF occurrence. As a result, between 2010 and 2013, health authorities and medical societies promptly issued guidelines according to which, along with other recommendations, administration of certain GdCA belonging to the linear molecular class was contraindicated in patients with an estimated glomerular filtration rate less than 30 mL/min/1.73 m^2.

In 2015, Kanda et al. demonstrated that repeat injections of GdCA induce a Gd retention in the Brain (91). This has been first reproduced in a rat model by the Guerbet research group (66), providing a translational model that replicates the Gd brain accumulation and cerebellum T1 signal intensity reported in patients.

Data for Gd retention in tissues such as skin, bone and brain may be linked with chemical stability of contrast agent. The higher is the stability (macrocyclic agents) the lower is the Gd retention in all organs and tissues.

Recent studies have provided important insights into the molecular form of Gd present in the brain and highlights a clear difference in the fate of Gd in the brain following administration of either linear or macrocyclic agents with, in the case of linear GdCAs, the concomitant presence of 3 separate and distinctive forms (70). As described in this document, our group reproduced these results (demonstration of the modification of the chemical form of Gd after

linear contrast agent repeat injection) and extended these observations to long-term follow-up (up to 5 months after the last injection).

Based on current available nonclinical data, one can conclude that both linear and macrocyclic agents have the ability to distribute into the brain and other tissues such as skin and bones. Gd deposits after linear agents are retained and persist for up to one year or longer in rats. Macrocyclic agents are much faster cleared from the brain, resulting to a 30-fold lower concentration in cerebellum 5 months after the last injection. Furthermore, it has been shown that different chemical forms of Gd are present in the brain with linear GdCA, where no evidence of Gd release has been observed with macrocyclic agents. Investigations to better characterize these Gd form(s) into the brain are still going on.

Histological toxicity of Gd ion realised by low stability GdCA is extensively demonstrated as well as skin lesion in renally-impared rats and healthy rats. Increased morbidity is found after repeat administration of the less stable GdCA gadodiamide.

No studies have reported any signs of neurotoxicity associated with retained Gd up to 50 weeks post-dosing, so far. No histopathology findings have been reported with Gd levels up to approximately 4 nmol/g brain tissue. Although no clinical effects regarding Gd deposition has been reported, it is important to note that long-term safety data are very limited.

As a summary:

- GdCA entrance into the brain through the CSF route (plexus choroids) have been demonstrated
- Based on analytical measurement methods, Gd was detected in brain regions with all GdCA tested, with a 4 to 30 fold increase for linear agents compared to macrocyclic agents. Furthermore, the Gd clearance from brain tissue of macrocyclic agents occurred at a much faster rate.
- Based on MRI, T1 enhancement in the cerebellum/DCN was observed only with linear agents.
- Based on speciation analysis, it has been evidenced that different chemical forms of Gd were detected with linear agents (insoluble form, soluble form associated to macromolecules, small molecule soluble form attributed to intact GdCA, insoluble form) whereas only small molecule soluble form attributed to intact GdCA was observed for macrocyclic agents.
- Based on analytical measurement methods, Gd retention in tissues such as skin, bone have been observed with a similar behaviour but in higher quantity than in the brain.The highest is the stability (macrocyclic agents) the lower is the Gd retention in all organs and tissues.
- Data on kinetic and thermodynamic stabilities, as well as in vitro and nonclinical studies, strongly suggest that linear gadolinium-containing contrast agents (GdCAs) release gadolinium from the ligand molecules.
- So far, no animal studies have reported any signs of neurotoxicity.

5.2 PHARMACOKINETIC DATA

In a recent meta-analysis, Lancelot has compared the pharmacokinetic profiles of the different GdCAs in humans (77). A long-term residual excretion phase in urine was found suggesting

the existence of a deep compartment for gadolinium storage, slow release into the blood stream and slow excretion via the renal route. As illustrated in the figure below, there was a correlation between the slope of this residual excretion phase and the thermodynamic constant of the GdCAs.

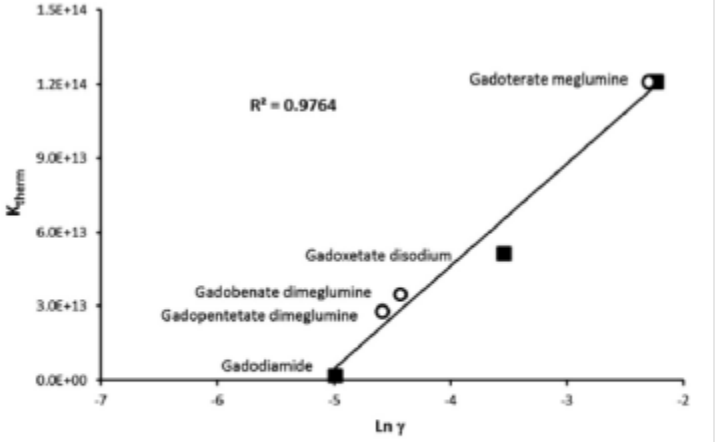


FIGURE 4. Correlation between the thermodynamic stability constants (K_{therm}) and the logarithm of the rate constants (γ) of the residual excretion phase of GBCAs. Each point represents a different contrast agent. The values were calculated from plasma and urine data from healthy volunteers (black dots) or animals (white dots).

(From Lancelot, 2016 (77))

This correlation means that the lower the thermodynamic stability of the GdCAs, the more prolonged their residual excretion and thus the higher the Gd accumulation in a deep compartment.

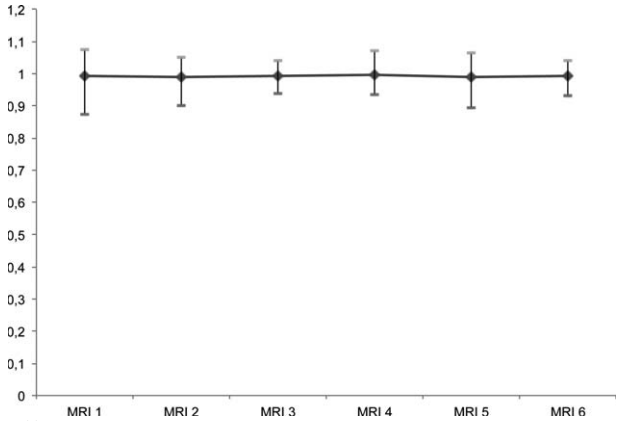
5.3 CLINICAL STUDIES

5.3.1 Gadolinium accumulation in brain

5.3.1.1 Patients with relapsing–remitting multiple sclerosis (RRMS)

Patients suffering from RRMS have an increased permeability of the blood–brain barrier as part of the inflammatory process in the brain parenchyma, which theoretically might increase the risk of gadolinium deposition. Eisele et al. showed, after at least 6 (6 to 12) gadolinium-enhanced examinations with a single dose of Dotarem® in 41 RRMS patients, that signal intensity (SI) ratio differences did not differ between the first and last MRI examination, neither for the dentate nucleus (DN)-to-pons ratio (P=0.594) nor for the DN-to-cerebellum ratio (P=0.847) (92). A detailed focus is shown on Figure 45 that illustrates the stability of DN-to-pons signal intensity ratio of 6 MRI examinations in chronological order of all included patients. Furthermore, the study showed no correlation between the mean DN-to-pons, or between the mean DN-to cerebellum SI ratio and the number of MRI examinations (P=0.848 and 0.891), disease duration (P=0.676 and 0.985), and expanded disability status scale (EDSS) (P=0.639 and 0.945).

Figure 45: Plot of the dentate nucleus-to-pons signal intensity ratio of 6 MRI examinations in chronological order of all included patients demonstrating stable signal intensities throughout the observation period



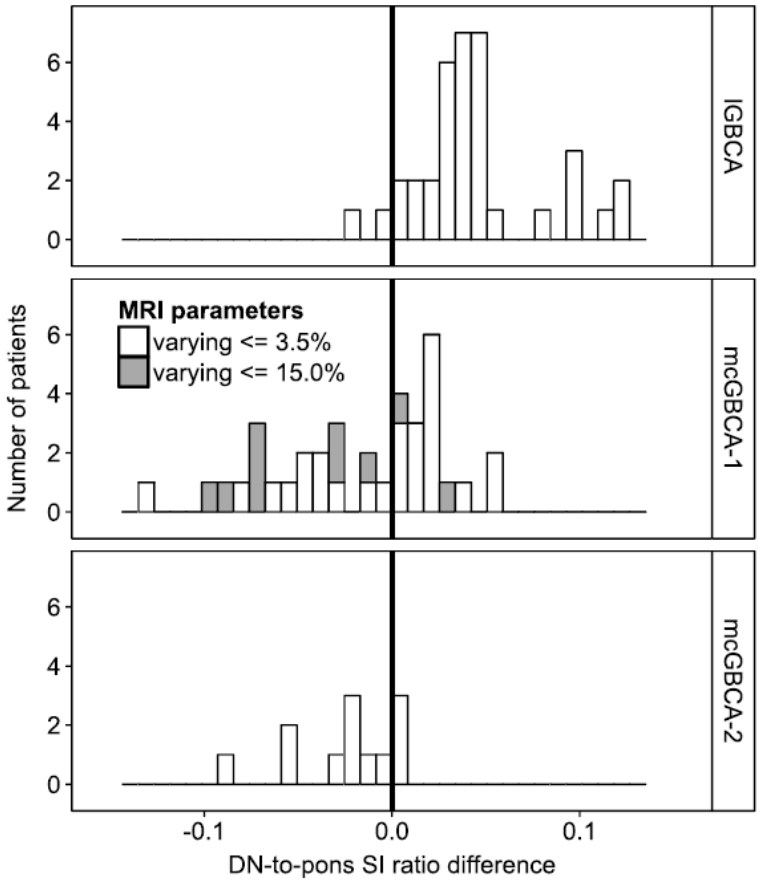
(from Eisele P et al. 2016 (92)).

5.3.1.2 Comparison of L-GdCAs versus M-GdCAs

The results published by Eisele only concerned gadoterate. A comparison between several M-GdCAs, including gadoterate and L-GdCAs was performed by Radbruch et al. in two studies summarized below.

