GE Healthcare

Omniscan™ (gadodiamide) Injection

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Briefing Document for MIDAC

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ADVISORY COMMITTEE BRIEFING MATERIALS:
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List of Abbreviations

Abbreviation	Meaning
ACR	American College of Radiology (ACR)
ADR	Adverse Drug Reaction
AE	Adverse Event
BBB	Blood-brain Barrier
BG	Basal Ganglia
CE	Contrast-enhanced
CI	Confidence Interval
CLD	Chronic Liver Disease
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
DCN	Deep Cerebellar Nuclei
DMIP	Division of Medicinal Imaging Products
DN	Dentate Nucleus
DTPA-BMA	Diethylenetriamine Pentaacetic Acid Bis(methylamide)
EBGM	Empiric Bayes Geometric Mean
EDS	Energy Dispersive X-ray Spectroscopy
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EU	European Union
FAERS	Food and Drug Administration Adverse Event Reporting System
FDA	Food and Drug Administration
FLAIR	Fluid-attenuated Inversion Recovery
GAED	Global Adverse Events Database
GBCA	Gadolinium-based Contrast Agent
Gd	Gadolinium
Gd^{+3}	Gadolinium (III) Ion
GDD	Gadolinium Deposition Disease
GEHC	GE Healthcare
GFR	Glomerular Filtration Rate
GP	Globus Pallidus
H&E	Hematoxylin and Eosin
HILIC	Hydrophilic Interaction Liquid Chromatography
HSR	Hypersensitivity Reactions
ICP-AES	Inductively Coupled Plasma-atomic Emission Spectroscopy
ICP-MS	Inductively Coupled Plasma Mass Spectrometry
ICP-SF-MS	Inductively Coupled Plasma-sector Field Mass Spectrometry
ICSR	Individual Case Safety Report
IND	Investigational New Drug
ISMRM	International Society for Magnetic Resonance in Medicine

Abbreviation	Meaning
IV	Intravenous
MCDA	Multi-criteria Decision Analysis
MCI	Mild Cognitive Impairment
MCSA	Mayo Clinic Study of Aging
MPRAGE	Magnetization-prepared Rapid Acquisition of Gradient Echo
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NMOsd	Neuromyelitis Optica Spectrum Disorder
NSF	Nephrogenic Systemic Fibrosis
nSI	Native T1 Signal Intensity
PRR	Proportional Reporting Ratio
PV	Pharmacovigilance
PVS	Perivascular Space
qT1	Quantitative T1 Value
RITA	Registry of Industrial Toxicology Animal-data
RMP	Risk Management Plan
SE	Spin Echo
SI	Signal Intensity
SIR	Signal Intensity-Ratio
T1w	T1-weighted
TSI	Tracked Safety Issue
US	United States

1   INTRODUCTION

Gadolinium-based contrast agents (GBCAs) are intravenously administered drugs that help radiologists interpret magnetic resonance imaging (MRI) examinations by enhancing contrast in body tissues where the GBCA is located. Based on chemical characteristics, a GBCA can be classified as linear or macrocyclic, as ionic or non-ionic, and as protein-binding or non-protein-binding.

OMNISCAN™ (gadodiamide) is a linear, non-ionic, non-protein binding GBCA indicated for diagnostic magnetic resonance imaging to visualize lesions with abnormal vascularity in the brain, spine and associated tissues and to facilitate the visualization of lesions with abnormal vascularity within the thoracic, abdominal, pelvic cavities and the retroperitoneal space. Since commercial launch in 1993, Omniscan has been administered to an estimated 80,000,000 patients and is marketed in over 100 countries worldwide, including the United States. Numerous clinical studies and decades of clinical use support the efficacy and safety of Omniscan for its intended uses. These uses are similar to those across the class of GBCAs.

GEHC acknowledges that recent publications on brain gadolinium (Gd) have identified a potential risk that requires further evaluation and applauds the Food and Drug Administration's (FDA's) efforts to do so. GEHC has already undertaken additional research to better understand the issue and is fully committed to undertake further nonclinical and clinical research to evaluate if there is any short, medium, or long-term risk to patients. Our understanding in this matter today is consistent with the FDA's safety communication briefing on this matter and communication from the American College of Radiology (ACR) and the ISMRM. While we believe that there are trace amounts of Gd retained in the brain, there are no harmful effects to date with brain Gd retention.

GBCA's are used in clinical practice because of their utility. All GBCAs result in Gd detectable in the brain as well as other parts of the body; thus, the differences are currently quantitative rather than qualitative.

- Whilst acknowledging the well-known limitations of AE reporting, it remains a fact that after hundreds of millions of Gd-enhanced imaging procedures over many years of use, we are not aware of any established clinical consequences of brain Gd.

- Without clinical consequences (and a correlation with brain Gd) it is impossible to establish a level of brain Gd that could trigger a safety concern.

- Given the state of knowledge, labelling changes can be made for the entire class of GBCAs highlighting the current observations, and emphasizing that GBCAs should be used only when clinically necessary in accordance with the appropriately calculated dose. Modified labelling has proven to be effective in mitigating a known adverse event Nephrogenic Systemic Fibrosis (NSF) over the last 9 years.

This Briefing Document summarizes GEHC's understanding of current knowledge on this topic and plans for further research to improve understanding of GBCA retention in the body. The benefits of Omniscan and the indications are all well-known and available in the US package insert, and therefore are not covered in detail.

2   BACKGROUND

Like all other approved GBCAs, Omniscan uses the paramagnetic element Gd to produce magnetic resonance (MR) image contrast, and the Gd is bound to a chelating agent to limit toxicity following intravenous administration. Omniscan is distributed in the body's extracellular fluid, and is eliminated by the kidneys at a rate related to the glomerular filtration rate (GFR). In patients with severe renal impairment, the elimination of Omniscan and other GBCAs is prolonged.

The most important clinical risks for the class of agents include immediate acute hypersensitivity reactions, including fatalities, NSF, and acute kidney injury.

Acute hypersensitivity reactions have been described for all agents in the class. Although the majority of reactions are minor and resolve spontaneously, they remain problematic for patients and health care providers as they typically cause sufficient discomfort to cause patient motion in the MR scanner or the need to abort the study. Patient motion causes artifacts in images and the potential for misdiagnosis, while aborted scans require a rescheduled exam with repeated dosing with another GBCA agent or the use of other imaging modalities such as CT with risks from iodinated contrast media and ionizing radiation. More serious reactions are less common but require medical treatment, and in some cases, can be fatal despite local acute care. Previously, a large number of independent clinical studies have shown concordant results, and demonstrate that nonionic, linear GBCAs such as Omniscan have measurably lower acute hypersensitivity reaction (HSR) rates than other agents in the class, as discussed further below. The second major risk concern for the class is for NSF. In December, 2009, all manufacturers including GE Healthcare (GEHC) provided a comprehensive review of Omniscan safety at a joint meeting of the Cardiovascular and Renal Drugs Advisory Committee and the Drug Safety/Risk Management Advisory Committee. Labeling changes were subsequently implemented, including class warnings and, for some agents (including Omniscan), contraindications. These measures have been particularly successful in avoiding further cases of NSF, as there have been no medically confirmed reports of NSF associated with a post-September 2008 administration of Omniscan (over 25 million administrations). To our knowledge, rare recent reports of NSF for the class of GBCAs appear to be associated with exposure prior to 2007 [Yang et al. 2012].

NSF risk appears to be confined to patients with severe or acute renal impairment, and may be associated with prolonged retention of the GBCA in some organs including skin and bone. Modified labelling has proved to be effective in mitigating a known adverse event (AE) NSF over the last 9 years.

In contrast to the situation with severe renal impairment, most of a dose of Omniscan and other GBCAs is eliminated within 24 hours in patients with normal renal function. However, recent evidence shows that small amounts may be retained in the body, including in the brain, and this has received considerable attention from academic and industrial researchers as well as regulatory authorities. Long-term retention of trace levels of Gd has been described in several organs after intravenous doses of all agents in the GBCA class, including the brain, and this constitutes a potential risk for the class. The clinical significance of brain Gd remains unclear, as there is no evidence of harm from it. Review of the current evidence base and associated risks to public health form the basis for the upcoming FDA MIDAC Meeting and form the body of this submission, in which we describe and analyze available evidence on the topic of brain and tissue Gd retention.

2.1 Brain Gd Retention

In July 2015, the FDA issued a Drug Safety Communication stating that it is unknown whether Gd retention within the brain is harmful or could lead to adverse health effects [FDA 2015]. The communication emphasized the importance of limiting use of GBCAs to circumstances in which the information provided by the contrast agent is necessary; additionally, healthcare professionals were encouraged to reassess the necessity of repetitive GBCA examinations. No drug labeling alterations were assessed as necessary at that time and further research was encouraged to clarify any potential risks.

Since this time, GEHC has had several interactions with the FDA, aiming at a revision of the FDA posting by providing new and balanced data to clarify our position and avoiding potential misleading of the readers.

In May 2017, FDA issued an update to its 2015 Drug Safety Communication, which stated that FDA has identified no harmful effects to date from brain retention of GBCA, but that they will continue to review the issue [FDA 2017].

GEHC has completed a comprehensive review of published reports of brain Gd retention, thoroughly assessed clinical adverse event reports in the Omniscan pharmacovigilance (PV) program, spoken extensively with physicians and scientists in the USA regarding the benefits and risks of GBCAs. In addition, we have initiated an extensive research program to evaluate the nonclinical and clinical risks of toxicity to characterize the nature and potential consequences of brain Gd retention. The following points summarize the key observations:

- Peer-reviewed publications provide MR imaging evidence of prolonged brain Gd retention following the administration of all studied linear (Magnevist, Omniscan, MultiHance and Eovist) and macrocyclic (ProHance, Dotarem and Gadavist) GBCAs. Brain structures particularly involved were the globus pallidus (GP) and dentate nucleus (DN). Prolonged retention in other tissue has not been systematically examined using imaging techniques.

- Non-contrast, T1-weighted (T1w) MR imaging shows signal hyperintensities in the DN and GP after repeated GBCA administrations, typically being visible after more than 4 doses. These findings occur in patients with normal or impaired renal function. It remains unclear if there are subgroups who do not exhibit this phenomenon.

- Human autopsy studies using direct chemical analytical methods (inductively coupled mass spectrometry – ICP-MS) corroborate the presence of Gd within the DN and GP, as well as lower levels within other regions of the cerebellum and cortex. However, these methods are unable to discern whether the retained Gd remains within a chelated structure. Limited available data indicate that the majority of the Gd may be localized near the basal lamina of the endothelial cells, while some Gd appears to reach the neuropil.

- Review of GEHC-sponsored nonclinical studies verified no histopathological neurotoxicity following single and repeat-dose intravenous Omniscan administration studies in rats, rabbits, and monkeys.

- Recent, well-controlled and published animal studies after repeated dosing show trace levels of Gd retention in the brain with all agents studied, including linear and macrocyclic agents. Levels vary by product, and are generally higher after linear agents, though still at trace levels representing about one-millionth of the injected dose.

- Several studies conducted by different manufacturers and independent researchers show no evidence of inflammation or histopathology in light micrographs or TEM ultrastructural abnormalities at 1-week post-dosing; one study also shows normal histology and ultrastructure at up to 50 weeks post-dosing. Animal studies have investigated doses between 20 to 80x human equivalent doses.

- Animal studies and limited human reports also indicate retained Gd in other tissues at higher levels than in the brain.

- Gd tissue levels may be a poor surrogate marker for potential toxicity, as demonstrated by the severe kidney toxicity observed only with the macrocyclic GBCA with the lowest levels of retained Gd in a rat model.

- The GEHC ongoing PV assessment of Omniscan indicates no change in the drug's safety reporting profile since the NSF-related labeling changes of 2007, based upon a survey of neurological symptoms or lasting symptoms. The PV experience includes reports of imaging and autopsy evidence of brain Gd retention that are not associated with neurological or clinical symptoms. A focused PV examination of individual case safety reports (ICSRs) shows no identifiable pattern of signs or symptoms attributable to potential injury of the brain DN or GP from brain Gd retention.