The aim of the first study was to compare DN-pons SI ratio changes on unenhanced T1-weighted MRIs in patients who first received a series of administrations of gadopentetate dimeglumine (L-GdCA), and subsequent serial applications of the M-GdCAs gadobutrol (M-GdCA-1) and gadoterate (M-GdCA-2) (93). A total of 36 patients were included. Most of them presented a glioma (n=21), the other patients, a lymphoma (n=3) or other medical condition (n=1). All patients underwent at least 5 consecutive administrations of gadopentetate dimeglumine followed by an equal number of consecutive administrations of gadobutrol. In 12 of the 36 patients, 5 or more final consecutive injections of gadoterate were analyzed additionally. The difference of DN-pons SI ratios on unenhanced T1-weighted images was calculated by subtracting the ratio at the first examination from the ratio at the last examination in each of the 3 periods. The results showed that the mean DN-pons SI ratio difference in the gadopentetate dimeglumine period was significantly greater than 0 (mean ± SD, 0.0448 ± 0.0345; P< 0.001), whereas the mean DN-pons SI ratio difference in the subsequent gadobutrol and gadoterate period was significantly smaller than 0 (gadobutrol: −0.0178 ± 0.0459, P= 0.026; gadoterate meglumine: −0.0250 ± 0.0284, P= 0.011). The authors concluded that the application of gadopentetate dimeglumine was associated with a DN-pons SI ratio increase, whereas subsequent applications of gadobutrol or gadoterate in the same patients were not. Rather, the current data tentatively suggested a decrease in preexisting hyperintensities over time when L-GdCAs are changed to M-GdCAs, potentially indicating a washout effect or precipitation of gadolinium. Figure 46 illustrates the distribution of patients among the 3 sequences: L-GdCAs, M-GdCAs-1 and M-GdCAs-2 (gadoterate).

Figure 46: Distribution of DN-to-pons SI ratio differences for L-GdCA (gadopentetate dimeglumine), M-GdCA-1 (gadobutrol), and M-GdCA-2 (gadoterate)



(from Radbruch A et al. 2016, (93)

For M-GdCA-1, the additionally assessed subgroup with MRI parameters varying between 3.5% and 15% is displayed with grey bars.

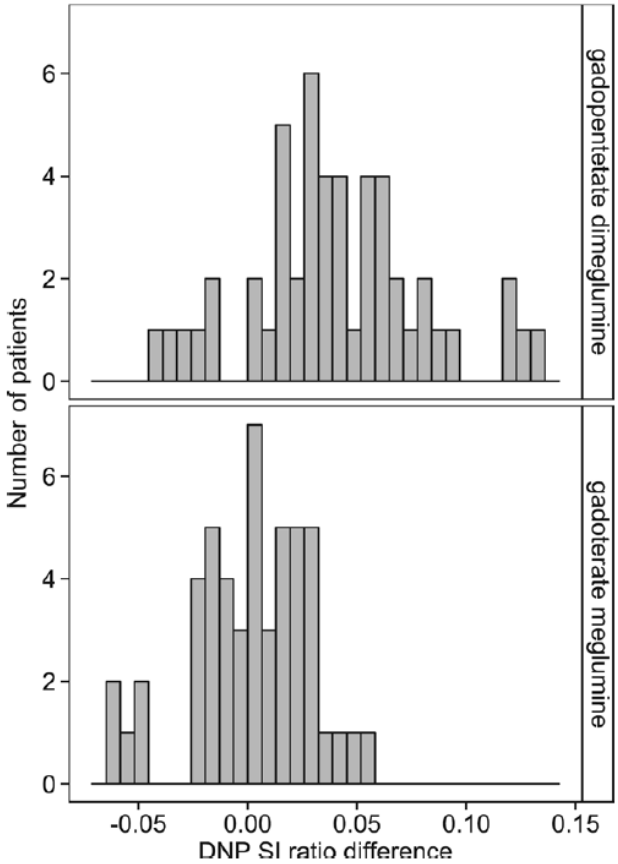
The second study aimed to compare, retrospectively, changes in SI ratios of the DN and the GP to those of other structures on unenhanced T1-weighted MR images between L-GdCAs and M-GdCAs in two groups of 50 patients (94).

The patients underwent at least six consecutive MR imaging examinations with the exclusive use of either gadopentetate dimeglumine or gadoterate. The difference in mean SI ratios of DN-to-pons and GP-to-thalamus on unenhanced T1-weighted images from the last and first examinations was calculated. One-sample and independent-sample *t* tests were used to assess the difference in SI ratios for both groups, and regression analysis was performed to account for potential confounders.

The results showed that the SI ratio difference in the linear group was greater than 0 (mean DN difference +/- standard deviation, 0.0407 +/- 0.0398 [P <0.001]; GP, 0.0287 +/- 0.0275 [P <0.001]) and significantly larger (DN, P <0.001 and standardized difference of 1.16; GP, P<0.001 and standardized difference of 0.81) than that in the macrocyclic group, which did

not differ from 0 (DN, 0.0016 +/- 0.0266 [P = 0.680]; GP, 0.0031 +/- 0.0354 [P = 0.538]). The SI ratio difference between the last and first examinations for the DN remained significantly different between the two groups in the regression analysis (P < 0.001) as shown on Figure 47.

Figure 47: Distribution of DN-to-pons SI ratio differences between the last and first MR imaging examinations for the two patient groups



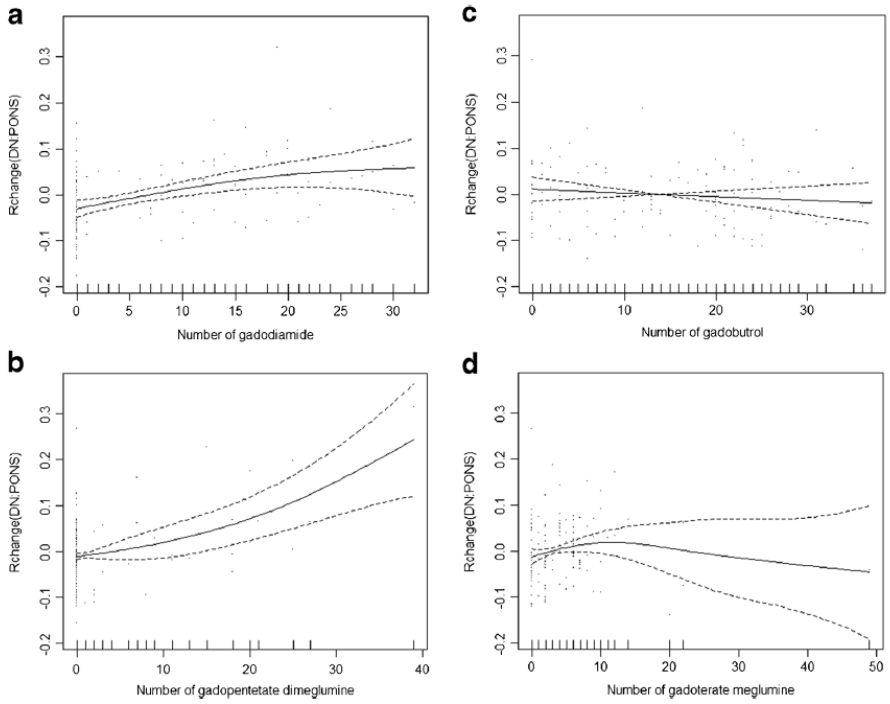
[From Radbruch et al. 2015, (94)]

This study indicates that an SI increase in the DN and GP on T1-weighted images is caused by serial application of gadopentetate dimeglumine but not by gadoterate. However, the number of MR imaging procedures might not be sufficient to detect any SI increase with M-GdCAs.

To answer this question, in a retrospective study where 122 patients underwent a least ten-times a double-dose GdCA-enhanced MRI, Bae et al. analysed GP-to-thalamus (TH) SI ratio, DN-to-pons SI ratio and relative change (Rchange) between the baseline and final examinations (95). The relationships between Rchange and several factors, including number of each GdCA administrations, were analysed using a generalized additive model. In total, 6 patients (4.9%) received L-GdCAs (mean 20.8 number of administration; range 15–30), 44 patients (36.1%) received M-GdCAs (mean 26.1; range 14–51, including 30 patients who received gadoterate) and 72 patients (59.0%) received both types of GdCAs (mean 31.5; range 12–65). Inter-observer agreement was almost perfect (0.99; 95% CI: 0.99–0.99). Rchange (DN:pons) was associated with gadodiamide (p= 0.006) and gadopentetate dimeglumine (p < 0.001), but not with other GdCAs, Figure 48. Rchange (GP:TH) was not associated with GdCA

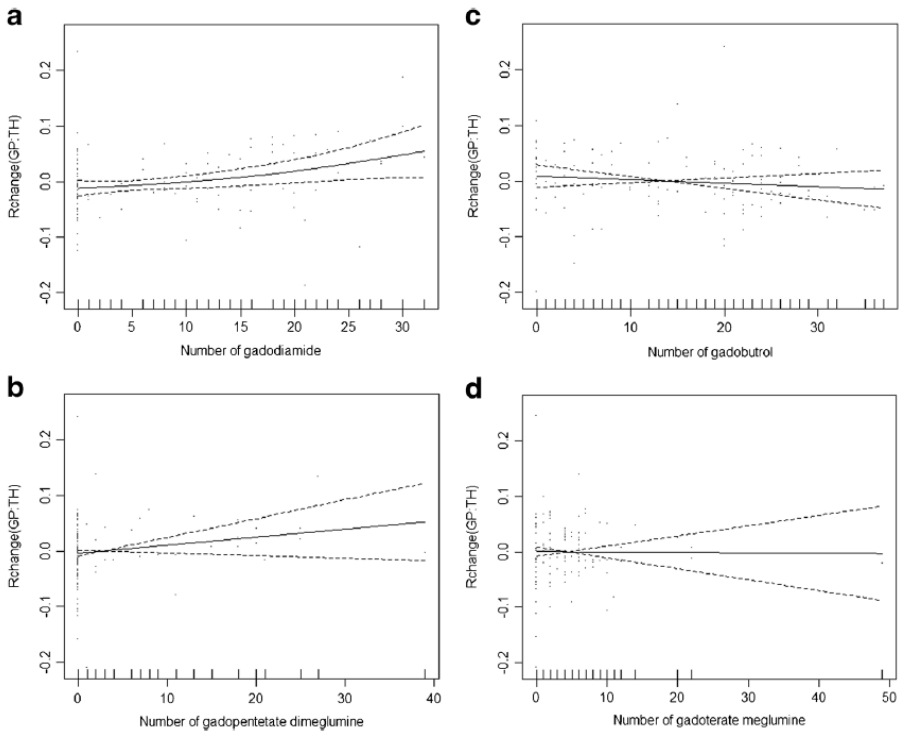
administration, Figure 49. The authors concluded that previous administration of linear agents gadodiamide and gadopentetate dimeglumine is associated with increased T1 signal intensity in the DN, whereas M-GdCAs do not show any association.

Figure 48: Rchange for DN:pons between the baseline and final MRI according to the number of administrations of (a) gadodiamide, (b) gadopentetate dimeglumine, (c) gadobutrol and (d) gadoterate meglumine



(From Bae S. et al. 2017, (95)).

Figure 49: Graphs of Rchange for GP:TH between the baseline and final MRI according to the number of administrations of (a) gadodiamide, (b) gadopentetate dimeglumine, (c) gadobutrol and (d) gadoterate meglumine

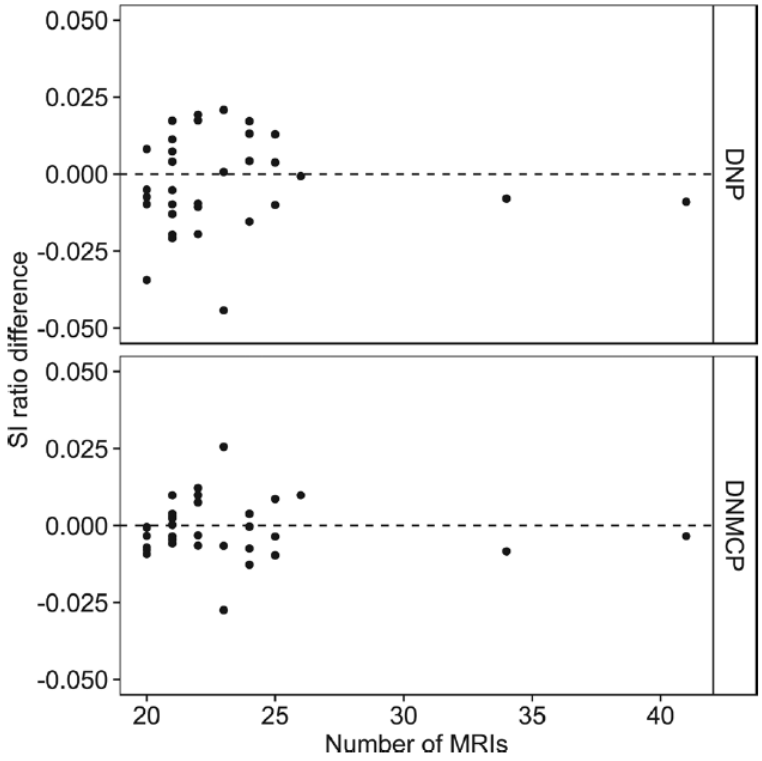


(From Bae S. et al. 2017, (95)).

Another retrospective study analysed the effect of more than 20 serial injections of M-GdCAs on the SI of DN on unenhanced T1-weighted MR images (96). In the study, 33 patients underwent at least 20 consecutive MR imaging examinations (plus an additional MR imaging for reference) with the exclusive use of M-GdCAs (gadoterate or gadobutrol). SI ratio differences were calculated for DN-to-pons and DN-to-middle cerebellar peduncle (MCP) ratios by subtracting the SI ratio at the first MR imaging examination from the SI ratio at the last MR imaging examination. One-sample *t* tests were used to examine if the SI ratio differences differed from 0, and Bayes factors were calculated to quantify the strength of evidence for each test.

In all, the patients underwent a mean of 23.03+/-4.2 GdCA administrations (mean accumulated dose, 491.21+/-87.04 mL of a 0.5 Mol/L GdCA solution) with an average of 12.09+/- 2.16 weeks between every administration. As shown on Figure 50, the distribution of SI ratio difference is on both sides of zero without statistical significance (DN-to-pons ratio: -0.0032 +/- 0.0154, P = 0.248; DN-to-MCP ratio: -0.0011 +/- 0.0093, P = 0.521).

Figure 50: Scatterplot of the number of enhanced MR imaging examinations and the SI ratio differences between the first and last MR imaging examination by using either the DN-to-pons (DNP) or the DN-to-MCP (DNMCP) ratios



(From Radbruch A. et al. 2017 (96)).

The authors concluded that 20 or more serial injections of M-GdCAs administered with on average 3 months between each injection are not associated with an SI increase in the DN.

Altogether, the results of the 5 studies quoted above did not evidence any SI increase in the DN after Dotarem® administration, even after numerous injections to the same patients. The studies were performed in adults and the results were not yet described in children, a population also potentially exposed to GdCAs and at risk, particularly in very young children, due to age-related immature renal function.

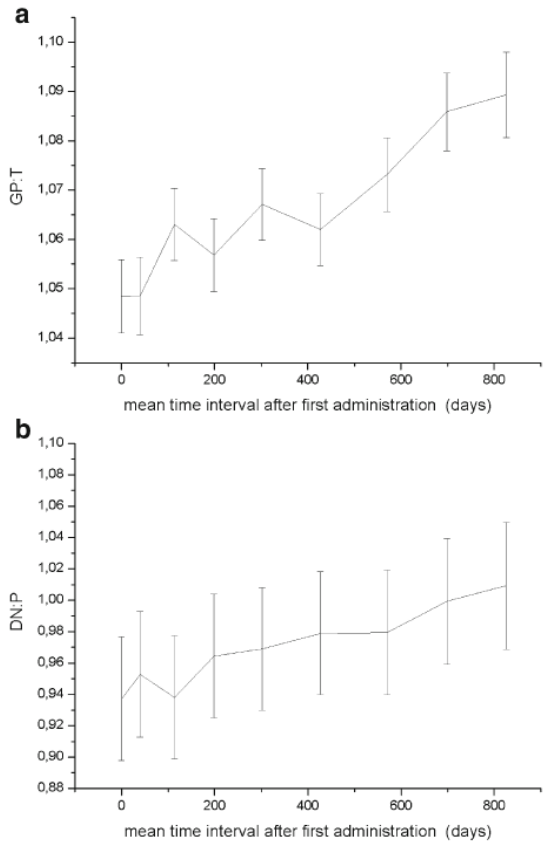
5.3.1.3 Comparison of L-GdCAs versus M-GdCAs in children

For this purpose Espagnet et al. studied the effect of multiple administrations of a M-GdCA on signal intensity in the globus pallidus and dentate nucleus of the pediatric brain on unenhanced T1-weighted MR images (97). They performed a retrospective study with 50 patients, mean age: 8 years (SD: 4.8 years), with normal renal function and exposed to ≥6 administrations of Dotarem® (see Table 39). The patients were partially compared to a control group of 59 age-matched GdCA-naïve patients.

The results of the study showed a significant effect of the number of GdCA administrations on relative SI GP-to-thalamus (P=0.002) and dentate nucleus-to-pons (P=0.021) over time (see Figure 51): the relative signal intensities were higher at last MR examination than at baseline (P<0.001). The authors concluded that quantitative analysis evaluation of GP:thalamus and

DN:pons of the pediatric brain demonstrated an increase after serial administrations of M-GdCA and that further research was necessary to fully understand GdCA pharmacokinetic in children.

Figure 51: Signal intensity by increasing number of administrations of gadoterate meglumine. The x-axis measures time (days) from the first gadolinium administration. a Relative signal intensity globus pallidus-tothalamus (GP:T). b Relative signal intensity dentate nucleus-to-pons (DN:P)



[From Rossi Espagnet MC et al. 2017 (97)]

Table 39: Demographic and patient characteristics by group

Characteristic	Patients (*n*=50)	Controls (*n*=59)
Age (years)	8±4.8 (2–18)[a]	8.4±4.2 (2–18)
Male	32/50 (64%)	30/59 (51%)
Number of MRI examinations	10±2.8 (6–18)[a]	1
Mean interval between first and last MR examinations (days)	933.5±391.6 (235–1692)[a]	N/A
Mean interval between MR examinations (days)	104±78.3 (1–532)[a]	N/A
Diagnoses	Pilocytic astrocytoma of the posterior fossa (*n*=5), craniopharyngioma (*n*=4), dysembryoplastic neuroepithelial tumour (*n*=1), IV ventricle ependymoma (*n*=4), gangliogliomа (*n*=2), grade II astrocytoma (*n*=1), grade III astrocytoma (*n*=3), glioblastoma (*n*=2), pineal gland germinoma (*n*=4), acute lymphoblastic leukemia (*n*=2), non-Hodgkin lymphoma (*n*=1), medulloblastoma (*n*=11), diffuse intrinsic pontine glioma (*n* = 1), brainstem astrocytoma (*n*=1), brain metastases from neuroblastoma (*n*=1), neurocytoma (*n*=1), primitive neuroectodermal tumor (*n*=2), myeloid sarcoma (*n*=1), cavernoma (*n*=1), rhabdomyosarcoma (*n*=1), pineoblastoma (*n*=1).	Headache (*n*=34), mental retardation (*n*=15), epilepsy (*n*=10).
Brain radiotherapy	32	0
Chemotherapy	27	0

N/A not applicable

[a] Mean ± standard deviation (range)

[From Rossi Espagnet MC et al. 2017 (97)]

After reading the article, questionable aspects of the study arose, Guerbet wrote some comments in a letter dedicated to the editor of the review as follows:

> *Dear Editor,*
>
> *Rossi Espagnet and colleagues reported significant increases of the globus pallidus-to-thalamus (GP:T) and the dentate nucleus-to-pons (DN:P) signal intensity (SI) ratios on unenhanced T1-weighted brain magnetic resonance (MR) images from children exposed to multiple injections of the mGdCA, gadoteric acid (Dotarem®) (97). However, this study contains several important inconsistencies and limitations.*
>
> *In the Methods section, the authors wrote that each control subject was matched to a patient for age at both first and last MR examinations. Both groups did not differ statistically at baseline but the results of the comparison at the last examination were not presented, thus precluding any interpretation of the SI ratio increases. Age-dependent changes in native T1-weighted MR contrast of the brain may well account for these effects.*
>
> *In the Results section, the authors correlated the increases in GP:T and DN:P SI ratios to the number of GdCA injections. This association is not consistent with the data from previous studies reporting an absence of correlation between these parameters in children after serial administrations of a linear GdCA (98, 99).*
>
> *In Figure 2 [Figure 51 above], the authors showed the relationships between the SI ratios and the mean time intervals from the first administration. These graphs are misleading because the standard deviations of the time intervals at each GdCA injection were not presented. According to Table 1, the mean interval between the MR examinations varied from 1 day to 532 days. It is likely that the mean time intervals*

reported in Figure 2 [Figure 51 above] were highly heterogeneous from one patient to another or between two injections in the same patient. Short time intervals of one to several days may have resulted in SI increases due to incomplete wash-out of the GdCA molecules from the brain, and possibly to a significant SI ratio increase in some patients.

The authors excluded the effect of a history of radiation therapy to the brain as a possible cause for the SI ratio increases. However, it is probable that these patients with brain tumors underwent additional radiotherapy sessions during the study period. Blood brain barrier disruption induced by radiotherapy may contribute to SI increases following mGdCA injection.