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- Two large clinical studies on brain Gd effects show well-powered evidence that motor and cognitive function is not affected in long-term follow up of cases exposed to repeated GBCA dosing. One of these studies shows that in a cohort of over 1,300 patients, progression of an elderly cohort from normal cognition to mild cognitive impairment (MCI) was unaffected by Omniscan after repeated doses that reflect normal clinically indicated scans, and that neither motor function nor cognition were different from matched controls. These patients are monitored every 15 months with full access to all patient records.

Overall, cumulative clinical and nonclinical data show that GBCAs, including Omniscan, are associated with Gd retention in the body that appears dose-related and unrelated to renal function. No short or long-term clinical consequences have been attributable to these trace levels of retained Gd. Accordingly, we conclude that the benefit-risk balance remains positive for Omniscan.

GEHC has initiated a comprehensive nonclinical and clinical research program to address remaining gaps in knowledge. Enhanced vigilance and steps to assure that GBCAs are only used in situations where the diagnostic information is clinically important, and where doses are minimized, will help mitigate GBCA risks while researchers work to further understand any potential risks. Additionally, GEHC describes below potential amended labeling text to enhance the safe use of GBCAs.

2.2   MRI and GBCAs

MRI is a safe, non-invasive method of creating medically useful images of the inside of the body. MRI works by passing radio waves through the body while it is inside the strong magnetic field of the MRI scanner. Some of the waves are temporarily received by hydrogen atoms in water (H_2O) molecules in the body, and then re-transmitted. The re-transmitted waves are received by an antenna, and a computer converts the waves into images of the interior of the body.

Since its widespread introduction in the 1980s, MRI has become an indispensable diagnostic imaging method. Due to its unique soft tissue contrast capabilities, MRI excels at visualizing vascular and neoplastic lesions of the brain and spinal cord. However, in many clinical situations, plain MRI (i.e., MRI without contrast enhancement) is not sufficient, and use of an intravenous contrast agent is required to provide contrast enhancement of tissues.

One class of contrast agents is the GBCA, which are injected intravenously shortly prior to MRI scans. GBCAs exploit the highly paramagnetic properties of the chemical element Gd. In the body, GBCAs shorten the time (called T1) needed for hydrogen atoms to re-transmit absorbed radio waves, thereby increasing the intensity (brightness) of body regions containing the GBCA, and resulting in increased contrast between regions with and without the GBCA.

Virtually all GBCAs are complexes formed between a Gd(III) ion (Gd^{+3}) and an organic ligand, with electrostatic interactions keeping the Gd^{+3} complexed to the ligand. Without such complexation, Gd may be more toxic, as reported in previous animal studies.

GBCAs can be classified by the shape of the unbound ligand and the net charge on the Gd complex. Regarding shape, some GBCA ligands are large cyclic molecules, and GBCA formed from these ligands are accordingly called macrocyclic. Other GBCA ligands are non-cyclic, almost linear, and GBCA formed from these ligands are called linear. Regarding charge, GBCAs with a net charge are called ionic and those without a net charge are called non-ionic. GBCAs can be described by both characteristics; for example, GBCA can be linear ionic, macrocyclic non-ionic, etc. Some of the linear GBCA have the additional quality of transiently binding with serum protein to form larger complexes that enhance T1 relaxivity and confer partial hepatobiliary excretion.

Because the GBCAs are hydrophilic, they initially were not expected to cross an intact blood-brain barrier (BBB). Hence, GBCAs were shown to be useful for enhancing lesions and tumors associated with BBB disruption, and GBCA appeared to enter the brain only in these conditions. Although a recent publication ([McDonald et al. 2015]) suggested that GBCAs may cross or bypass an intact BBB, on-label use of GBCAs has not been associated with any adverse clinical CNS syndrome linked to brain Gd exposure, despite over 20 years of post-market safety surveillance.

Table 1 lists the currently commercially available GBCA by their classifications.

Table 1   Gadolinium-based Contrast Agents (GBCAs)

Subclass	Trade (generic) Name*	Generic Name	US Approval
Linear Ionic	Magnevist®	gadopentetate dimeglumine	1988
	MultiHance®	gadobenate dimeglumine	2004
	Eovist®	gadoxetic acid disodium	2008
	Ablavar® *	gadofosveset trisodium	2008
Linear Non-ionic	Omniscan™	gadodiamide	1993
	OptiMARK®	gadoversetamide	1999
Macrocyclic Ionic	Dotarem®	gadoterate meglumine	2013
Macrocyclic Non-ionic	Gadavist®	gadobutrol	2011
	ProHance®	gadoteridol	

*No longer marketed in the US.

OMNISCAN™ (gadodiamide) is a linear, non-ionic, non-protein binding GBCA for enhancing MRI examinations. Omniscan has been investigated under IND 32,218 and approved under NDA 20-123 in 1993. Omniscan is marketed in over 100 countries worldwide, including the United States. Numerous clinical studies and decades of use in tens of millions of patients support the overall safety of Omniscan in its intended use. Identified class risks of GBCAs continue to be effectively mitigated through the label.

2.3   Safety of GBCAs

Historically, short-term safety profiles of GBCAs have indicated very good tolerability. Most approved GBCAs, including Omniscan, are distributed in the body's extracellular fluid following administration, and are eliminated renally at a rate equal to the glomerular filtration rate (GFR). With normal renal function, most of a dose of GBCA is eliminated within 24 hours. In impaired renal function, however, elimination is prolonged in inverse proportion to the GFR (i.e., the lower the GFR, the more prolonged the elimination).

Extensive post-marketing experience in renally impaired patients found that GBCA use in patients with severe renal impairment is associated with an increased risk for the development of NSF [Yang et al. 2012]. In 2007, manufacturers of the GBCAs approved in the US amended their drug labeling to include a warning of the risk of NSF in patients with severe renal impairment. This labeling change and other awareness measures have been successful in avoiding further cases of NSF. There have been no medically confirmed reports of NSF associated with a post-September 2008 administration of Omniscan, and we estimate over 25 million Omniscan administrations over that period. In 2011, manufacturers of three linear GBCAs (Magnevist, OptiMARK, and Omniscan) were asked by FDA to contraindicate use in severely renally impaired patients, adding another layer of patient protection. Again, these mitigation strategies appear to have been successful, because recent reports of NSF across the class of GBCA appear to be associated with exposure prior to 2007 [Yang et al. 2012].

In 2014, new data with unenhanced T1w MRI scans showed that areas of the dentate nucleus and GP appeared brighter than expected in patients with a prior history of multiple GBCA exposures **[Kanda et al. 2014]**, **[Errante et al. 2014]**, [Quattrocchi et al. 2015]). Subsequently McDonald [McDonald et al. 2015] showed that there was a strong correlation between T1-weighted hyperintensities in these regions and autopsy tissue content of Gd determined with very sensitive ICP-MS techniques.

In September 2014, FDA's Division of Medical Imaging Products (DMIP) contacted GEHC and other manufacturers of GBCAs, noting that FDA had reviewed published medical literature and had received a FDA Adverse Event Reporting System (FAERS) report of possible prolonged Gd retention in the brain of patients with a history of multiple GBCA MRI scans. FDA commented that the reporting frequency and significance of these findings were not clear and requested that GBCA manufacturers review PV data and provide an overview and summary of similar cases of Gd retention in the brain or other organs.

GEHC's response included a summary of 3 reported adverse events identified through searches of the GEHC pharmacovigilance database. All 3 reports originated from the 2 articles cited by the FDA in its inquiry to GBCA manufacturers [Errante et al. 2014]; [Kanda et al. 2014]. GEHC concluded that "the mechanism(s) behind this finding and its clinical significance are presently unknown."

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In June 2015, FDA notified the GBCA manufacturers that a TSI on the Gd retention issue for GBCAs, including Omniscan, had been initiated. The TSI was classified as standard, and the FDA indicated it would perform quarterly evaluations of the hazard and seriousness, and may propose further actions based on this ongoing evaluation. The following month, the FDA informed GEHC that the Agency would be issuing an Early Drug Safety Communication to "inform the public and practice community that we have reviewed the reports of gadolinium in the brain following multiple GBCA MRIs". FDA posted the communication on the FDA website and as a routine follow-up of their TSI. GEHC has since had several interactions with the FDA to provide new and balanced data.

In May 2017, the FDA issued a Drug Safety Communication indicating they had identified "no harmful effects to date with brain retention of gadolinium-based contrast agents for MRIs; review to continue".

As with any drug, the overall acceptability of a specific GBCA relies on a sound assessment of the drug's benefits and risks to patients. All drugs have risks, but drugs that are medically useful in clinical practice have benefits that outweigh those risks; i.e., there is a positive benefit-risk ratio or balance. Risks can be *identified* (actually observed) or *potential* (considered possible based on theoretical considerations, analogy, or precedent with other drugs). While potential risks warrant careful continuing PV, they are not typically weighted as heavily in a benefit-risk assessment as should be identified risks. As evident from the data shown below, the retention of Gd in the body currently is a *potential* risk, and the available evidence suggests lack of harm to patients. As such, it warrants continuing attention but no critical regulatory actions. Below, we propose actions that GBCA manufacturers may take to raise healthcare-provider awareness of the potential risk posed by Gd retention, to study it further, and to be able to rapidly identify any evidence of harm.

Although some literature refers to Gd deposition, this may imply a more or less irreversible presence of the Gd, whereas there is evidence to show at least some clearance of Gd from the brain over time, as discussed below. Thus, the term *Gd retention* is used herein to more accurately describe a situation of possible trace amounts of GBCAs or Gd in some form remaining in the body before subsequent wash-out or dissipation.

3   CLINICAL DATA ON GADOLINIUM RETENTION

This section summarizes Omniscan literature on Gd detection and quantification in the human brain. Earlier literature concluded that brain retention of Gd followed multiple administrations of only linear and not macrocyclic GBCAs. More sensitive ICP-MS studies and more recent MR imaging studies, with higher exposure and/or more sensitive quantitative techniques, have clearly shown brain Gd presence after repeated exposure to macrocyclic (ProHance and Gadavist) as well as linear (Magnevist, Omniscan, MultiHance, and Eovist) GBCAs.

3.1 MRI Evidence of Gd Retention in Brain

Concern over Gd retention in brain was initiated by reports of unexpected increased MR signal on T1w unenhanced MR images (called T1w hyperintensity) in patients who had previously received multiple doses of one or more GBCA. Most of the published literature on Gd retention reports MR evidence of Gd retention, and this section summarizes that literature. However, MR is not as sensitive as other analytical methods (e.g., inductively coupled plasma – mass spectrometry, or ICP-MS) for detecting Gd, as discussed in Section 3.1.2, below. Virtually all of the literature to date is based on brain imaging; we are unaware of any reports of MR hyperintensity outside the brain. The majority of reports have been in adults. In some reports, the hyperintensity was visually apparent; in other reports, it was detectible only by quantitative image analysis of regions of interest (such as the GP and DN). Following is a summary of the available literature. It is quite clear that retention happens with MR administration of all types of GBCAs. With the T1w-based hyperintensity MR imaging studies it is important to note the limitations of the detection technique and methodology used before drawing broad conclusions about presence or absence of retention with a specific type or class of agents.

None of these studies found clinical sequalae or correlates for increased signal intensity (SI) in the brain.

Key early studies in adults that focused on the linear class of agents and highlighted the phenomenon are: [Kanda et al. 2014], [Errante et al. 2014], [Quattrocchi et al. 2015]. There were several studies done to speculate that hyperintensity exists only with linear agents but not with macrocyclics [Radbruch et al. 2015a], [Radbruch et al. 2015b]. Other studies ([Vatnehol et al. 2016], [Marsecano et al. 2017], [Bjornerud et al. 2017], [Moreno Negrete et al. 2017], [Kang et al. 2017]) showed that broad deduction that the phenomenon does not exist in macrocyclic agents is incorrect. Also, most of the linear agent studies involved Magnevist and Omniscan. Studies now indicate that MultiHance and Eovist also exhibit this T1w hyperintensity phenomenon [Metting et al. 2016], [Kahn et al. 2017].