Some of the data reported by the authors in the Results section are not consistent with those that they presented graphically. The authors wrote that the GP:T SI mean value at first MR examination was 1.06±0.04 whereas it was rather equal to 1.048 according to the Figure 2a [Figure 51a above]. Such a mistake may have affected the statistical analyses.

Moreover, Flood and colleagues found that the DN:P SI ratio difference between the last and first MR examinations in children exposed to a linear GdCA was: 1.035-0.995 = 0.04 (98). In the present study, the difference between the DN:P SI mean values was 1.02-0.95 = 0.07. It is difficult to understand how Dotarem® could have triggered a greater SI difference than a linear GdCA without inducing any visible signal enhancement.
Altogether, this exploratory study presented major inconsistencies which could have biased the interpretation of the results.

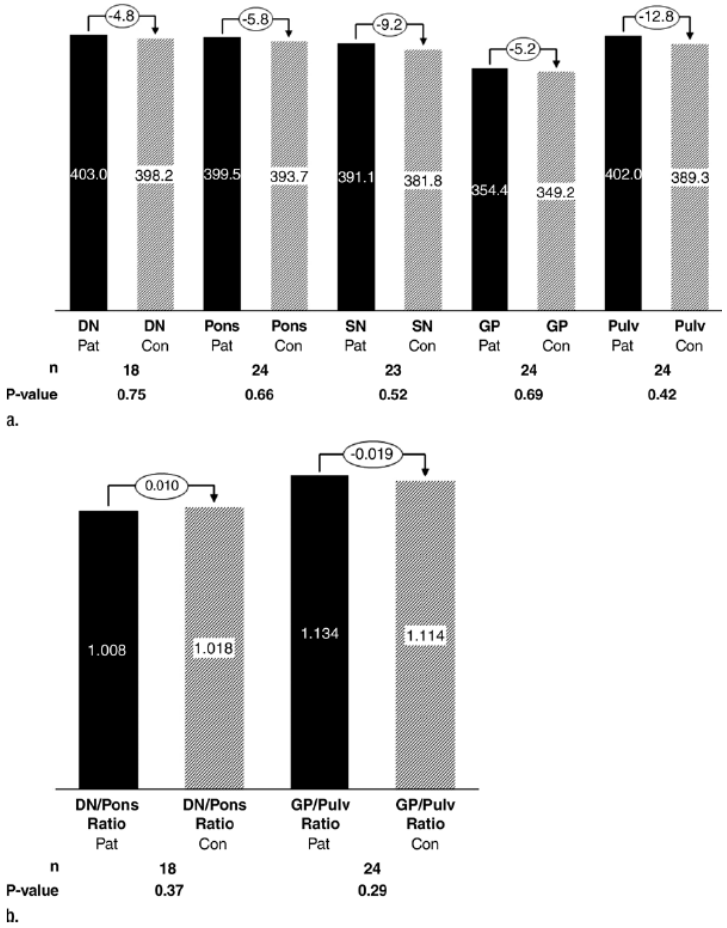
The Guerbet's comments on the likely biases weaken the conclusion of the authors. Moreover, this conclusion is undermined by the results of the study published by Tibussek et al. in 2017 on the same topic (100).

This study aimed to determine whether SI in T1 sequences as a potential indicator of gadolinium deposition in brain, increased after repeat administration of the mGdCAs gadoteridol and gadoterate meglumine in a pediatric cohort.

In this retrospective case-control study, 24 patients aged 5–18 years and appropriate control patients with non-pathologic MR neuroimaging findings (and no GdCA administration), matched for age and sex, were included. SI was measured on unenhanced T1-weighted MR images for the following five regions of interest (ROIs): DN, pons, substantia nigra (SN), pulvinar thalami, and GP. The mean number of 14.2 GdCA administrations was distributed between gadoterate (from 5 to 20) and gadoteridol (from 0 to 6). The results showed that there were no significant differences in mean SI for any ROI and no group differences were found when DN-to-pons and GP-topulvinar ratios were compared (DN-to-pons ratio in case patients: mean, 1.0083 ± 0.0373 [SD]; DN-to- pons ratio in control patients: mean, 1.0183 ± 0.01917; *P*= 0.37; GP-to-pulvinar ratio in case patients: mean, 1.1335 ± 0.04528; and GP-to-pulvinar ratio in control patients: mean, 1.1141 ± 0.07058; *P*= 0.29), see Figure 52 below. Furthermore,

no correlation was found between the number of GdCA administrations or the total amount of GdCA administered, and signal change for any ROI. The authors concluded that multiple intravenous administrations of gadoterate and gadoteridol in children were not associated with a measurable increase in SI in T1 sequences as an indicator of brain gadolinium deposition detectable by using MR imaging.

Figure 52: Bar graphs show mean SI in case patients *(Pat)* and control patients (Con) and their differences for (a) DN, pons, SN, GP, pulvinar (Pulv), and (b) DN-to-pons ratio and GP-to-pulvinar (Pulv) ratio. Below the graphs are results of paired t testing



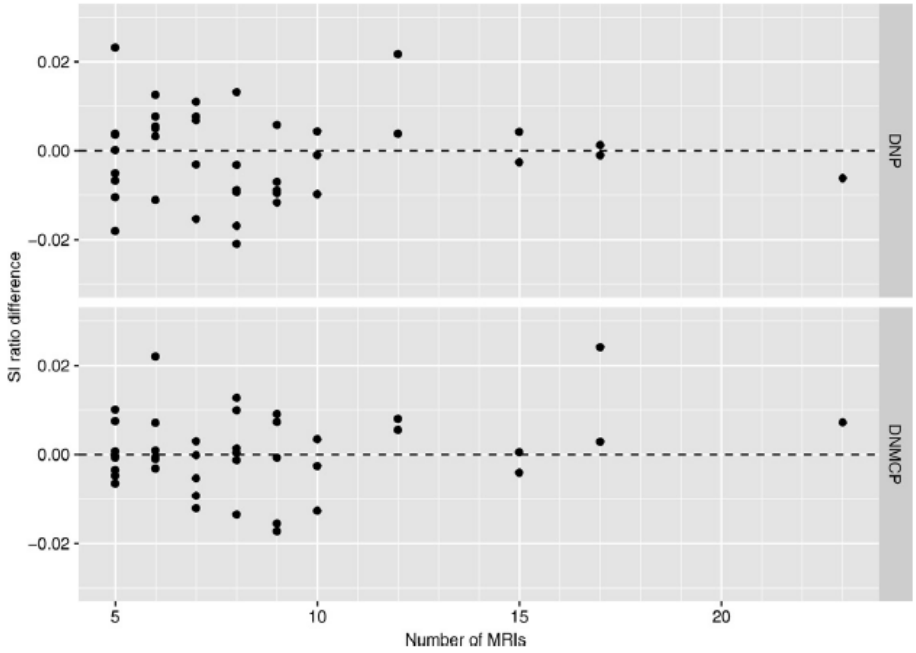
[From Tibussek D. et al. 2017 (100)]

The results that showed no SI increase at the DN level were confirmed with gadoterate by Radbruch et al. in children (101). In a retrospective study, 41 pediatric patients (age range, 3–17 years) were imaged in at least five consecutive MR examinations with the exclusive use of gadoterate. SI ratio differences between the first and last MR examination were calculated for DN-to-pons and DN-to-middle cerebellar peduncle (MCP) ratios. One-sample t-tests were used to examine if the SI ratio differences differed from 0. Bayes factors were calculated to quantify the strength of evidence for each test. In all, the patients underwent a mean of 8.6 +/- 3.9 GBCA administrations with a mean accumulated dose 32.07 mmol +/- 17.62, with an average of 16.7 weeks +/- 7.9 between every administration. Both ratio differences did not differ significantly from 0 (DN-to-pons ratio: -0.0012 +/- 0.0101, P= 0.436; DN-to-MCP ratio:

0.0007 +/- 0.0088, P = 0.604) and one-sided Bayes factors provided substantial evidence against an SI ratio increase (0.10 for DN-to-pons ratio; 0.27 for DN-to-MCP ratio), see Figure 53.

The authors concluded that there was no increase of the SI in the DN after a mean of 8.6 serial injections of gadoterate in pediatric patients, confirming previous studies that did not find this effect after serial injections of M-GdCAs in adults.

Figure 53: Scatterplot of the number of enhanced MR examinations and the SI ratio differences between the first and last MR examination by using either the DN-to-pons or the DN-to-MCP ratio



[From Radbruch A, et al. 2017 (101)]

5.3.2 Gadolinium deposition in other organs than brain

5.3.2.1 Study on hepatic gadolinium deposition in children

Apart from the brain, the presence of gadolinium in tissues was described by Maximova et al. in the liver of children with sickle cell disease (102).

The retrospective study aimed to determine if hepatic gadolinium deposition occurred in pediatric patients with iron overload but normal renal and hepatic function who had undergone GdCA–enhanced magnetic resonance imaging. For this purpose, 21 children, recipients of allogeneic hematopoietic stem cell transplants who underwent GdCA-enhanced MR imaging for suspected infection or relapse followed by liver biopsy were included. The number of GdCA-enhanced MR examinations and cumulative gadolinium dose for each patient was analyzed by comparing liver histologic analysis and iron and gadolinium liver concentration (GLC). Eight patients had siderosis and underwent chelation therapy. The study group was compared with four control patients who were never exposed to GdCA. Statistical analysis was performed with Spearman rank coefficient for correlation. The results showed that all the 21 patients had positive correlations between GLC and total GdCA dose (r = 0.4486; P < 0.05)

and between GLC and liver iron concentration ($r = 0.56$; $P < 0.05$). The patients who underwent deferoxamine therapy had a significant reduction of GLC (from 0.64 µg/g +/- 0.29 to 0.20 µg/g +/- 0.17 [SD]; $P < 0.05$). The authors concluded that in the presence of siderosis, a transmetallation mechanism may be set off between ferric ion and gadoterate meglumine. According to them, the Deferoxamine appeared capable of binding to gadolinium ion and chelation should be considered in patients with iron overload and a history of GdCA exposure.

Face to the results of this study, Guerbet answered to the authors as follows.

> *Dr Maximova and colleagues, in an article recently published online in Radiology, suggested that the gadolinium-based contrast agent (GdCA) gadoterate meglumine (Dotarem; Guerbet, Roissy, France) undergoes a transmetallation in the liver of pediatric hematopoietic stem cell transplant recipients, but without robust evidence (102). In their study, the number of patients in the study group (hematopoietic stem cell transplant recipients with repeated GdCA exposure) and control group (hematopoietic stem cell transplant recipients without GdCA exposure) were markedly imbalanced (n = 21 vs n = 4). In the study group, Dr Maximova and colleagues correlated ductopenia (a marker of bile duct injury) to liver iron concentration (LIC) but not to liver gadolinium concentration (LGC). Then, by choosing an arbitrary LGC threshold of 0.1 µg/g without scientific justification, they differentiated patients with high versus low ductopenia. Interestingly, according to the data from* Table 40 *below], no, severe, and total ductopenia occurred with the same frequencies in the "more than 0.1 µg/g" patients, "less than 0.1 µg/g" patients, and control patients, thus demonstrating that bile duct loss is independent from gadolinium concentration. Obviously, these injuries are only related to iron deposition: In both groups, patient distribution was approximately 25%, 50%, and 25% in the mild, moderate, and high LIC categories and in the no, severe, and total ductopenia categories, respectively. Dr Maximova and colleagues proposed that deferoxamine binds and removes gadolinium from the liver. They reported LGC time courses for the treated patients but not for the others, thus precluding any comparison. Moreover, only those who received a chelation therapy had a baseline LGC greater than 0.1 µg/g. They were more iron sick than the others, and the effect of deferoxamine on LGC was probably more related to iron chelation. In hematopoietic stem cell transplant recipients, iron also deteriorates cardiac function (103). As a consequence, increased hepatic sinusoid pressure induces bile duct damage while stagnant blood flow results in liver thrombosis (104). Hepatic veno-occlusive disease is another frequent complication (105). In the present cohort, we suggest that liver blood perfusion was significantly affected and that gadoterate meglumine was, in fact, trapped in clots and occluded vessels. By improving cardiac function and tissue perfusion (106, 107), deferoxamine stimulated the whole-body hemodynamics, leading to a better liver perfusion and subsequent clearance of gadoterate meglumine. In conclusion, the results of this study are quantitatively and qualitatively not strong enough to support the hypothesis that gadoterate meglumine underwent a transmetallation in children with iron overload. It is the most stable contrast agent and is therefore the least likely to undergo a transmetallation, even in highly competing conditions.*

Table 40: Clinical Characteristics of Study Population

Group and Patient No.	Age at First Biopsy (y)	No. of MR Examinations with GBCA	Cumulative Gadolinium Dose (mg)	No. of Liver Biopsies	Interval between First MR Examination and First Biopsy (mo)	Interval between First MR Examination and Last Biopsy (mo)	Highest Liver Gadolinium Concentration (μg/g)	Mean eGFR (mL/min/1.73 m²)*	Biliary Ductopenia†	LIC MR Imaging Evaluation (μmol/g)	LIC Histologic Evaluation Grade
GBCA Group											
Patient 1	17	2	1886.41	2	22	35	0.06	88.5 (85–92)	2/16	40	1
Patient 2	9	1	675.96	1	7	7	0.09	143	11/11	230	3
Patient 3	17	3	3819.96	3	21	31	0.7	119.3 (112–129)	1/8	55	2
Patient 4	7	2	1006.08	1	7	7	0.07	114.5 (98–131)	13/13	90	2
Patient 5	12	1	1006.08	1	2	2	0.73	95	0/6	310	4
Patient 6	3	1	220.08	2	1	22	0.29	151	1/10	300	4
Patient 7	13	6	7074	3	13	32	0.39	132.5 (121–145)	2/12	80	1
Patient 8	11	1	597.36	1	8	8	0.03	139	10/10	70	2
Patient 9	7	1	455.88	1	8	8	0.07	146	12/12	85	2
Patient 10	16	1	974.64	2	2	12	0.05	152	2/10	70	2
Patient 11	10	1	534.48	1	1	1	0.07	132	15/15	30	0
Patient 12	7	4	1886.4	3	30	49	0.68	149 (142–157)	7/16	270	4
Patient 13	6	1	408.72	2	6	12	0.04	162	1/9	90	2
Patient 14	12	1	707.4	2	16	22	0.03	128	0/8	35	1
Patient 15	2	1	204.36	2	1	5	0.93	154	4/33	240	3
Patient 16	5	3	1414.8	2	1	6	0.96	120.6 (115–126)	0/12	190	3
Patient 17	6	2	911.76	2	11	18	0.08	142 (140–144)	2/11	65	1
Patient 18	15	1	1053.24	2	10	16	0.05	110	2/11	210	3
Patient 19	14	2	1383.36	2	42	48	0.49	89 (76–102)	0/13	350	4
Patient 20	10	1	487.32	2	2	5	0.28	158	0/9	270	3
Patient 21	12	1	628.8	1	1	1	0.08	133	0/9	160	3
Control Group											
Patient 1	5	0	0	1	NA	NA	0	146	13/13	90	2
Patient 2	7	0	0	1	NA	NA	0	139	5/15	40	1
Patient 3	12	0	0	1	NA	NA	0	88	1/12	210	3
Patient 4	6	0	0	1	NA	NA	0	131	0/13	290	4

Note.—Data in parentheses are range. NA = not applicable.

* eGFR measured in days of MR imaging.

† Data are number of interlobular bile ducts/number of portal tracts.

(from Maximova N. et al. 2016, (102)).

5.3.3 Conclusion

From all the well designed retrospective studies published in humans, either in adults or children, it can be concluded that there is no T1 shortening effect or T1 hypersignal in the brain and thus no Gd accumulation in the brain or other tissues after repeat administration of Dotarem®. Its high kinetic and thermodynamic stability considerably limits the possibility of dissociation of the Gd from its ligand. This is particularly true when the data are compared to L-GdCAs but also with other M-GdCAs, Dotarem® being the most stable.

However, this stability does not prevent the transient presence of Gd in the CNS measured after Dotarem® administration, which reduces over time after a physiologic mechanism of wash-out. This elimination phenomenon needs more time in patients with renal failure who clearly benefit from using a more stable GdCA.

As of today, the clinical consequences of this presence of Gd in tissues remains unknown even with L-GdCAs. A careful safety monitoring of literature as well as of individual case safety reports is one of the best ways to detect any potential safety signal in a large scale population.

5.4 PHARMACOVIGILANCE DATA

It is estimated that the following number of doses have been administered worldwide:

- Optimark : more than 22 million doses since January 2000
- Dotarem: more than 65 million doses since March 1989

Since the first marketing authorizations of Optimark® and Dotarem®, all pharmacovigilance cases reported spontaneously or in the context of post-marketing clinical studies, have been registered in Guerbet's Pharmacovigilance Database.

A retrospective study of individual case safety reports received until January 31, 2017 for Dotarem® and Optimark® has been done with the aim of assessing the occurrence of brain T1 hypersignals and the potential clinical consequences of brain Gd deposition/accumulation.

- *Dotarem*

A search in the Global Guerbet safety database was built up to retrieve cases with potential signs of gadolinium retention by using a specific list of selected codes from the MedDRA dictionary (V18.1) (see appendix). It includes a broad range of potential situations such as abnormal images or prolonged pharmacokinetics.

Two cases were retrieved for Dotarem® by using this method, one with a patient presenting a hypersignal on brain MRI and the other one with abnormal breast enhanced-MRI images after contrast media injection. The second case was retrieved through a broad term "MRI abnormal" but did not concern hypersignal on cerebral unenhanced-MRI images. Only the first case may answer some questions as regards to potential gadolinium retention in brain after Dotarem administration and is summarized below.

Case CH-20160001:
This case report was described in a Swiss literature by Barbieri et al. and was completed with additional information given by the last author (80).

The patient was a female patient born in 1952, weighing 66 kg in 2013, who was diagnosed in January 1970, with autoimmune polyendocrine syndrome type 2: Schmidt's syndrome with a replacement therapy for adrenal gland insufficiency and a replacement therapy for hypothyroidism Hashimoto's thyroiditis (06/2013 TSH 36.13 mU/l; dosis of Euthyrox (levothyroxin) increased to 0.1mg/d). In 1986 at the age of 34, she was diagnosed with a Systemic Lupus Erythematosus which led subsequently to chronic renal failure with a lupus nephritis type IV observed on kidney biopsy in December 1999. Hemodialysis was started in September 2000 and the patient was kidney transplanted in June 2005. Various MRIs had been performed during this time period without clear indication:

- Chest MRI in May 2000 with 30 ml (15mmol) of Omniscan,
- Abdominal MRI in September 2000 with 30 ml (15 mmol) of Omniscan,
- Kidney MRI in January 2002 with 32 ml (16 mmol) of Prohance.
- In October 2005, the patient was administered 15 ml (7.5 mmol) of Dotarem for an MRI of pelvis and femur, for connective tissue induration of the thighs.

Close to Dotarem administration biological analysis revealed: Serum Creatinine at 106, eGFR 55ml/min, ASAT 26,GGT 54; Albumin 40; CRP less than 3; Ferritin 1152; PTH 105; Haemoglobin at 126; Haematocrit at 0.37; Lc 10.3.

In December 2005, further histological workup of the skin revealed a septal fibrotic panniculitis and septal fibrosis compatible with nephrogenic systemic fibrosis in January 2006 at 54 years old (i.e 3 months after Dotarem administration).

In the years after onset of connective tissue disorders, the patient presented with calciphylaxis with skin involvement in 2011. She also presented with peripheral arterial disease stage IV, hypertensive heart disease, type-2 diabetes mellitus, several episodes of infections and depression.

In August 2013, a CT of the head (unclear if with contrast media or not) was performed because of a subcutaneous fronto-temporal hematoma caused by a fall. Aphasia and decreased vigilance of the patient were noted. An MRI without further administration of contrast agent was performed as well to exclude intracranial haemorrhage. This MRI showed considerable vascular calcifications but no ischemia or bleeding. Moreover the control of the MRI in late 2015 revealed a well visible T1 Hyperintense enhancement in the Dentate Nucleus (DN) and Globus Pallidus (GP) also in comparison to neighbouring reference tissue of Pons (P) or Thalamus (T). DN-P ratio and GP-T ratios were reported with 1.13 / 1.14 compatible with results of previous studies analysing the cumulative effect of multiple administrations of GBCA's in subjects with normal renal function (Kanda T et al, 2014/2015 (91, 108) or Radbruch A et al, 2015 (94)). The authors speculate about a saturation of these structures for further uptake of Gd as the present case had a transient renal insufficiency, but with an eGFR of more than 60ml/min/m2 normalized later on. The total cumulative dose was approximately 53.5 mmol/66kg = 0.81mmol/kg including 0.45mmol/kg of linear Gd.