Studies in pediatric populations have also been performed with linear as well as macrocyclic agents and the findings are similar ([Hu et al. 2016], [Flood et al. 2017], [Espagnet et al. 2017]). These reports indicate that T1w hyperintensity also occurs in children, with both linear and macrocyclic agents in a dose dependent manner. As in adults, none of these reports indicated any harm in association with the brain hyperintensity.

A brief synopsis for each of the studies on this topic is found in [Appendix A].

These reports were important in raising the possibility of Gd retention in the brain, and the fact that MR imaging itself can be used as a detection tool despite all its limitations. There is increasing evidence that while there are likely differences in the extent of hyperintensity, the phenomenon exists in all agents. None of these reports indicated any level of patient harm in association with the hyperintensity. The discrepancy in results across the various GBCAs is likely due to limitations of the detection technique, methodology used, and study design. These prompted others

to perform direct quantification of brain Gd using more sensitive methods such as ICP-MS (see Section 3.1.2).

3.1.1 Other Possible Causes of T1 Hyperintensity

In considering reports in the literature of Gd retention in brain based on findings of unexpected increased MR signal on T1w hyperintensity, it is important to keep in mind that there are other possible causes of T1 hyperintensity not associated with Gd, as discussed next.

3.1.1.1 Medical Conditions Associated with T1 Hyperintensity in Brain

A wide range of clinical pathologies may be associated with hyperintensity on T1w images that are not due to Gd (Table 2). The table below displays the underlying clinical conditions and specific location of hyperintensity within the brain.

The implication of these observations is that when reading and interpreting MRI images, radiologists must be knowledgeable about both the T1 signal increases after repeated administrations of GBCAs and also about the T1 increases in CNS locations that may be due to the underlying clinical pathologies, and must consider the differential diagnosis appropriately. The hyperintensity finding associated with multiple GBCA administrations should be added to the differential diagnosis of a high SI in DN and GP.

Table 2   Hyperintensities in DN and GP vs Brain Pathologies

Author	Hyperintensity in DN on T1	Hyperintensity in GP on T1	Hyperintensity elsewhere on T1	Underlying diagnosis
[Absinta et al. 2011]	Bilateral			MS with mild disability
[Roccatagliata et al. 2009]	19.3%			MS with severe disability and with high T2 lesion load.
[Zimny et al. 2013], [Ginat and Meyers 2012]	Bilateral		Basal ganglia, thalamus, semi oval center	Fahr's syndrome. Bilateral striato-pallido-dentate calcinosis
[Ginat and Meyers 2012]	Yes		Lentiform nuclei	Cockayne syndrome
[Ginat and Meyers 2012]		Bilateral	Substantia nigra bilaterally	Hepatic encephalopathy
[Ginat and Meyers 2012]		May be present	Substantia nigra (potentially)	Neurodegeneration with brain iron accumulation
[Ginat and Meyers 2012]		May be present		Type 1 neurofibromatosis if located there
[Kasahara et al. 2011]	May be seen			After brain irradiation (but question what the diagnoses behind were)

In patients who undergo serial MR examinations for disease surveillance, any T1w hyperintensities would also need to be considered. For example, in patients with multiple sclerosis (MS), guidelines recommend that serial MR examinations be performed every 6 to 24 months to look for dissemination of the disease, as well as treatment-related adverse reactions such as progressive multifocal leukoencephalopathy [Traboulsee et al. 2016], and it would be important to compare scans within a series to detect T1w hyperintensity and to avoid misinterpretation.

3.1.1.2   Other Metals in the DN and GP

It is important to note that some other metals and some naturally occurring substances also can accumulate in the brain and increase the T1 signal in direct proportion to the concentration of the accumulated substance. These substances include methemoglobin, melanin, lipids, proteins, and metals (e.g., manganese, copper, iron, and calcium). Calcifications may exhibit high signal on T1w images if they contain diamagnetic calcium salts. Paramagnetic cations such as iron and manganese may also cause shortening of T1 relaxation time [Ginat and Meyers 2012]; [Zimny et al. 2013]. The DN is particularly metal-rich with copper localized to the periphery and iron and zinc abundant centrally [Popescu et al. 2009]. The accumulations of calcium and iron are usually incidental findings with no known toxicological importance. In contrast, accumulations of manganese and copper may have toxicological importance, depending on concentration. However, no conclusions about the potential biological effects of retained Gd can be drawn from studies of the toxicology of manganese or copper because of each of these metals has its own chemical properties and specific biochemical behavior. For example, some manganese ions are powerful oxidants.

3.1.2   Direct Sensitive Detection of Gd in Brain Tissue

As mentioned, above, MR hyperintensity is not the most sensitive method for detecting Gd, and it also is not specific for Gd (e.g., various pathologic conditions and other metals may also cause hyperintensity). More sensitive and specific methods such as ICP-MS can detect lower concentrations of Gd and can also directly identify Gd through its unique atomic weight, using mass spectrometry. Unfortunately, these methods require a sample of tissue, which must be collected via biopsy or autopsy. In this section, we summarize literature on direct detection and quantification of Gd in the brain, in adults and children. Unless mentioned otherwise, each study was conducted in adults.

[McDonald et al. 2015] first reported the results of an autopsy study that sought to directly determine if the prior reports of SI following multiple GBCA administrations were associated with detectable brain Gd. The SI from unenhanced T1w MR images and the post-mortem neuronal tissue samples from 13 subjects who previously had 4 to 29 brain MR examinations using Omniscan (gadodiamide; linear non-ionic; cumulative dose 52 to 420 mL) were compared with those of 10 GBCA-naive controls. All subjects in the contrast group had brain tumors of different types or metastases. Neuronal tissues from GBCA patients contained 0.1 to 58.8 μg-Gd/gram-tissue, and tissue from the control group had no detectable Gd. A significant, moderate to strongly positive dose-dependent relationship correlated with SI changes on T1w MR images in all

neuroanatomic areas studied (i.e., DN, pons, GP, thalamus), most notably the DN (ρ = 0.49–0.93), but the correlation was weaker for GP (the GP correlation coefficient = 0.49, p = 0.08). All subjects in the GBCA group had normal renal function at the time of MR examination (eGFR were $\geq$60 mL/min/1.73 m^2 in 12 and 57 mL/min/1.73 m^2 in 1). Median eGFR was weakly associated with tissue Gd concentration. Gd was observed only in the contrast group, predominantly in the capillary endothelium, but also present in the neural interstitium.

X-ray microanalysis confirmed Gd in brain tissue, prominently clustered in large foci within the endothelial wall; however, densitometry performed with wider-field views suggested that 18% to 42% of Gd appeared to have crossed the BBB and had passed into the neural tissue interstitium. However, the exact location of Gd was not established with certainty. Importantly, there are some technical limitations when assessing how much Gd in the brain tissue has crossed the BBB. The difficulty in preserving morphology of cadaveric specimens can make interpretation difficult and quantitation of potential interstitial levels by densitometry is an indirect estimation of Gd concentration (as acknowledged by the authors).

McDonald's results showed a significant dose-dependent relationship between multiple intravenous (IV) GBCA administrations and subsequent presence of Gd in the brain, independent of age, sex, baseline renal function, or interval between GBCA exposure and death. No clinical signs or symptoms correlated with brain Gd were reported.

In summary, there was a correlation between cumulative dose, the amount of Gd measured in autopsy samples (µg-Gd/g-tissue), and the observed increases in T1 SI on unenhanced MRI following repeated GBCA doses. The authors concluded that IV GBCA exposure is associated with the presence of Gd in the brain of subjects who had "relatively normal" renal function. The authors listed the following study limitations:

- The currently available tissue-based assays can detect Gd, but sample preparation destroys the GBCA organic ligand. Thus, the chemical form of Gd in brain tissues (i.e., chelated or not) is unclear. Identifying the chemical form of Gd is important to understand the mechanism of and risks associated with Gd in tissue.

- Estimates of the relative amounts of Gd in the neural tissue interstitium should not be viewed as an exact quantitative assay of the amount of intracellular Gd that has crossed the BBB.

The novelty of the McDonald study is confirmation of brain Gd at the sites of enhanced T1 signal. There was a strong statistical correlation between: cumulative Gd dose and T1 signal; cumulative Gd dose and the Gd brain concentration; and T1-signal intensities and Gd concentration in the DN (although this correlation was weaker for some brain regions [e.g., the GP correlation coefficient = 0.49, p = 0.08]). This study provided evidence that the observed T1 enhancement may be related to Gd in the brain, although the relationship is stronger in some regions than in others, suggesting that additional factors may contribute to T1 SI in certain brain regions. *The chemical form of Gd is unclear, as is the clinical significance of the brain Gd*.

Caution should be exercised in interpreting the Gd concentrations reported because the denominator (gram of tissue) may exceed the weight of the relevant brain structure. For example, the volume of the DN was reported by [Diedrichsen et al. 2011] to be 362.8 (left side) and 366.1 (right side) mm^3, respectively, which would give a total volume of 728.9 mm^3, or 0.7289 cm^3. Assuming the density of brain tissue to be 1.04 g/cm^3 [McDonald et al. 2015], then the weight of the DN would be 1.04 g/cm^3 x 0.7289 cm^3 = 0.7581 grams. Thus, the total Gd burden in the DN of the patient with the highest reported concentration (58.8 mcg/g) would actually be 0.7581 g x 58.8 mcg/g or 44.6 mcg. This represents 0.000135% of the cumulative dose of Omniscan.

Using post-mortem tissue analysis with ICP-MS, [Murata et al. 2015] (abstract previously authored by [Huang et al. 2015]), aimed to determine whether Gd is retained in brain tissue in patients without renal dysfunction receiving either macrocyclic or linear GBCAs. Brain tissue was collected at autopsy from 9 decedents with available medical records that documented history of MRIs with or without GBCA exposure. Nine subjects with no prior MRI or non-Gd MRI served as controls. Tissue samples from the white matter, putamen, GP, caudate nucleus, pons, and DN were analyzed for Gd (ICP-MS). When available, bone and skin samples were also analyzed as a reference. No decedents had severe renal failure, based on eGFR. Of the 9 cases who had been administered GBCA, there were 2 subjects with Gadavist (gadobutrol; macrocyclic non-ionic), 5 with ProHance (gadoteridol; macrocyclic non-ionic), 1 with Eovist (gadoxetate; linear ionic), and 1 with MultiHance (gadobenate; linear ionic). Total administered dose ranged from 5 to 126 ml, and total number of CEMR examinations ranged from 1 to 11. Control subjects showed Gd levels at or below limits of measurement in all brain tissue areas, including the GP and DN. Gd was detected in all brain regions sampled after only a single dose of contrast (Gadavist). Interestingly, one patient had significant levels of Gd present in the dentate nucleus and globus pallidus more than 1 year after the final exposure to 2 doses of Gadavist. The levels observed in this patient were more than 100-fold higher than could be measured in any of the 9 control patients without prior GBCA exposure. This study shows that, similar to linear agents, exposure to macrocyclic agents results in the presence of Gd in the human brain that can persist for longer than 1 year. Bone samples showed significantly higher Gd levels than the brain and a correlation of retention between brain and bone was observed. The investigators concluded that Gd retention in normal brain and bone tissue occurs with macrocyclic and linear GBCAs in patients with normal renal function.

[Kanda et al. 2015b] used mass spectroscopy to evaluate the presence of Gd in brain tissues, including the DN and GP. Brain tissues obtained at autopsy from 5 subjects who had received at least 2 administrations of a GBCA (GBCA group) and 5 subjects with no history of GBCA administration (non-GBCA group) were evaluated. All subjects had eGFR $\geq$45 mL/min/1.73 m^2. All subjects in the GBCA group had received a dose of 0.1 mmol/kg for each examination. Subjects in the GBCA group received Magnevist (gadopentetate; linear ionic), Omniscan (gadodiamide; linear non-ionic) and ProHance (gadoteridol; macrocyclic non-ionic). Three patients had Magnevist only. No subject received either ProHance or Omniscan alone; therefore, 2 cases were confounded by the administration of multiple contrast media. Gd was detected in all specimens from the GBCA group, with significantly higher concentrations reported than in

specimens from the corresponding region from subjects in the non-GBCA group. The reported presence of Gd in the control (non-GBCA) group suggests prior unreported Gd administration, environmental exposure, or possibly specimen contamination during the preparation process. This very small cohort study confirms that Gd may be detected in the brain after multiple administrations of Magnevist and possibly other GBCAs (Omniscan and ProHance).