On an unknown date, the patient died of unspecified cause. No autopsy report was available.

Author comments:
The reporter rated the causal relationship for NSF with the administration of Omniscan as possible, while rather unlikely for Dotarem and Prohance. Later effects such as aphasia and reduced vigilance with T1 hyperintensity on the non-enhanced MRI are possibly related to previous Gadolinium administrations (causing deposits in the dentate nucleus and globus pallidus), with higher causal relationship to Omniscan, but potentially also to total cumulative dose including all agents. Other potential reasons for the hyperintensity are discussed as for example the calcification or minerals supplied during haemodialysis.

Company comment:
As regards to NSF:
Additional clinical and histological patterns confirming the diagnosis of NSF in this patient remain lacking, only skin biopsy with septal fibrosis compatible with NSF was reported. Nevertheless the patient, suffering from systemic lupus erythematosus and Schmidt's syndrome as autoimmune diseases, had a medical history of chronic renal failure, she was under hemodialysis while she received GdCA and she underwent pro-inflammatory events

such as fistula placement, sepsis, renal transplant which are co-factors for the development of NSF. It has also to be noted that, before Dotarem administration, the patient received several GdCAs and already presented with connective tissue induration, this latter being the indication of Dotarem-enhanced MRI. Therefore, confounding factors may have contributed to the onset of NSF and the causal role of Dotarem was unlikely. The evolution of the disease was difficult to distinguish from concomitant pathologies (calciphylaxis, peripheral arterial disease stage IV, hypertensive heart disease, type-2 diabetes mellitus, several episodes of infections, depression and related medication).

As regards to hyperintensity in brain:
T1 Hyperintense enhancement was observed in the Dentate Nucleus (DN) and Globus Pallidus (GP) on unenhanced-MRI images obtained 13 years after the first administration of GdCA and 8 years after the last one. The patient suffered from chronic renal failure with a lupus glomerulonephritis type IV at the time of the two linear GdCA injections; the administration of Gadavist was performed after the start of the haemodialysis in this patient; while Dotarem was administered after renal transplant with an eGFR at about 55ml/min at the same period. No history of hypersignal since the first MRI was provided to get a dynamic aspect of the presumptive gadolinium accumulation; therefore no conclusion on the contribution of each GdCA and on the role of renal function or any underlying disease as risk factor may be established in the gadolinium retention in brain. Nevertheless as the Dotarem–enhanced MRI was specifically performed for connective tissue induration of the thighs that may be regarded as first sign of NSF, Gd accumulation in tissue and organ may have started prior to the administration of Dotarem. In addition, without accurate description and evolution of the cognitive disorders observed in 2013 in the patient, the causal relationship with gadolinium accumulation in brain cannot be established. Furthermore, it cannot be excluded that vascular calcification or minerals supplemented during dialysis were additional causes for the observed signal hyperintensities as mentioned by the authors.

Conclusion for Dotarem:
The Pharmacovigilance department recorded only one case report into the global Guerbet safety database with a description of T1 hypersignal in brain. This case concerns a female patient with renal insufficiency due to auto-immune disease and who received several linear and macrocyclic GdCAs. She was also suspected to experience NSF but the diagnosis based on Girardi score remains to be confirmed. Thirteen years after the first known MRI procedures, and 8 years after the last one, unenhanced MRI revealed hyperintensities in Dentate Nucleus and Globus Pallidus and the patient showed neurological disorders with aphasia and vigilance decreased. The case is lacking important information on history of hypersignal in this patient between her first MRI and the beginning of neurological signs, therefore no conclusion can be drawn on the role of Dotarem, and on the contribution of potential confounding factors such as inflammatory conditions, renal insufficiency, arterial disease or calciphylaxis in the occurrence of these brain intensities.

- *Optimark*

There was no case of brain T1 hypersignals or suggesting potential clinical consequences of brain Gd deposition/accumulation.

6 GUERBET'S POSITION, PROPOSED ACTIONS AND RISK MITIGATION MEASURES

GdCA are indispensable agents for the diagnostic and follow-up of many diseases using MRI. Outside the hepato-specific agent gadoxetic acid (Eovist®), which has a corresponding specific clinical use, the other GdCAs all belong to the non-specific category. **While having similar diagnostic efficacy, diagnostic performance and short term (immediate) safety profile, they strongly differ in terms of thermodynamic and kinetic stability.**

Short term (acute) adverse reactions, particularly the severe and potentially life-threatening reactions, are very rare, well-known, and are adequately addressed in the GdCA package inserts (contraindication, warning & precautions, etc) and by the radiological community. The 1st long-term adverse reaction described with some GdCA was NSF, occurring in patients with severe renal impairement. Gd deposition in skin with subsequent inflammatory reaction was a strongly suggested cause for NSF, and such a Gd deposition is directly linked with the stability of the GdCA. This is why the immense majority of NSF cases were described after L-GdCA exposure or multiple agent exposure but always involving one or several injections of L-GdCAs. NSF risk was concentrated on a very specific patient population (with severe renal impairment), and so this risk has been adequately managed by contraindicating the less stable GdCAs in those populations and introducing various warnings and precautions for all GdCAs in patients with moderate renal impairement.

Outside the skin, there are now evidences of Gd deposition in multiple organs after exposure to less stable GdCAs. This Gd deposition is becoming a Gd accumulation in case of repeat exposure to low stability GdCAs. The brain Gd deposition/accumulation is the subject of many scientific publications for the last months. Even if no adverse consequence has been described so far, it is a growing concern in view of still unknown potentially long term consequences. However, there is a significant difference with the NSF issue: Gd brain deposition risk is not restricted to a specific patient population. It has been reported in patients, either adults or children, with normal renal function. It is therefore not possible to fully address the problem by restricting the use of at-risk GdCAs in some specific populations.

Regarding the Guerbet/Liebel-Flarsheim Company LLC product portfolio, Dotarem® is a macrocyclic and ionic GdCA with a long worldwide marketing history and a well-established safety profile. Having the highest stability in the class and no sign of Gd deposition/accumulation, there was no confirmed unconfounded case of NSF after more than 65 millions of injected examinations.

From an efficacy perspective, no difference between Dotarem® and L-GdCAs has been conclusively reported.

From a safety perspective, no brain T1 hyperintensities have been reported with Dotarem®, either in adults or children, contrarily to what has been repeatidly reported with L-GdCAs. As far far as acute or immediate reactions are concerned, no difference between Dotarem® and L-GdCAs have been reported.

Overall, the Dotarem® benefit/risk balance remains favorable and unchanged.

Given the existence of macrocyclic alternatives with a more favorable benefit/risk balance, as well as for commercial reasons and product portfolio rationalization, Guerbet/Liebel-Flarsheim Company LLC has decided to phase out Optimark® progressively from the US market. This follows the decision of Guerbet to not to renew the Optimark® EU centralized marketing authorization which has expired on 25 July 2017. Before the decision of phasing out Optimark® from the US market, Guerbet has voluntarily proposed a labeling modification for Optimark® to the FDA medical imaging division, in order to inform the radiologists and the patients about the brain deposition risk. In collaboration with FDA, the following statement has been added in August 2016, in section "12- Clinical Pharmacology / 12.3 Pharmacokinetics" of the Optimark® US-PI:

Deposition with repeated dosing
Increased signal intensity on non-contrast T1-weighted images within the brain, mainly the globus pallidus and the dentate nucleus, has been observed after multiple administrations of linear (ionic and nonionic) gadolinium-based contrast agents due to gadolinium deposition.

Following repeated GBCA administration, gadolinium deposits may be present for months or years in bone, liver, skin, brain, and other organs. Deposition depends on multiple factors and may be greater following administration of gadoversetamide and other linear GBCAs than following administration of macrocyclic GBCAs. GBCAs have been associated with the development of NSF in patients with renal impairment [see Boxed Warning]. The clinical significance of gadolinium retention in the body and brain is otherwise unknown.

It is in Guerbet's opinion that the precautionary principle should be applied when using a GdCA, particularly in patients susceptible to receive multiple GdCA injections during their life (patients suffering from cancer, multiple sclerosis, other inflammatory and neurodegenerative diseases, etc) and in fragile populations (pediatric patients). Because it is neither deemed feasible nor justified to restrict the repeat use of GdCAs during life, as some patient populations require such repeat imaging procedures for the diagnostic and follow-up of their disease (see above) and because it is impossible in practice to identify properly in advance such "at-risk populations," **a restriction of use of non-specific L-GdCAs should be considered**.

Therefore, the following risk mitigation measures are proposed by Guerbet:

- Use the GdCA at the lowest approved diagnostic dose. It is not recommended to use lower doses as the one approved for each GdCA, as there is no robust data to demonstrate effectiveness at a lower dose.
- Choose preferentially a M-GdCA due to the higher stability and a very low propensity to release toxic free Gd. **Restrict the use of non-specific L-GdCAs to 2nd line agents, if a M-GdCA cannot be used (history of hypersensitivity to a M-GdCA, unavailability of M-GdCA, etc)**. This is in agreement with the National Institute of Health (NIH) recommendations issued in 2016 (109). All approved indications and populations of L-GdCA are covered by M-GdCA, so there will be no diagnostic gap created by a drastic restriction of use of L-GdCA, or even by a NDA withdrawal of

those agents. Gadoxetic acid has to be considered separately here as it is a liver-specific agent needing a separate risk-benefit assessment.

6.1 US PACKAGE INSERT MODIFICATIONS

The statements proposed to be added in US-PIs of GdCAs are detailed in Table 41.

6.2 DHCP LETTER

A DHCP letter should be sent to US radiologists, once FDA has finalized its assessment. The same DHCP should be distributed by all companies/NDA holders, once its content has been agreed upon with the FDA.

6.3 PHARMACOVIGILANCE MONITORING

Guerbet/Liebel-Flarsheim Company LLC will continue to monitor the safety profile of Optimark® (until final market withdrawal) and Dotarem® through its pharmacovigilance system. Guerbet is also continuously monitoring the emergence of new safety signals for its products and will handle them according to standard operating procedures (SOPs) in place and USA/international regulations.

Guerbet/Liebel-Flarsheim Company LLC will continue to work closely with the FDA on the issue of brain Gd deposition.

6.4 PROPOSED NEW STUDIES

6.4.1 Nonclinical studies

Guerbet proposes to perform nonclinical studies for a better understanding of the mechanism of long-term Gd deposition and for the evaluation of a potential induced-toxicity:

- Behavioral tests
  - In-depth behavioral and MRI study of GdCA-treated adult rats
  - In-depth behavioral study and MRI of GdCA-treated juvenile rats
- Speciation : Gd microscopic analysis, HPLC- soluble forms
  - Investigation of long term accumulation of different chemical forms of Gd in several areas (brain, bone, …)
  - Transmission electron microscopy studies of brain areas associated with electron-energy loss spectroscopy characterization of Gd and various elements
  - Detailed investigations of Gd brain deposits with X-ray fluorescence and various chemical imaging methods
- Impact of Gd deposits
  - Histopathological studies of brain tissues associated with Gd deposition
  - Investigation of the impact of Gd deposition on endogenous species expression (metabolic fingerprinting and biomarkers profiling approaches)

6.4.2 Clinical and epidemiological studies

Guerbet would like to support academic clinical studies in which Dotarem will be studied:

- Mainly registries, either retrospective or prospective in targeted populations exposed to multiple administrations to GdCA, including gadoteric acid, investigating the potential brain hypersignal in non CNS indications such as women at high risk of breast cancer or children with cancer.
- Functional imaging to explore the potential neurological consequences of Gd brain deposition using PET or SPECT to detect possible changes in tissue density or metabolic function in patients without any pre-existing CNS disease. In particular, the assessment of multi-exposure patients in MR spectrometry could be an interesting way to identify some metabolic changes possibly related to gadolinium deposition. Those imaging tests could be coupled with neuropsychological cognitive tests.

Clinical studies, observational or interventional, to fully understand the clinical consequences of Gd accumulation in the brain would be extremely difficult to conduct within a reasonable period of time mainly because of the requirement for a long term follow-up and the large heterogeneity of the patient population exposed to injected MRI.

No clinical study is planned with Optimark® knowing the on-going progressive phasing-out of the product.

6.4.2.1 Ongoing Guerbet sponsored clinical studies

There is no ongoing Guerbet sponsored clinical studies related to Gd deposition in brain. However there are two ongoing Guerbet sponsored clinical studies related to Gd deposition in other anatomical territories (bone, skin), as described in Table 42.

6.4.2.2 Ongoing or planned non-Guerbet sponsored clinical studies supported by Guerbet as part of Investigator Initiated Studies program

Five academic clinical studies supported by Guerbet are ongoing or at preparation phase on various populations and with several endpoints related to brain hypersignal and/or Gd deposition. Details are provided in Table 43.

Table 41: Proposed statements to be added in US-PI for GdCA

Proposals for added statements **PI Section**	**L-GdCA**		**M-GdCA**	**Remarks**
	Magnevist®, MultiHance®, Omniscan® & Optimark®	**Eovist®**	**Dotarem®, Gadavist® & ProHance®**	
Black Box Warning	WARNING: GADOLINIUM DEPOSITION IN ORGANS <*name of product*> has been associated with a higher risk of Gd deposition and accumulation in various organs, including the brain. <*name of product*> should only be used if a macrocyclic GBCA cannot be used (e.g. history of hypersensitivity to a macrocyclic GBCA), and after a careful risk-benefit assessment, particularly for use in patient populations susceptible to receive multiple administrations of linear GBCA during life and in pediatric patients. [*see Indications and Usage (1); Pharmacokinetics (12.3)* and *Animal Toxicology and/or Pharmacology (13.2)*] Do not exceed the recommended <*name of product*> dose.	No modification of the current one (NSF)	No modification of the current one (NSF)	For L-GdCA : this statement will be added in the black box in addition to the existing (unchanged) NSF warning

Proposals for added statements **PI Section**	**L-GdCA**		**M-GdCA**	**Remarks**
	Magnevist®, MultiHance®, Omniscan® & Optimark®	**Eovist®**	**Dotarem®, Gadavist® & ProHance®**	
1- Indications and Usage	<*name of product*> should only be used if a macrocyclic GBCA cannot be used (e.g. history of hypersensitivity to a macrocyclic GBCA), and after a careful risk-benefit assessment, particularly for use in patient populations susceptible to receive multiple administrations of linear GBCA during life and in pediatric patients. <*name of product*> has been associated with a higher risk of Gd deposition and accumulation in various organs, including the brain [*see Pharmacokinetics (12.3)* and *Animal Toxicology and/or Pharmacology (13.2)*]	None	None	
2- Dosage and administration 2.1 Dosing guidelines	Use the lowest dose that provides sufficient enhancement for diagnostic purposes. Do not exceed the recommended dose per kilogram of body weight detailed in this section.	Use the lowest dose that provides sufficient enhancement for diagnostic purposes. Do not exceed the recommended dose per kilogram of body weight detailed in this section.	Use the lowest dose that provides sufficient enhancement for diagnostic purposes. Do not exceed the recommended dose per kilogram of body weight detailed in this section.	Same statement for all GdCAs

Proposals for added statements PI Section	L-GdCA		M-GdCA	Remarks
	Magnevist®, MultiHance®, Omniscan® & Optimark®	**Eovist®**	**Dotarem®, Gadavist® & ProHance®**	
12- Clinical Pharmacology 12.3 Pharmacokinetics	Deposition with repeat dosing Increased signal intensity on non-contrast T1-weighted images within the brain, mainly the globus pallidus and the dentate nucleus, has been observed after multiple administrations of linear (ionic and nonionic) gadolinium-based contrast agents due to gadolinium deposition. Following repeat GBCA administration, gadolinium deposits may be present for months or years in bone, liver, skin, brain, and other organs. Deposition depends on multiple factors and may be greater following administration of <*name of product*> and other linear GBCAs than following administration of macrocyclic GBCAs. GBCAs have been associated with the development of NSF in patients with renal impairment [see Boxed Warning]. The clinical significance of gadolinium retention in the body and brain is otherwise unknown.	Deposition with repeat dosing Increased signal intensity on non-contrast T1-weighted images within the brain, mainly the globus pallidus and the dentate nucleus, has been observed after multiple administrations of linear (ionic and nonionic) gadolinium-based contrast agents due to gadolinium deposition. Following repeat GBCA administration, gadolinium deposits may be present for months or years in bone, liver, skin, brain, and other organs. Deposition depends on multiple factors and may be greater following administration of <*name of product*> and other linear GBCAs than following administration of macrocyclic GBCAs. GBCAs have been associated with the development of NSF in patients with renal impairment [see Boxed Warning]. The clinical significance of gadolinium retention in the body and brain is otherwise unknown.	Deposition with repeat dosing Increased signal intensity on non-contrast T1-weighted images within the brain, mainly the globus pallidus and the dentate nucleus, has been observed after multiple administrations of linear (ionic and nonionic) gadolinium-based contrast agents due to gadolinium deposition. Following repeat GBCA administration, gadolinium deposits may be present for months or years in bone, liver, skin, brain, and other organs. Deposition depends on multiple factors and may be greater following administration of <*name of product*> and other linear GBCAs than following administration of macrocyclic GBCAs. GBCAs have been associated with the development of NSF in patients with renal impairment [see Boxed Warning]. The clinical significance of gadolinium retention in the body and brain is otherwise unknown.	Same statement for all GdCAs (already present in Optimark® US-PI)

Proposals for added statements **PI Section**	**L-GdCA**		**M-GdCA**	**Remarks**
	Magnevist®, MultiHance®, Omniscan® & Optimark®	**Eovist®**	**Dotarem®, Gadavist® & ProHance®**	
13- Nonclinical Toxicology 13.2- Animal Toxicology and/or Pharmacology	Recent studies conducted in healthy rats injected repeatedly with linear or macrocyclic GBCAs demonstrated that linear agents were associated with progressive and persistent T1-weighed hyperintensity on MRI in the deep cerebellar nuclei (DCN). Signal enhancement in the globus pallidus (GP) could not be seen in the animals. No changes in signal intensities in either DCN or GP were observed for the macrocyclic GBCAs. Quantitative results using mass spectrometry demonstrated that the total gadolinium concentrations were significantly higher with the linear GBCAs than with the macrocyclic GBCAs. These studies reported no abnormal behavioural changes suggestive of neurological toxicity.	Recent studies conducted in healthy rats injected repeatedly with linear or macrocyclic GBCAs demonstrated that linear agents were associated with progressive and persistent T1-weighed hyperintensity on MRI in the deep cerebellar nuclei (DCN). Signal enhancement in the globus pallidus (GP) could not be seen in the animals. No changes in signal intensities in either DCN or GP were observed for the macrocyclic GBCAs. Quantitative results using mass spectrometry demonstrated that the total gadolinium concentrations were significantly higher with the linear GBCAs than with the macrocyclic GBCAs. These studies reported no abnormal behavioural changes suggestive of neurological toxicity.	Recent studies conducted in healthy rats injected repeatedly with linear or macrocyclic GBCAs demonstrated that linear agents were associated with progressive and persistent T1-weighed hyperintensity on MRI in the deep cerebellar nuclei (DCN). Signal enhancement in the globus pallidus (GP) could not be seen in the animals. No changes in signal intensities in either DCN or GP were observed for the macrocyclic GBCAs. Quantitative results using mass spectrometry demonstrated that the total gadolinium concentrations were significantly higher with the linear GBCAs than with the macrocyclic GBCAs. These studies reported no abnormal behavioural changes suggestive of neurological toxicity.	Same statement as requested by Health Canada Same statement for all GdCAs

Table 42: Ongoing Guerbet sponsored clinical studies

Study title and identification	Study objectives and location(s)	Study status and interim results if applicable
"BONE study" Exploratory evaluation of the potential for long-term retention of Gadolinium (Gd) in the bones of patients who have received Gadolinium based Contrast Agents (GdCAs) according to their medical history Guerbet study No. DGD-44-056 – Sponsor Study No. ALS-Gd64/001 – EudraCT No. 2012-001439-30 **Sponsor:** Ecron Acunova GmbH, Hahnstrasse70, D-60528 Frankfurt/ Main, Germany Study conducted on behalf of Guerbet, GE Healthcare and Bayer Pharma AG.	Primary objective: to prospectively explore the potential for long-term retention of Gd in the bones of patients who have received a single dose of GdCA or multiple doses of the same GdCA, with moderate or severe renal impairment or stable renal function (estimated glomerular filtration rate >60 ml/min/1.73 m^2) at the time of GdCA injection. Main secondary objective: to evaluate skin samples for Gd concentration. Participating countries: Germany, Italy, Japan, Korea, Poland, Spain, Turkey, USA	**Ongoing study** Overall number of stratified patients : 76 including: Control: 18 Gadobutrol: 22 Gadodiamide: 10 Gadopentetic acid: 7 Gadoteric acid: 14 Gadoversetamide: 2 Gadoxetic acid: 3 Last patient last visit expected by October 2017 (resulting from a study amendment approved by EMA) No interim results available yet; an interim analysis is planned once at least three patients have been recruited to all the single exposure subgroups for the 4 agents gadobutrol, gadoteric acid, gadodiamide, and gadopentetic acid. Final results expected in 2018 (to be confirmed)