Another abstract by [McDonald et al. 2016c], sought to determine if brain Gd might be related to BBB integrity by studying adult patients in the absence of intracranial pathology that might affect the permeability of the BBB. They compared post mortem neuronal tissue samples (the DN, GP, and thalamus) from 5 patients who received 4-16 MRI exams using Omniscan (gadodiamide; linear non-ionic) to 10 Gd-naive (controls). Tissues from the 4 neuroanatomical regions of Gd-exposed patients contained 0.1-19.4 µg-Gd/g-tissue in a significant dose-dependent relationship (GP: rho: 0.90, p = 0.04). The control group sample had no Gd detected by ICP-MS. Two of the 5 contrast patients had borderline renal function (eGFR ~ 30) and hepatobiliary dysfunction at the time of MRI examination(s). Brain Gd in the contrast group was localized to the capillary endothelium and neuronal interstitium using TEM-EDS. The authors concluded that Gd retention can occur following GBCA exposure without intracranial pathology that might affect BBB permeability, and did not report any clinical sequelae related to brain Gd.

To date there appears to be one study directly detecting brain Gd in children. [McDonald et al. 2016b] examined 3 pediatric patients (age 6-13) to determine if repeated IV exposures to Omniscan were associated with detection of elemental Gd in neuronal tissues (DN, pons, GP, and thalamus). These subjects were compared to 3 GBCA-naive pediatric patients (age 5-7). Gd tissue concentrations were quantified by ICP-MS and localized using TEM with electron dispersive spectroscopy (TEM-EDS). All contrast-exposed patients underwent MRI for evaluation of a primary CNS neoplasm whereas control patients underwent MRI for non-neoplastic intracranial processes. All contrast-exposed patients had normal renal and hepatobiliary function near the time of Gd exposure. Following 4-11 IV GBCA doses, the brain of the contrast exposed group contained between 0.1-3.0 mg Gd/g tissue in a significant dose-dependent trend (DN: rho = 0.99, p<0.0001). Control patients had undetectable levels of Gd in all sampled neuroanatomical locations. Gd in the capillary endothelium and neural interstitium was observed only in the contrast-exposed group using TEM-EDS. The authors concluded that in the pediatric population, intracranial Gd in the brain from IV GBCAs occurs in a dose-dependent manner in the setting of normal renal and hepatobiliary function and an intact BBB. No clinical sequelae to brain Gd were reported. We know that the abstract has a misprint ("mg Gd/g tissue" printed instead of "µg Gd/g tissue") (McDonald, personal communication).

These reports confirm brain Gd retention at low levels in adults and in children as young as 6 years old, with linear and macrocyclic GBCA.

3.1.3   Mechanism of Gd Distribution to Brain with Normal BBB

To date, the precise mechanism involved in transfer of GBCA from the blood to the brain through a normal BBB is unknown. Recent literature reports that Gd may be permeating from the blood

vessels into the CSF space and perivascular spaces, which could be the route by which GBCA are distributed to brain parenchyma in subjects with normal BBB.

[Naganawa and Taoka 2016] observed increased signals in the perivascular space (PVS) in MR images obtained 4 hours after IV administration of GBCA in humans without renal insufficiency. Contrast enhancement of CSF was also observed. The authors concluded that GBCA might have permeated from the blood vessels into the CSF space and PVS, which could be the route by which GBCA are distributed to brain parenchyma in subjects with a normal BBB. The type of GBCA was not specified in the abstract.

[Cao et al. 2016b] compared 36 patients on chronic hemodialysis who received GBCA (Omniscan, Magnevist, MultiHance) to 3 groups of control patients. Cao observed a trend toward increased choroid plexus SI after GBCA exposures, adding support to a hypothesis that Gd may reach the brain parenchyma via the CSF (see additional details on the [Cao et al. 2016b] study above).

3.1.4 Detection of Gd in Non-Brain Tissues

Most of the reports of Gd retention pertain to the brain, and few studies of Gd retention outside the brain have been reported. Below are summaries of literature reports of detection of extracranial Gd in patients with apparently normal renal function. Reports of extracranial Gd detection in NSF patients have been excluded.

Using ICP-AES, [Gibby et al. 2004] measured bone (femoral head) Gd levels in patients who received 0.1 mmol/kg of either linear gadodiamide (n = 10) or macrocyclic gadoteridol (n = 8) within 3 to 8 days before total hip arthroplasty with removal of the femoral head, and compared them to similar results obtained in age-matched controls (n = 7). There were no significant differences between the 3 groups in average age, and no significant difference between the GBCA groups in the average time from GBCA administration to surgery. The average concentrations (SD) of Gd, in mcg/g-fresh bone, were 1.18 (0.787) in the gadodiamide group and 0.466 (0.387) in the gadoteridol group (difference significant; p = 0.0165). The ratio of the bone concentrations (1.18/0.466 = 2.5) is about 10 times smaller than what would be expected based on the ratio ($10^{17.2}/10^{14.8} = 251$) of their conditional stability constants [Sherry et al. 2009], and about 3 million times smaller than what would be expected from the ratio of their thermodynamic stability constants ($10^{23.8}/10^{16.9} = 3,177,312$), suggesting that chelate stability does not explain the relative amounts retained.

[White et al. 2006] reported using ICP-MS to analyze different samples of the **bone** specimens previously analyzed in [Gibby et al. 2004], although the numbers of patients in each group differed from the original article, without explanation. As before, the mean femoral head bone Gd level (mcg/g-fresh bone) was significantly (p < 0.02) higher in the gadodiamide group (1.77 [SD 0.704]; n = 9) than in the gadoteridol group (0.477 [SD 0.271]; n = 10). As before, the ratio (3.7) of Gd level in the gadodiamide group to the Gd level in the gadoteridol group differs considerably from what would be predicted based on conditional and thermodynamic stability constants, suggesting that the difference in Gd level is not explained by the relative GBCA stabilities.

Using ICP-MS, [Darrah et al. 2009] measured Gd levels in bone tissue from the femoral heads from 31 patients who had undergone total hip replacement, 13 of whom had undergone prior Gd-MRI examinations up to 8 years before surgery ("exposed" group; 6 with gadodiamide, 5 with gadoteridol, and 2 with unknown GBCAs; reasons for surgery were osteoarthritis in 7 cases, and fracture in 6 cases), and the remaining 18 of whom had surgery for osteoarthritis with no history of Gd exposure ("control" group). Patient renal function, number of Gd exposures, and doses of GBCA were not reported. In cortical bone, Gd levels (nmol/gram) ranged from 0.01 to 1.86 in the control group and from 0.07 to 31.0 in the exposed group. Excluding the outlying value of 1.86 from the control group, the range was 0.01 to 0.06, with a mean value of 0.03 (95% CI 0.023, 0.041). In the exposed group, the mean was 9.36 (95% CI 4.09, 14.63). The difference between the mean Gd levels was significant (p <0.001). In trabecular bone, the Gd levels in the control group ranged from 0.02 to 6.54; after excluding the outlier, the range was to 0.02 to 0.19, with a mean of 0.08 (95% CI 0.054, 0.107). The trabecular Gd levels in the exposed group ranged from 0.11 to 39.5, with a mean of 16.05 (95% CI 8.09, 24.0). The difference in mean trabecular Gd levels was significant (p < 0.001). There were no significant differences in mean bone Gd levels between the group that received gadodiamide and the group that received gadoteridol.

[Roberts et al. 2016b] reported measuring Gd levels in the skin of a patient diagnosed with glioblastoma at age 19, who subsequently underwent at least 61 Gd-MRI scans over the next 11 years with a variety of GBCAs (possibly gadobenate, gadopentetate, gadodiamide, and gadoteridol, with the greatest exposure said to likely be to gadobenate), with the last MRI occurring 8 months before skin biopsy. The patient's renal function was stated to have remained normal throughout the 11-year period; however, his eGFR values were stated to have been greater than 59 mL/min/1.73 m^2. Since normal eGFR would be $\geq$90 mL/min/1.73 m^2 [National Kidney Foundation 2002], it is unclear if the patient had renal impairment or not. Starting about 3 years before biopsy, the patient developed joint contractures that eventually made him non-ambulatory. The last MRI was performed 8 months before biopsy. The patient was reported to have progressive hyperintensity of the DN and GP on unenhanced T1w MRI. The reason for the skin biopsy is unclear, as the patient had no skin-related symptoms and had a negative examination by a dermatologist. The level of Gd determined in the skin was 14.5 ± 0.4 μg/g. Hydrophilic interaction liquid chromatography was performed on extracts of the skin biopsy to try to detect the GBCA. Peaks corresponding to gadobenate and gadopentetate were seen and increased on co-injection with authentic materials, tentatively identifying them as the GBCAs (however, no definitive identification such as high resolution mass spectrometry was performed). An unidentified peak with the shortest retention time (corresponding to the lowest hydrophilicity) was also seen. The authors recommended exercising caution in administering high cumulative doses of GBCA and keeping records of the GBCA(s) and dose(s) used.

These reports show that Gd can be retained both in and outside of the brain. Retention has been reported in skin and bone. To date, no evidence of harm has been presented.

3.1.5   Clinical Significance of Gd Retention

3.1.5.1   Adverse Effects Expected from DN and GP Pathology

A consideration of the normal functions of the DN and GP may provide insight into possible symptoms to expect if any of these structures are in fact affected by toxicity.

The DN and GP are neural structures located respectively, in the cerebellum and telencephalon. The cerebellum is located at the back of the brain and accounts for 10% of the brain's volume but contains over 50% of all neurons in the brain. The cerebellum is considered part of the motor system, though motor commands are not initiated there. Rather, the cerebellum modulates the motor commands of the descending pathways to make movements more adaptive and accurate [Glickstein et al. 2009]; [Popa et al. 2014]; [Voogd and Glickstein 1998]. The cerebellum is involved in:

- Maintenance of balance and posture

- Coordination of voluntary movements

- Motor learning (such as learning to hit a ball with a racquet)

- Certain cognitive functions [Tedesco et al. 2011]; [Salih et al. 2010] and language (though this function remains poorly understood).

All cerebellar output originates in the deep cerebellar nuclei; therefore, an injury to the cerebellar nuclei has the same result as a lesion involving the entire cerebellum. Although the DN is of primary interest to this report, the other cerebellar nuclei include the fastigial, interposed, and vestibular nuclei. The DN is the largest of the cerebellar nuclei and receives afferents from the cerebral cortex and projects to the red nucleus and the ventrolateral thalamic nucleus. In addition, the DN together with the lateral hemispheres constitutes the cerebrocerebellum, the largest functional unit of the cerebellum. More recently, imaging has played a central role in identifying the functional circuitry of the cerebellum [Kuper et al. 2012].

[Schmahmann et al. 2004] provided a concise and very detailed and extensive description of clinical cerebellar manifestations and their development. According to Schmahmann, the cerebellar motor syndrome is characterized by the following:

- Incoordination of balance, gait (ataxia)

- Extremity incoordination (dysmetria)

- Disordered eye movements

- Language/speech related (dysarthria)

- Impaired swallowing (dysphagia)

- Tremor

In addition to the information from autopsy studies, much of the knowledge on cerebellar and DN function comes from studies of subjects or experimental animals with focal damage to the DN and cerebellum [Manto 2008]; [Mamourian et al. 2000]; [Manto and Pandolfo 2002], with data on structural [Habas 2010] and functional properties provided by imaging [Timmann 2009]. As described above, damage to the cerebellum and DN is characterized by a lack of coordination, as opposed to the absence or poverty of movement frequently seen with basal ganglia (BG) damage [Jueptner and Weiller 1998]. *Ataxia* is the general term used for lack of coordination, and all or some of the following abnormalities are seen with cerebellar or DN damage:

- Posture or gait disturbance (e.g., a gait with a wide stance)

- Decomposition of movement: movements are deconstructed and executed in a serial rather than coordinated manner

- Dysmetria: excessive or inappropriate grabbing of objects

- Dysdiadochokinesia: inability to perform rapidly alternating movements

- Scanning speech: sliding and stretching of words, and slurring of phonation

- Hypotonia

- Intention tremor

- Nystagmus

- Delay in initiating movements

- Cognitive deficits: difficulty in estimating time intervals [Gooch et al. 2010]

The GP is 1 of 4 components that make up the BG [Parent and Hazrati 1995]. The other 3 are the caudate nucleus, the putamen, and the nucleus accumbens. The BG influence and modulate the activity of the motor cortex and descending motor pathways according to the site of involvement [Lanska 2010]. The putamen and GP are collectively known as the lenticular or lentiform nucleus and connect directly with the substantia nigra. The GP does not receive cortical afferents and therefore is not modulated by the neocortex. Furthermore, the GP is divided into 2 segments, the internal and external. The BG are involved in motor and cognitive functions:

- Motor functions: These are not fully understood but appear to be involved in the enabling of practiced motor acts and in gating the initiation of voluntary movements. Thus, voluntary

movements are initiated in the BG; however, their proper functioning is necessary for the motor cortex to relay the appropriate motor commands to lower levels of the neural hierarchy.

- Cognitive functions: It appears that the BG are involved in certain types of learning, including certain forms of implicit memory tasks.

Mechanistically, the GP is involved in the regulation of voluntary movement by providing inhibitory control that balances the excitatory action of the cerebellum. The results are smooth and controlled movements. Symptoms characteristic of damage to the BG and GP include:

- Dyskinesias: abnormal involuntary movements

- Akinesias: abnormal involuntary postures

More specifically, these include:

- Resting tremor

- Athetosis: involuntary writhing movements

- Chorea: writhing movements of the entire body

- Ballismus: involuntary ballistic movements of the extremities

- Rigidity: resistance to passive movement

- Dystonia: abnormal posture

- Bradykinesia: slowness of movement

In summary, damage to the GP and/or DN can produce a broad range of predominantly motor coordination-clinical manifestations, depending on whether one, both, or only parts of each nucleus are affected. The nature of the injury also influences the manifestation of the disease because the speed and extent of damage influence the clinical presentation. Finally, redundancy in the system and the brain's inherent plasticity contrive to further modulate signs and symptoms. Nevertheless, damage to the GP and/or DN is most likely to manifest as a movement disorder, a cognitive disorder, or a combination of all 3. In general, DN or GP toxicity would be expected to cause some form of characteristic motor dysfunction, that has not yet been reported as a result of GBCA exposure.

3.1.5.2   Lack of Evidence for Parkinsonian Effects from GBCA Exposure

Reasoning that Gd has been found in the GP, and that injury to the GP may induce parkinsonian symptoms, [Welk et al. 2016] studied 246,557 patients who underwent at least one Gd-MR to look for subsequent Parkinsonism onset. Patients whose initial MR was of the CNS and those with prior Parkinsonism or neurosurgery were excluded. In the Gd-MRI group, 81.5% had 1 Gd-MRI and

2.5% had ≥4 Gd-MRIs. The percentages of patients with new Parkinsonism in the Gd-exposed and unexposed groups were analyzed in a Cox regression analysis to determine the hazard ratio (HR; risk of Parkinsonism per additional Gd exposure); a HR of 1 would indicate no difference in Parkinsonism risk between groups. In an unadjusted analysis, the HR (1.08; 95% CI 1.04-1.13) was significantly greater than 1 (p <0.001). However, after adjusting for potential confounders and baseline characteristics that were unbalanced between the groups, the HR (1.04; 95% CI 0.98-1.09) was no longer significant (p = 0.18). In two sensitivity analyses, neither HR was significant. Importantly, the unadjusted Parkinsonism rates (cases/1000 patient-years) were unrelated to GBCA dose: 2.71 (95% CI 2.59-2.84) for no exposure, 3.17 (95% CI 2.99-3.36) for ≥1 Gd-MRI, and 2.56 (95% CI 1.54-4.02) for ≥4 Gd-MRIs. Notably, the Parkinsonism rate in the ≥4 Gd-MRI group is *lower* than the rate in the non-exposed group, and the 95% CIs for the unexposed and ≥4 Gd-MRI groups overlap considerably, suggesting no significant difference. A lack of dose effect provides strong evidence against causality. This well-designed study showed no association between GBCA exposure and Parkinsonism, and shows the feasibility of conducting large clinical studies of possible Gd effects.

A recent, currently unpublished sub-analysis of data collected in a longitudinal study reportedly found that exposure to gadodiamide was not associated with cognitive decline (McDonald, 2017, personal communication).

3.1.5.3 Reports of Symptoms Attributed to Gd Retention

Articles reporting the results of patient surveys have reported symptoms attributed to Gd retention. These retrospective surveys collected patient-reported symptoms that were not reported to have been medically confirmed. Medical history and concomitant medication use were not reported, and no control groups matched for age, sex, race, and other potentially relevant demographic data were studied. No determinations of tissue Gd or T1w hyperintensity were reported. In some cases, urinary levels of Gd were determined and reported to be higher than expected, as evidence of Gd retention. The results in these publications should be interpreted with caution given the unverified information presented. GEHC regularly searches its PV database as well as the scientific literature for case reports signaling a safety concern, and has not identified a manifest signal.

[Burke et al. 2016] published a collated survey and description of self-reported symptoms experienced by individuals with normal renal function (self-reported) after GBCA administration. The methodology utilized an anonymous survey of respondents to a link posted on a private blog site where members discuss Gd toxicity, and a public Gadolinium Toxicity Facebook page. The survey consisted of 9 open and closed questions. The respondents were asked to confirm the number of GBCA doses, types of GBCA received, what symptoms were present, how soon after IV administration of the GBCAs the symptoms began, and whether the respondents attributed feelings of unwellness/sickness to Gd. The respondents were also asked whether they underwent testing to detect Gd in various tissues following GBCA exposure and whether the respondent had a personal or family history of kidney disease. All 50 respondents (100%) received IV Gd contrast with an average of 4.2 doses (range 1-23), Self-reported GBCAs included 1 Gadavist, 11 Magnevist, 5 MultiHance, 9 Omniscan, 6 OptiMARK 4 multiple agents, and 11 unknown. The

scan numbers only totaled 47 GBCA exposures among 50 respondents despite a reported average of 4.2 GBCA exposures; mathematically, the cited experience should have totaled about 200 GBCA exposures.

It is difficult to discern a unifying diagnosis or potential clinical syndrome associated with these findings. Most of these, or very similar symptoms, are described in the prescribing information for Omniscan. They may relate to Gd, gadodiamide, patients' underlying disease, or patients' perceptions of disease. Unfortunately, none of the data presented in the study was medically verified, nor was correlated with brain MRI showing increased T1w signals on unenhanced scans, or histological correlates. Additionally, the study was uncontrolled, and introduced selection bias and reporting biases that cannot be quantified.

In several recent articles, Semelka ([Semelka et al. 2016a], [Semelka et al. 2016b], and [Semelka et al. 2016c]) proposed to classify asymptomatic and symptomatic Gd retention as medical conditions ("Gd storage condition" and "Gd deposition disease"), respectively, citing literature on Gd detection in bone, skin, other tissues, and brain, papers on NSF, as well as patient-reported symptoms from patient advocacy websites. Without presenting supportive data, the authors suggested that the least stable GBCAs appear to most likely result in the Gd storage condition while the stable GBCAs either do not cause or cause it at a very low level. However, recent literature now confirms that brain Gd presence occurs in both linear and macrocyclic agents. In [Murata et al. 2016], Gd tissue presence was shown even after 1 dose of macrocyclic Gadavist, and brain Gd was retained for longer than 1 year. Currently available evidence does not support recommendation of one type of agent over another with regard to Gd retention. We believe the suggested classification of Gd retention as a medical condition is inappropriate, as neither human nor animal investigations suggest any toxicity related to the long-term presence of very low levels of Gd. Therefore, the asymptomatic presence of Gd does not define a disease, or imply toxicity.

3.1.5.4   Potential for Harm through Misdiagnosis

GBCA are used to help in medical diagnosis; an incorrect diagnosis could result in patient harm through incorrect management. The finding of hyperintensity in some brain regions on unenhanced images raises the question of whether this could result in misdiagnosis. Therefore, it is important to consider whether the MR effects of Gd retention (T1w hyperintensity) might create a risk of misdiagnosis. The evidence suggests this is not a genuine risk.

To date, we have found no reports of misdiagnosis because of GBCA-associated T1w hyperintensity. As noted in Section 3.1.2 above, interpreters of MR images should be aware of GBCA effects, and in fact there seems to be good awareness of this in the literature, and a recent review on the dentate nuclei by [Khadilkar et al. 2016] mentions Gd associated hyperintensities in the dentate nuclei.

3.1.5.5   Clinical Adverse Effects following Intrathecal GBCA Administration

GBCA administration via an intrathecal route may represent the most extreme risk for CNS tissue toxicity, particularly acute toxicity, since it involves direct introduction of the GBCA into the

CNS. GBCAs have been administered intrathecally both as a form of "off label" clinical use of the drugs (for example, in the detection of CSF leaks) and as a consequence of medical errors. In a review of PubMed listings (based on the search terms, "gadolinium + intrathecal + risks"), 10 published reports were identified, inclusive of citations within the identified reports. A few reports described the "safe" use of GBCA administration via the intrathecal route [Algin and Turkbey 2013]; [Akbar et al. 2012]; [Muñoz et al. 2007]; [Eide and Rinqstad 2015]; [Chazen et al. 2014]. However, other reports described profound clinical signs and symptoms (e.g., aphasia, spasticity, delirium, seizures) following administration of Omniscan, Magnevist or Gadavist ([Kapoor et al. 2010]; [Reeves et al. 2017]; [Singh et al. 2016]; [Arlt et al. 2007]). Together, the reported experience illustrates the profound risks associated with intrathecal administration of GBCAs. However, these reports do not suggest clinical risk from Gd retention outside the intrathecal route of administration. Omniscan is currently the only marketed GBCA that states within drug labelling that it is "Not for Intrathecal Use."

3.1.6   Overall Clinical Conclusions

- Peer-reviewed publications of retrospective studies and case studies report that multiple IV GBCA exposure is associated with high SI in the DN and GP regions of the brain on unenhanced T1w MR images in both adults and pediatric populations in subjects without renal impairment, suggesting retention of Gd in some form in those structures.

- Gadolinium retention at low levels was confirmed by direct detection of Gd in brain tissues post-mortem. Most patients included in these publications had eGFR $\geq$60 mL/min/1.73 m^2 suggesting that brain Gd presence may occur without severe renal impairment. Quantification of Gd levels showed that the levels are in the microgram or sub-microgram range, and represent exceedingly small percentages of the cumulatively administered dose.

- Gd retention occurs with all studied agents, both linear (Omniscan, Magnevist, MultiHance, Eovist) and macrocyclic GBCAs (Gadavist, ProHance, Dotarem).

- To date, there is no evidence of adverse events related to brain Gd retention.

- Injury to the GP is most likely to manifest as a movement disorder, yet two large studies found no evidence of new Parkinsonism or motor deficits following GBCA exposure.

3.2   NONCLINICAL DATA ON GADOLINIUM RETENTION

Non-clinical studies have distinct advantages over clinical studies (which are necessarily retrospective given the nature of the safety concerns), including the ability to randomize doses and GBCA; to administer supraclinical doses; to directly analyze brain and other tissues; and to control confounding variables.