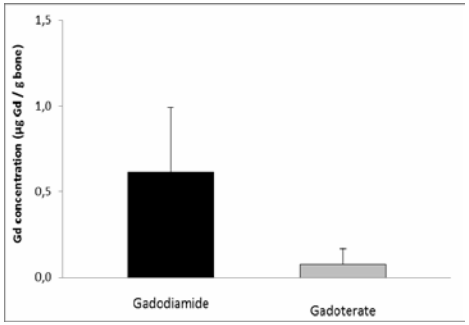
Study title and identification	Study objectives and location(s)	Study status and interim results if applicable
Comparison of Gd-DTPA-BMA versus Gd-DOTA for Gadolinium retention in human bone tissue with normal renal function Joint study between Guerbet Japan and Kobe University	Primary objective: to determine the Gd deposit in human bone tissue after administration of Gd chelates either macrocyclic (gadoteric acid) or linear (gadodiamide) at a standard clinical dose and to evaluate the potential correlation with renal function (eGFR). Participating country: Japan Location: Kobe University (PI: Pr. Kazuro Sugimura)	**Ongoing study** Actual enrolment : 19/20 evaluable patients The last available interim results are based on 15 patients (7 in the gadodiamide group and 8 in the gadoteric acid group).  Final results expected by end of 2017 (to be confirmed)

Table 43: Ongoing or planned non-Guerbet sponsored clinical studies supported by Guerbet as part of IIS program

Study Sponsor	Study design and objectives	Study status and interim results if applicable
HYPERSIGNAL / CNS indication		
Pr Houston (Dundee, UK)	Retrospective comparison between 3 groups of patients with various CNS diseases: -One group who received >5 injections of gadoteric acid (Dotarem) -One group who received >5 injections of a linear GdCA -One control group with no history of GdCA administration	**Ongoing study** Preliminary results in 50 patients with 5 or more injections of gadoteric acid who underwent brain scans have been analyzed. There is no significant difference between the last and the first MRI scans for the DN-P, DN-MCP and DN-CSF signal intensity ratios. Those preliminary results show the absence of T1-weighted hypersignal with gadoteric acid and are in agreement with retrospective cohorts already published (Radbruch 2015, Radbruch 2016, Eisele 2016). Results expected by end of 2017 (to be confirmed)
Pr Cotton (Lyon, France)	Retrospective multicentric study on a cohort of Multiple Sclerosis patients comparing 2 groups of 80 patients having received at least 5 injections of either gadoteric acid (Dotarem) or gadobenate dimeglumine (Multihance).	**Study in preparation phase** Results expected by mid of 2018 (to be confirmed)
HYPERSIGNAL and/or Gd DEPOSITION - PEDIATRIC Focus		
Pr D. Roberts (Charleston, SC, USA) Clinical study to better characterize the risk of brain deposition across the class	To assess gadolinium retention in the brain and bone of pediatric patients in two patient groups who received >5 IV administration of: (1) gadopentetate dimeglumine (Magnevist, retrospective cohort), (2) Gadoteric acid (Dotarem, prospective cohort) and gadobenate dimeglumine (Multihance, prospective cohort). Objective 1: To explore the correlation between the number of previous administrations of a GdCA and high signal intensity (SI) in the dentate nucleus and globus pallidus on non-enhanced T1-weighted MR images of patients who have received gadopentetate dimeglumine (n=15) and gadoteric acid (n=15). A control group of patients (n=15) who undergo non-enhanced MRI will also be included as well as another comparator group of patients who have received gadobenate dimeglumine.	**Ongoing study** First results on retrospective study published (110) Final results expected by mid-2018 (to be confirmed)

Study Sponsor	Study design and objectives	Study status and interim results if applicable
	Objective 2: To determine the gadolinium concentration present in skull bone tissue in 3 groups of pediatric patients requiring craniotomy as part of their standard clinical treatment: (1) patients who had not been exposed to GdCA prior to surgery, (2) patients who had undergone the administration of a linear GdCA (several times 0.1 mmol/kg IV gadopentetate dimeglumine), and (3) patients who had undergone the administration of a macrocyclic GdCA (several times 0.1 mmol/kg IV gadoteric acid). MRI scans : 1.5 T or 3T	
Pr A. Towbin (Cincinnati, OH, USA) Clinical study to better characterize the risk of brain deposition across the class	Retrospective review of MR images of pediatric patients with greater than 5 single MR contrast studies agent (one group Eovist, one group Dotarem and one group Magnevist of at least 50 patients each) Objective 1: Determine if there is a relationship between the pre-contrast T1-weighted signal intensity and lifetime total gadolinium dose for different GBCAs Objective 2: Determine the patterns of potential deposition (inferred by increased T1-weighted signal) within the brain and body for different GBCAs. The following specific body parts and their corresponding control region will be evaluated: 1. Brain: • Globus pallidus: thalamus, CSF of the ipsilateral ventricle (if on the same image) • Dentate nucleus: cerebellum, CSF in 4th ventricle, pons 2. Abdomen: skeletal muscle of: • Myocardial septum, Liver, Spleen, Pancreas, Renal cortex, Renal medulla 3. Hips: skeletal muscle of: • Femoral epiphysis, Femoral neck 4. Knees: skeletal muscle of: Femoral metaphysis, Femoral epiphysis, Tibial metaphysis, Tibial epiphysis	**Ongoing study** Final results expected by end of 2017 (to be confirmed)

Study Sponsor	Study design and objectives	Study status and interim results if applicable
CLINICAL EVIDENCE of NEUROTOXICITY or BIOLOGICAL EFFECTS related to Gd deposition		
Pr J. L. Abraham (Syracuse, NY, USA) Clinical study to better characterize the risk of brain deposition across the class and to understand: 1) the chemical form in which it is transferred and retained 2) the potential clinical manifestations of brain deposition	To determine if, and under what circumstances, the intra-cerebral deposition of Gd released from GdCAs used in MRI is harmful to the brain, as evidenced by the detection of neuropathological changes in autopsy tissue. Objective 1: to determine if insoluble deposits of Gd can be detected in paraffin tissue blocks of the cerebellar dentate nucleus and globus pallidus from subjects diagnosed with nephrogenic systemic sclerosis (NSF) secondary to Gd exposure and renal failure, and from subjects with multiple sclerosis (MS) with Gd exposure and normal renal function, and to characterize the frequency, composition, spatial distribution, and relative concentration of Gd in these deposits. Objective 2: to determine if Gd deposits are associated with immunohistochemical markers of neuropathological changes, including defects in the BBB, neuroinvasion by peripheral monocytic immune cells, gliosis, oxidative stress, apoptotic cell death, and axonal pathology.	**Ongoing Study** Preliminary results expected by the end of 2017 (To be confirmed)

7 CONCLUSION

Following the NSF pharmacovigilance cases, there are now evidences of Gd deposition in multiple organs after exposure to less stable GdCAs. This Gd deposition is becoming a Gd accumulation in the case of repeat exposure to low stability GdCAs. The brain Gd deposition/accumulation is the subject of many scientific publications for the last months. Even if no adverse consequence has been described so far, it is a growing concern in view of still unknown potential. Contrary to the NSF issue Gd brain deposition is not restricted to at-risk patient populations. It has been reported in patients, either adults or children, with normal renal function. It is therefore not possible to fully address the problem by restricting the use of less stable GdCAs in specific at-risk populations.

It is crucial to not create a fear of GdCA among physicians and patients as those agents are crucial to use for some diagnostics. It is in Guerbet's opinion that the precautionary principle should be applied when using a GdCA, particularly in patients susceptible to receive multiple GdCA injections during their life (patients suffering from cancer, multiple sclerosis, other inflammatory and neurodegenerative diseases, etc.) and in fragile populations (pediatric patients). Because it is neither deemed feasible nor justified to restrict the repeat use of GdCAs during life, as some patient populations require such repeat imaging procedures for the diagnostic and follow-up of their disease (see above) and because it is impossible in practice to identify properly in advance such "at-risk populations", a restriction of use of non-specific L-GdCAs should be considered.

Therefore, the following risk minimization / risk mitigation measures are proposed by Guerbet:

- Use the GdCA at its lowest approved diagnostic dose. It is not recommended to use lower doses as the one approved for each GdCA, as there is no robust data to demonstrate effectiveness at a lower dose.
- Choose preferentially a M-GdCA due to the higher stability and a very low propensity to release toxic free Gd. Restrict the indications of L-GdCA to second line agents, if an M-GdCA cannot be used (history of hypersensitivity to an M-GdCA, unavailability of M-GdCA, etc). This is in agreement with the National Institute of Health (NIH) recommendations issued in 2016 (108). All approved indications and populations of L-GdCA are covered by M-GdCA, so there will be no diagnostic gap created by a drastic restriction of use of L-GdCA, or even by an NDA withdrawal of those agents. Gadoxetic acid has to be considered separately here as it is a liver-specific agent needing a separate B/R assessment.

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APPENDIX

Code list used to identify cases with potential gadolinium retention reported as adverse event (Lowest Level Terms (LLT) from MedDRA version 18.1)

LLT Code	LLT Term
10053399	Drug half-life increased
10013716	Drug level change NOS
10013717	Drug level changed
10013722	Drug level increased
10013725	Drug level NOS changed
10013729	Drug level NOS CSF increased
10013733	Drug level NOS increased
10019356	Heavy metal NOS high
10019357	Heavy metal NOS increased
10021591	Inappropriate drug response
10028050	MRI abnormal
10029433	NMR abnormal
10029816	Nuclear magnetic resonance imaging abnormal
10029821	Nuclear magnetic resonance imaging gadolinium-enhanced abnormal
10037810	Raised drug level
10037812	Raised drug levels in cerebrospinal fluid
10062152	Scan with contrast abnormal
10039576	Scan with contrast NOS abnormal
10043412	Therapeutic effect unexpected
10053181	Therapeutic response delayed
10043415	Therapeutic response increased
10043416	Therapeutic response prolonged
10043417	Therapeutic response unexpected
10052807	Unexpected therapeutic drug effect
10045527	Unexpected therapeutic effect
10049463	Drug clearance decreased
10076885	Unexpected beneficial therapeutic response
10028050	MRI brain abnormal
10054077	Nuclear magnetic resonance angiography brain abnormal
10029818	Nuclear magnetic resonance imaging brain abnormal
10073474	Nuclear magnetic resonance imaging spinal abnormal
10069585	Nuclear magnetic resonance imaging spinal cord abnormal