The following section includes:

- A review of select nonclinical papers with respect to demonstrated brain Gd

- A review of relevant GEHC and supplementary published nonclinical studies with a focus on neurotoxicity and biodistribution

- Summary of the GEHC study B041015 of Gd in brain tissue following repeated doses of Omniscan

- Overview of further nonclinical research being implemented by GEHC

Wherever practical, concentrations of Gd are converted to mmol/kg for comparison to a typical Omniscan human dose of 0.1 mmol/kg. However, Omniscan distributes in an extracellular volume of 15 to 20 L (based on GBCA Vd of 210 – 280 mL/kg) [Aime and Caravan 2009]. Therefore, the theoretical initial concentration in this volume would be ~0.3 mmol/kg (i.e., the theoretical concentration achieved following the dilution of a 0.1 mmol/kg dose × 60 kg human bodyweight, which is then diluted into 20 L of extracellular fluid).

3.2.1 Gd in Brain Recent Nonclinical Publications

Five published works ([Robert et al. 2015], [Jost et al. 2016], [Robert et al. 2016], [Lohrke et al. 2017], [McDonald et al. 2017a] and [Bussi et al. 2017]) are considered in this section, where the presence of Gd was investigated by MR and/or chemical analysis.

[Robert et al. 2015] reported T1 hyperintensity and the detection of Gd presence in the deep cerebellar nuclei of healthy rats that had been dosed with GBCAs. The rat equivalent of the DN is one of the deep cerebellar nuclei (called the lateral "dentate" nucleus because it lacks the macroscopic teeth-like morphological features seen in humans). Gadolinium was measured in the blood plasma and in 3 brain anatomic regions; the cerebellum (DN is part of the cerebellum), the cerebral cortex, and the subcortical brain (the GP is subcortical brain). Key findings were:

- Measurable T1 hyperintensity was observed only after 8 administrations of gadodiamide—it was not evident after 4 administrations.

- T1 hyperintensity was not observed after administration of the macrocyclic comparator gadoterate meglumine.

- In gadodiamide-treated rats, measurable amounts of Gd were found in tissue from all 3 brain regions (between 1.5 and ~5 nmol/g; ~0.8 μg/g) but not in the blood.

- In gadoterate-treated rats, measurable amounts of Gd were found in tissue from all 3 brain regions (between 0 and 0.5 nmol/g; ~0.08 μg/g) but not in the blood. However, only the

concentration in subcortical brain was significantly different from that in saline-treated controls.

- Gd concentration in brain tissue was approximately 10-fold greater in gadodiamide-treated rats than in gadoterate-treated rats.

- No abnormal behavioral changes were observed.

The authors acknowledged the following limitations:

- Gd was measured in whole cerebellum; therefore, the concentration in the DN was potentially underestimated.

- Hyperintensity in the deep cerebellar nuclei was measured in relation to cerebellar grey matter, whereas most clinical studies measure it in relation to the pons.

- No histological assessment was undertaken.

- ICP-MS does not identify the chemical species of Gd present

- Further studies are needed to determine the species of Gd and potential neurotoxicological consequences.

This paper has high relevance to the clinical observations of Kanda et al ([Kanda et al. 2014]; [Kanda et al. 2015a]; [Kanda et al. 2015b]), McDonald et al ([McDonald et al. 2015]), and others identifying the T1 hyperintensity in the DN and GP of patients after repeat exposure to GBCAs. The model also presents evidence that this phenomenon can occur in healthy animals. However, this paper does not add to evidence of what form the Gd is in—the commonly cited assumption of dissociation is offered as a possible explanation, nor does it explore the microscopic localization of Gd.

The authors indicate that "no abnormal behavioral change suggestive of a putative neurological toxicity was observed during the study, regardless of the test compound" and acknowledge that "No histologic lesions were found in brain tissues of patients with T1w signal hyperintensity" either.

Most importantly, the paper presents an animal model to explore underlying mechanisms, localization, and possible clinical sequelae. The model is very well aligned with the methodology GEHC adopted for nonclinical study B041015 [Study B041015], which explores the potential for brain clearance over a longer time period (using chemical ICP-MS analysis) and includes a formal Good Laboratory Practice toxicological pathology assessment.

[Jost et al. 2016] used T1w imaging to demonstrate hyperintensity in the deep cerebellar nuclei (DCN) of rats following repeat dosing with linear and macrocyclic GBCA. The authors report

increased T1 signal in the DCN following treatment with gadodiamide (Omniscan) and gadobenate dimeglumine (MultiHance), mildly (but not significant) increased following treatment with Gadopentetate dimeglumine (Magnevist) and no signal increase following gadobutrol (Gadovist), gadoterate meglumine (Dotarem) or saline. The authors also used fluid-attenuated inversion recovery (FLAIR) to demonstrate that all GBCAs were present in the CSF. Although this paper does not include histological determination of Gd, it does present a potential explanation of brain exposure to intravenous Gd bypassing the BBB. Key findings were:

- T1 SI was increased with Omniscan and MultiHance but not with Magnevist, Gadovist or Dotarem.

- FLAIR demonstrates that all GBCA tested above were present in unquantified amounts in the CSF shortly after administration.

Limitations included:

- There was no direct measurement of Gd in the brain to corroborate the T1 SI.

- The T2 FLAIR signal in the CSF was not quantified.

The relevance of this study is that the T1 hyperintensity in the DCN appears to confirm that of [Robert et al. 2015] although the statistical rigor of the study may be questioned. The observation of GBCA in the CSF is of potential interest to how GBCAs may bypass rather than cross the BBB.

[Robert et al. 2016] followed up from their previous rat study by including another 2 linear agents (gadobenate dimeglumine and gadopentetate dimeglumine) in addition to gadodiamide and gadoterate. They also include 3 dosing regimens with equivalent cumulative dose over a 5-week period. The end points were similar to their previous study, Gd measurement in the cerebellum by ICP-MS and T1w DCN hyperintensity. An additional end point compared with their previous study is R1 mapping in the cerebellum. Key findings were:

- Gd measured in the cerebellum was increased with all 3 linear agents but levels detected after administration of the macrocyclic agent were not significantly different from saline controls.

- R1 mapping appears to show increased signal in the DCN in rats treated with linear agents compared to the saline and macrocyclic treated animals.

- T1w in the DCN as a ratio to cerebellar cortex increases fastest in gadodiamide treated rats with a steady increase in the other linear agent treated animals.

- T1w hyperintensity was increased in animals treated with linear agents irrespective of 1, 2 or 4 injections per week for equivalent cumulative doses.

- The levels retained in the brain are comparable to those determined by GEHC in Study B041015 both in absolute and %ID terms.

As a limitation, the authors noted that 5 GBCAs were not included in this study.

[Lohrke et al. 2017] studied the retention of Gd in the brain and selected other tissues following the administration of the linear GBCAs: gadodiamide and gadopentetate dimeglumine, and the macrocyclic GBCAs: gadobutrol and gadoteridol. The animals received 20 daily intravenous injections at a relatively high dose of 2.5 mmol Gd/kg body weight. Eight weeks after the last GBCA administration, the animals were killed, and the brain and other tissue samples (bone, skin and skeletal muscle) were dissected for analysis. Retained Gd was detected in the brain after administration of all agents in the following order; gadodiamide>gadopentetate>gadobutrol>gadoteridol, a ranking in the brain similar to that observed by others [McDonald et al. 2017a]. Consistent with this, in all brains from linear and macrocyclic GBCAs groups, a homogeneous distribution of Gd was observed throughout the brain. Increased local accumulation of Gd within the deep cerebellar nuclei and the granular layer was reported with linear agents, however the exact location of the brain slices and proximity to the DN was difficult to discern for animals treated with each agent in the figure shown. Importantly, histopathological analysis showed no evidence of tissue changes in the brain. Furthermore, electron microscopic examination of the ultrathin sections revealed a regular tissue architecture with the neurons, glial cells, and focally typical cerebellar structure (granular and Purkinje cells) in animals administered gadodiamide and saline. The authors did not perform electron microscopic analysis on tissue from animals treated with the other agents. Considering the other tissues assessed for levels of Gd retention, those in the skeletal muscle were similar to those in the brain, whilst higher levels were measured in the bone and skin, and these were higher with linear compared with macrocyclic GBCAs.

Whilst this study reported macroscopic and histological nephrogenic systemic fibrosis–like skin lesions following the administration of gadodiamide, data in rodents previously published by the same group and thought to support the theory that tissue retained Gd is relevant to NSF were retracted by the authors. [Sieber et al. 2008a], [Sieber et al. 2008b], [Pietsch et al. 2009] and [Steger-Hartmann et al. 2009] claimed to have developed an NSF model after showing that repeated high dose Omniscan resulted in the formation of skin lesions in the rat. In these studies, [Pietsch et al. 2009], [Sieber et al. 2008a] and [Sieber et al. 2008b] concluded that the amount of Gd in skin remaining after GBCA treatment was related to the in vitro stability of GBCAs since skin lesions following Omniscan treatment appeared to correlate with the amount of Gd in the skin. However, this hypothesis was withdrawn [Pietsch et al. 2011]. [Pietsch et al. 2011] later concluded that skin lesions are "dependent on the injection interval and not on the amount of Gd in tissue". In fact, this publication states that the amount of Gd present long-term in the tissue of rats is not directly correlated with skin lesions at all. They also state that the skin lesions resolve spontaneously and that the lesions were most likely an acute response to high dose GBCA.

[McDonald et al. 2017a] measured T1w DCN hyperintensity in rat lateral DN following both linear and macrocyclic GBCA (Figure 1).
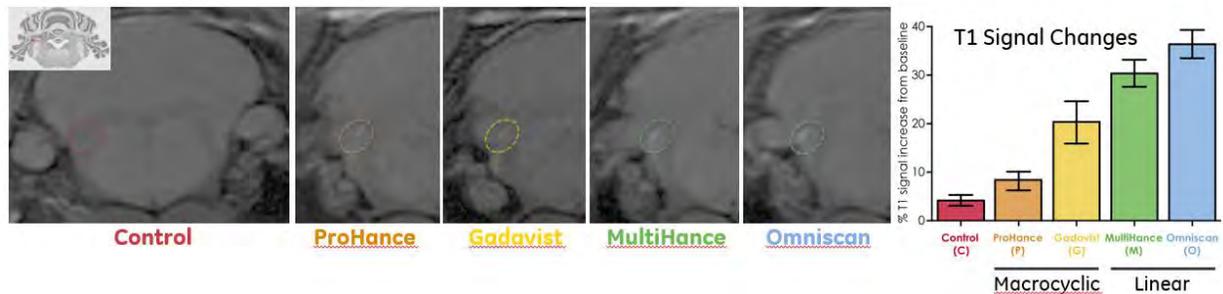

Figure 1 **Unenhanced axial T1w images through posterior fossa at DN level for a saline-exposed rat (Control) and GBCA-exposed rats (macrocyclics ProHance and Gadavist, linears MultiHance and Omniscan).** A dashed line outlines the DN. Bars = %change in unenhanced T1w SI for control and GBCA-exposed rats. Error bars = standard deviation.

In addition, the ranking of ICP-MS derived brain Gd levels 1 week after exposure (>500 rat plasma elimination half-lives; equivalent to >1 month in humans) ProHance (gadoteridol) <Gadavist (gadobutrol) <MultiHance (gadobenate) <Omniscan (gadodiamide) (Figure 1) mirrors that based on T1w DCN hyperintensity (Figure 1), showing that both linear and macrocyclic agents are associated with Gd in the brain and other tissues. The different levels between macrocyclics show they do not all behave the same in the rat model.

Figure 2 shows levels of Gd measured in the brain and selected peripheral tissues with examples of both macrocyclic and linear GBCAs. Whilst Gd retention was seen with all GBCAs 1 week after exposure, histopathological assessment found no tissue changes in any organ examined apart from the kidney. Interestingly, although ProHance had the lowest levels of retained Gd in the kidney, there was associated toxicity in the kidney not seen with other agents.
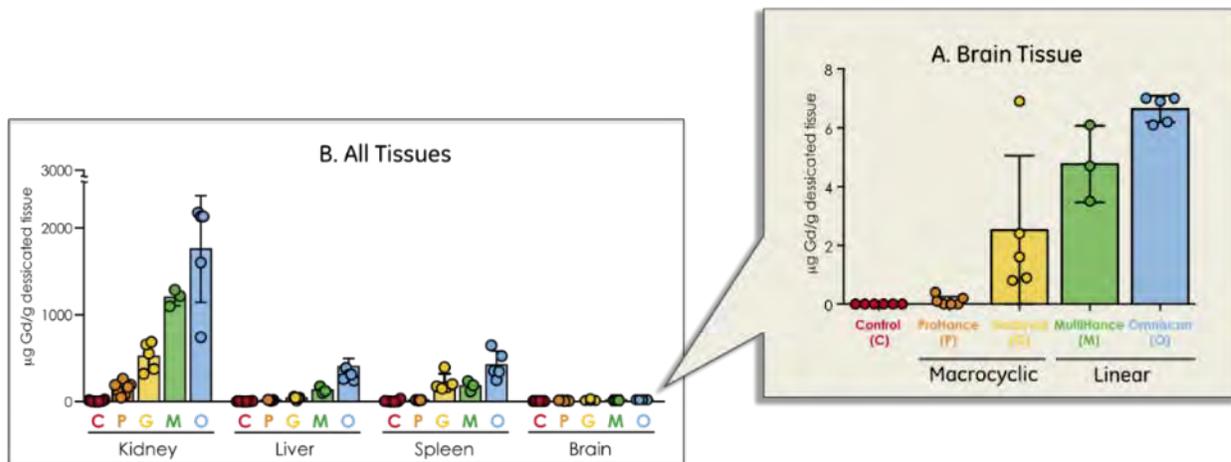
Figure 2   ICP-MS Gd levels in rat tissues for saline control rats and rats injected with ProHance, Gadavist, MultiHance, and Omniscan in the DN (Panel A) and liver, spleen, and kidney (Panel B). Bars = mean level, error bars = standard deviation, and circles = individual levels.

Figure 3 shows histologic and ultrastructural changes (often associated with early cellular apoptosis) in the kidney following ProHance administration, which had the lowest kidney Gd concentration, and pathological changes that were not observed with the other agents tested, including Omniscan which showed the highest kidney Gd concentration.

Figure 3   Renal Toxicity Following Administration of GBCA with the Lowest Tissue Gd Concentration (Macrocyclic ProHance)

Representative images of renal tissues of control (Panels A-D) and ProHance exposed (Panels E-H) rats for H&E stained light microscopy samples (Panels A, E) and TEM samples (Panels B-D, F-H). TEM images show the proximal convoluted tubule (PCT) (Panels B, F), Bowman's capsule of the glomerulus (Panels C, G), and mitochondria (Panels

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D, H). ProHance-exposed renal tissues demonstrated advanced ultrastructural changes that were less severe with other gadolinium contrast agents and include advanced loss of normal cytoarchitecture of the proximal convoluted tubule (E), alterations in glomerular structure and filling of Bowman's space with matrix and cellular debris (G), and complete loss of the outer mitochondrial membrane (H) that is often associated with early cellular apoptosis. These effects were not observed with the other agents tested, including Omniscan which showed the highest Gd concentration in the kidney (McDonald et al. 2017, in press).
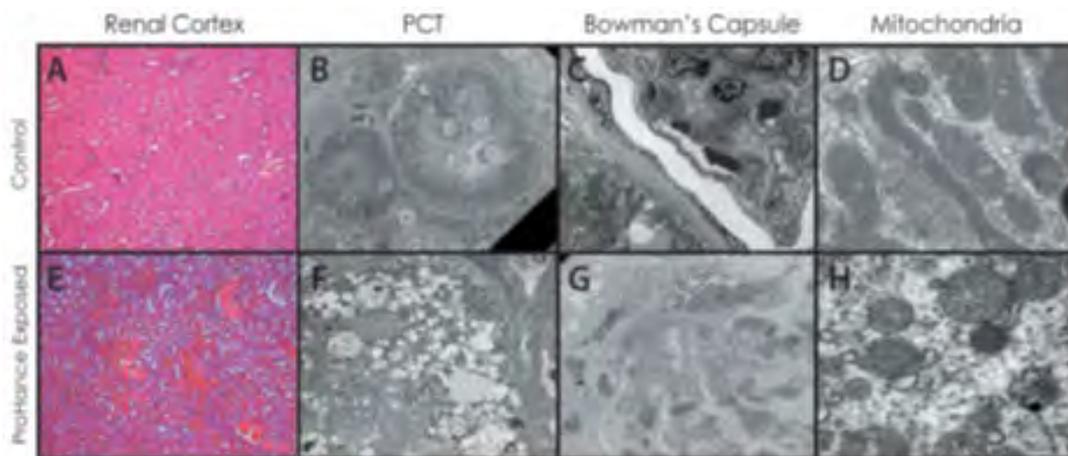
Since ProHance had the lowest concentration of Gd measured in the kidney (and the brain) in this study, these data clearly demonstrate that tissue Gd concentration cannot be used as a surrogate measure for potential toxicity. Similarly, when considering the brain, and in the absence of any known adverse effects, there is no reason to assume that the level of Gd retained is a more important risk factor than any other factors related to the biological properties of the parent GBCA molecule.

[Bussi et al. 2017] compared the levels of gadolinium in the blood, cerebrum, cerebellum, liver, femur, kidneys, and skin in rats after 20 repeated doses of the macrocyclic GBCAs gadoterate, gadobutrol, and gadoteridol. After a 28-day recovery period animals were sacrificed and blood and tissues were harvested for determination of Gd levels by ICP-MS. Whilst no Gd was found in the blood, liver, or skin of any animal in any group, significantly lower levels of Gd were noted with gadoteridol compared to gadoterate and gadobutrol in the cerebellum (0.150 vs. 0.292 and 0.287 nmol/g), cerebrum (0.116 vs. 0.250 and 0.263 nmol/g) and kidneys (25 vs. 139 and 204, respectively). Higher levels of Gd were noted in the femur (7.48 vs. 5.69 and 8.60 nmol/g, respectively) with significantly less Gd determined for gadoterate than for gadobutrol and gadoteridol. The authors concluded that differences exist between macrocyclic agents in terms of their propensity to accumulate in tissues, which is consistent with the work described above by McDonald et al. [McDonald et al. 2017a].

Considering the publications described above, it is clear that Gd retention in the brain and other tissues is observed with both linear and macrocyclic GBCAs. Whilst linear GBCAs were generally associated with higher levels of retained Gd, the differences observed were not large and in the order of approximately 2- to 10-fold in the brain. Furthermore, there are clearly differences between GBCAs of the same sub-class, for example with differences observed between individual macrocyclic GBCAs.

3.2.2   Relevant GEHC Nonclinical Studies and Supplementary Publications

3.2.2.1   Pharmacokinetics/Distribution

Several internal and external studies have examined the pharmacokinetics/distribution of Omniscan. A review of the general pharmacokinetic findings is presented with a separate focus on the brain.

(a)   **General Pharmacokinetics and Distribution - GEHC Studies**

Kinetic studies with gadodiamide have been conducted in rats, rabbits, and monkeys ([Study SAL 88-30]; [Study SAL 88-35]; [Protocol no. DV-7572 (OLI-025)]; [Study SAL 88-7]; [Study SAL 89-75]; [Study FT-PAH 6-88]; [Study HUK 5780-668/2]; [Brixham Lab. study no. Study R507/A]; [Study SAL 89-52]; [Study FT-PAH 7-89]).

Omniscan is an extracellular agent that is rapidly distributed between the blood pool and total extracellular fluid (excluding the brain) and is rapidly eliminated, with about 95% of the injected dose present in the urine by 24 hours and only a small amount (about 1%) in the faces. In monkeys, the distribution half-life is 6.8 ± 1.78 minutes and the elimination half-life is 75.26 ± 14.59 minutes and is close to that of humans [Study SAL-041-1009]. Apparent volumes of distribution and total volumes of distribution are similar across the species. In monkeys, Gd content of the plasma was below detectable levels 16 hours after administration. Gadodiamide does not bind to human serum proteins [Study SAL 89-32], and significant metabolites were not detected in the rat [Nycomed Project Report 041BK01091-F]. There was no evidence from these studies that Omniscan crosses an intact BBB.

(b)   **Published Biodistribution Studies**

Two biodistribution studies have been published in mice and rats [Tweedle et al. 1995]; [Kindberg et al. 2010].

[Tweedle et al. 1995] reported higher [153]Gd present in bone and liver at the longer time points up to 14 days post-administration with the (formulated) linear chelates, gadopentetate and gadodiamide, than in the animals injected with the macrocyclic chelates, gadoteridol and gadoterate. While the authors suggest that this indicated a higher level of dechelation in vivo with the linear agents, it is important to note that this methodology does not differentiate between free and chelated Gd. A GEHC study published in 2010 [Kindberg et al. 2010] investigated the biodistribution of Gd (measured by ICP-AES and inductively coupled plasma-sector field mass spectrometry [ICP-SF-MS]) and ligand (^{14}C-labelled GdDTPA-BMA) in rats. The injected dose of 0.5 mmol/kg formulated gadodiamide was rapidly excreted, with only 1.0% remaining in the body at 24 hours. The radioactivity at later time points had cleared from the brain and was mainly associated with kidney cortex, liver, lung, muscle, and skin, with a similar rate of clearance for both ligand and Gd from these tissues. The ratio between ^{14}C-labelled substance and Gd was not significantly different from that of the injected substance in most tissue samples up to 24 hours after injection; the ratio then decreased slowly over time. The data showed that measurements of Gd concentration alone in tissue samples from animals injected with GBCAs cannot be used as a measure of Gd released from the ligand. In this study, Gd levels were measured only in selected organs, and levels in the brain were not determined. However, levels of the ^{14}C-labelled chelate in the brain were below the detection limit within 24 hours.

(c)   **Pharmacokinetics with Respect to the Brain**

After single-dose administration, readily detectable levels are seen rapidly in all organ systems. The low levels of Gd and DTPA-BMA detected in the brain at early time points (5 minutes to 4 hours) [Tweedle et al. 1995]; [Kindberg et al. 2010] are washed out and are at or below the limit of detection within 24 hours [Tweedle et al. 1995]; [Kindberg et al. 2010]; [[Study SAL 88-30]; [[Study SAL 88-35]; [Protocol no. DV-7572 (OLI-025)]. The detection limits in these assays are generally one order of magnitude less sensitive than those (e.g. ICP-MS) used to measure the level of Gd in human autopsy brain samples ([McDonald et al. 2015]; [Kanda et al. 2015a]).

Repeat dose biodistribution studies are uncommon. [Bussi et al. 2007] described limited tissue distribution of Gd in naïve rats following single dose and repeat dose intravenous administration of 3 GBCAs. The levels of Gd measured in the brain 24 hours following a single dose of 1 mmol/kg Omniscan was 0.000344% of injected dose (~84 ng Gd/g brain). The level of Gd in the brain 48 hours after 6 repeat doses was lower at 0.000191% of injected dose (46 ng/g brain). Moreover, in all organs examined the 48-hour post treatment measures (even following 6 repeat doses) were lower than in the 24-hours post-single dose measurement indicating ongoing clearance between 24- to 48-hours post-administration. To conclude, trace levels of Gd were detected by ICP-AES but were still clearing from the brain at 48 hours after administration of Omniscan. In addition to these Omniscan data, Gd brain presence at similar levels (within a 2 to 3-fold difference) was also observed following MultiHance (linear, ionic GBCA) and Gadavist (macrocyclic, non-ionic) administration [Bussi et al. 2007].

(d)   **Concentrations of Omniscan Within the Body**

A routine clinical intravenous dose of Omniscan is 0.1 mmol/kg. After the initial distribution phase, the theoretical concentration of Omniscan within the interstitial fluid is ~0.3 mmol/kg because the dose of 0.1 mmol/kg distributes within the extracellular volume, which is approximately 1/3 [Aime and Caravan 2009] of body volume.

3.2.2.2   Safety Toxicology

The acute-dose and repeat-dose safety toxicity studies conducted for formulated gadodiamide injection were conducted in mice, rats, and nonhuman primates. None reported neurotoxicity.

(a)   **General Toxicology**

During product development, several toxicology studies were conducted. In most of these, the formulated product (gadodiamide injection) was administered intravenously – the rationale being that gadodiamide injection is the final product for clinical use and is given by the intravenous route to patients.

(i)   Single-dose Toxicity

Single-intravenous-dose toxicity studies were conducted in rats, mice, and cynomolgus monkeys, and these establish the median lethal dose (LD_{50}) values of >20 mmol/kg or 200 times the clinical dose of 0.1 mmol/kg ([Study PH 407-SA-002-88]; [Study SAL 88-43]; [Study SAL 88-79]; [Study SAL 88-31]; [Study PH 406-SA-006-88]; [Study FT-PAH-5-88]; [Study SAL 88-60]; [Daiichi study no. 0589]). In addition, a series of acute studies comparing several formulations of gadodiamide (with and without excess chelating ligands) were undertaken in mice [Study FT-PAH 2-89]. These studies support the formulation of gadodiamide injection containing excess ligand [CaNa DTPA-BMA, caldiamide]. After the first registration application, single-dose studies in rats treated with Gd DTPA-BMA supplemented with different amounts of CaNa DTPA-BMA ([Daiichi study no. P124]; [Daiichi Pharmaceutical 1991]) confirmed the increased single-dose tolerance for the formulation with excess CaNa DTPA-BMA; the LD_{50} of Gd DTPA-BMA increases from 14 mmol/kg to >30 mmol/kg with the addition of 5% (mole) CaNa DTPA-BMA [Study FT-PAH 2-89].

Neurotoxicity was not reported in any of these studies.

(ii)   Repeat-dose Toxicity

Repeat-dose toxicity studies were conducted in rats, rabbits, and monkeys ([Study SAL 88-7]; [Study HLA 2493-112]; [Study H-618]; [Study H-657, 658]; [Study H-688]; [Study DSC 86/91112]; [Study no. DSC 85-G/91182]; [Study H-690]; [Study H-697]; [Study EPL 105-024]; [Study HUK 5780-668/2]). Adverse effects were seen mainly in rats, and the probable etiology of these changes was considered to be altered zinc metabolism/status. An additional repeat-dose study demonstrated that both supraclinical doses of gadodiamide injection (5.0 mmol/kg) and caldiamide sodium (0.25 mmol/kg) can affect zinc homeostasis by causing a profound increase in urinary zinc excretion [Study no. 340]. The data obtained in this study provide some evidence that the subchronic toxicity of gadodiamide injection may be related to zinc depletion.

Clinical observations were recorded with all studies and evidence of neurotoxicity was not reported in any of these studies. Three repeat dose studies specifically included gross and histopathological examination of the brain ([Study DSC 86/91112]; [Study no. DSC 85-G/91182]; [Study HUK 5780-668/2]) and no treatment-related effects were observed.

(b)   Neurotoxicity

Data regarding potential neurotoxicity of Omniscan in nonclinical studies includes:

- Systemic exposure (via intravenous administration) in acute and repeat-dose studies,

- Intracisternal administration, and

- Intravascular administration after BBB disruption.

(i)   Systemic Exposure

Intravenous administration is the clinical route of administration, and this leads to systemic exposure. Repeat-dose safety toxicity studies of formulated gadodiamide injection in rats and nonhuman primates did not find neurotoxicity following doses of up to 0.25 mmol/kg daily for 28 days in rats and 1.25 mmol/kg daily for 28 days in cynomolgus monkeys.

Under normal circumstances, GBCAs are not thought to cross the BBB. Elsewhere in the body, most GBCAs enter the extracellular space [Aime and Caravan 2009].

(ii)   Intracisternal Administration and Intravascular Administration After BBB Disruption

An important difference between intravascular administration with BBB disruption and intracisternal administration is the volume of distribution of the final concentration the CNS is exposed to. Intravascular administration distributes into the entire extravascular space of the body (~20 L for *Homo sapiens*) and BBB disruption adds only a little extra (the CSF and brain interstitial volume) to this volume, so theoretical initial concentrations are ~0.3 mmol/L. In contrast, with direct administration into the CSF (either intracisternal or intraventricular) where the entire dose is limited to a volume of 150 to 200 mL (in humans); in this case, peak brain concentration of a dose of 0.1 mmol/kg may be of the order of 40 mmol/L.

(iii)   Intravenous Administration with BBB Disruption

Most GBCAs distribute within the extracellular fluid compartment (~0.2 L/kg in adult humans, or ~14 L for a 70-kg adult) and do not normally cross the BBB. Even if the BBB were compromised, the additional distribution volume (~1.5 L in adult human) does not significantly alter the theoretical peak interstitial volume concentration of approximately 0.5 mmol/L (following intravenous administration of 0.1 mmol/kg). Neurotoxicity reported in nonclinical models is rare following intravenous administration, even when the BBB is deliberately compromised; no neurotoxicity is reported in most studies ([Study no. 1391]; [Study PRL-67A]; [Study SAL 90-30]) but was reported in 2 out of 10 rats receiving 3 mmol/kg Omniscan intravenously following BBB disruption, although this level of neurotoxicity was similar to that observed with Gadavist and lower than that observed with ProHance [Takahashi et al. 1996].

(iv)   Direct Administration to the Brain (Intracisternal and Intraventricular)

Intracisternal administration is not the clinical route of administration and presents the highest exposure to the CNS. In a pilot study, supraclinical doses of 1.25 and 2.5 mmol/kg of gadodiamide injection and gadopentetate dimeglumine induced neurological intolerance in mice [Studies K.nr. 041/90 and K.nr. 042/90]. However, more clinically relevant doses of up to 0.3 mmol/kg (albeit still through the more direct intracisternal route) were generally well tolerated [Study FT-PAH 2-91]. These doses, while comparable to the usual clinical dose of 0.1 mmol/kg, are likely to provide much greater exposure to the CNS than would normally be achieved through intravenous

exposure. Indeed, 0.3 mmol/kg intracisternal dose represents a theoretical CSF concentration of ~120 mmol/L (Table 3) - 400 times the theoretical initial concentration of Omniscan in the peripheral interstitial fluid (0.3 mmol/kg) following the recommended clinical dose.

Table 3   Intracisternal and Intraventricular Induced Neurotoxicity in Rats and Mice

Study	Species	Dose (mmol/kg)	CSF/interstitial theoretical concentration, mmol/L	Effects
Intracisternal				
[Studies K.nr. 041/90 and K nr. 042/90]	Mice	1.25	500	Neurotoxicity
[Study FT-PAH 2-91]	Mice	0.3	120	No neurotoxicity
Intraventricular				
[Ray et al. 1998]	Rats	0.016	25	Neurotoxicity
	Rats	0.008	12.5*	No neurotoxicity

For humans, intracranial volume is ~1.4 L. For mice, intracranial volume is ~0.4 mL. For mice, b.w. is ~25 g. So, for a 1.25 mmol/kg intracisternal dose, the administered dose is 0.025kg *1.25 mmol/kg = 0.031 mmol in a volume of 0.04 mL (10% of 0.4 mL) or approximately 500 mmol/L.
* Histological changes are observed in non-neuronal cell populations above 0.5 µmol/g brain.

A published study of intraventricular administration of a gadodiamide formulation (including caldiamide) noted neurotoxicity at a concentration of 2.5 µmol/g brain in rats [Ray et al. 1998]. This study further demonstrated that this toxicity was due to the gadodiamide rather than to caldiamide. At 1.25 µmol/g brain, there was no overt neurotoxicity although there were some histological changes present.

Through these preclinical studies (Table 3), it is possible to estimate concentrations at which gadodiamide injection may induce neurotoxicity.

3.2.2.3   Potential Toxicological Significance

The reported levels of Gd in the human DN represent a theoretical interstitial concentration of up to 0.4 mmol/kg, an approximately 200-fold increase above the concentration that induces apoptosis in cultured neuronal cells ([Feng et al. 2010]; [Xia et al. 2011]).

Subclinical levels of toxic oxidative damage in neurons (and/or glia) – e.g., mitochondrial or endoplasmic reticulum perturbation or other evidence of as seen by $GdCl_3$ *in vitro* ([Feng et al. 2010]; [Xia et al. 2011])—would require ultrastructural analysis (electron microscopy), which may not be feasible in cadaveric human tissue.

However, if neuronal cell death had occurred in the DN in these autopsied subjects, it would undoubtedly have produced both ante mortem clinical and post-mortem histopathologic evidence. As neither of these is reported, it appears likely that the Gd present is in a form that has low bioavailability.

Several studies demonstrate normal tissue and subcellular organelles through light and electron microscopy [McDonald et al. 2015], [Lohrke et al. 2017], [McDonald et al. 2017a], [Smith et al. 2017].

3.2.3   Potential Route of Uptake into the Brain

No mechanism of uptake of Gd into the brain has been identified or reported and it is only possible to speculate on a potential mechanism at this point in time. It has long been considered that GBCAs do not cross the intact BBB and it remains to be determined whether potential interstitial levels of Gd have crossed an intact BBB. [McDonald et al. 2015] demonstrate that the majority of Gd detected in the brain is within the endothelial wall of the BBB. However, the recently described glymphatic system could transport GBCAs into the brain from the CSF. A recent study described above has preliminary evidence in the rat model that a small fraction of all intravenously administered GBCAs is detectable in the CSF.

3.2.4   GEHC Study B041015

GEHC designed a study of rats exposed to supra-clinical doses over a period of 5 weeks. Dose dependency was examined by choosing dosing regimens equivalent to 10- and 20-times the human imaging dose. Potential washout was assessed by measuring Gd levels 1 week post dosing and 20 weeks post dosing: the equivalent of approximately 500 and 10,000 serum elimination half-lives. Finally, standard toxicological histopathology was performed on all animals to determine if there were any toxicological consequences of either the intermediate or high doses, either acutely or more chronically. These were the 3 primary endpoints of the study reported in a recent publication in *Radiology* [Smith et al. 2017]. The study also included a group of high-dose animals to study later point (approximately 1 year after dosing) and brain tissues were processed using methods that would enable further characterization by electron microscopy.

After study initiation, others showed that the hyperintensity in the deep cerebellar nuclei and Gd was measurable in a naive rat model [Robert et al. 2015]. The primary endpoints [Smith et al. 2017] showed that there were dose-dependent trace levels of Gd in the brain, that this had partially cleared between weeks 1 and 20, and that there were no histopathological changes. At this point it was decided to publish the results as intended but the additional group of high-dose animals was maintained to examine if there was further clearance of brain Gd after a further 30 weeks (50 weeks post dosing). Further assays on the material collected were initiated to see if there were subtle toxicological effects only apparent at the ultrastructural level by electron microscopy and to examine the Gd distribution across the brain by laser ablation ICP-MS and at the microscopic level by TEM-EDS.

Trace levels of Gd were detected in the brain at 1 week post dosing with Omniscan (2.49 nmol/g brain tissue ± 0.30 at 1 week, equivalent to 500 serum elimination half-lives,) and were reduced by approximately 50% by week 20 (1.38 ± 0.10 nmol/g) [Smith et al. 2017]. The data collected at 50 weeks post-dosing indicated the persistence of very low amounts of Gd in the brain of rats but importantly without histopathological sequelae. Gd levels measured in the brain at 20- and 50-

weeks post dosing (1.38 ± 0.10 and 1.56 ± 0.30 respectively) were a small fraction of the total dose (~1/1000000th of the injected dose). Histopathology assessment of hematoxylin and eosin (H&E) sections at 3 standard anatomic levels showed no evidence of neurotoxicity despite the presence of Gd at these levels for approximately 1 year. Further data from electron microscopy ultrastructural studies have found no evidence of toxicity or ultrastructural changes in any of the cell types present in the DCN (including neurons, astrocytes, oligodendrocytes, microglia, pericytes or endothelial cells) for up to 1 year. TEM-EDS analysis of Gd localization in the DCN showed approximately 100-nanometer foci located in the basal lamina, abluminal to the endothelium. We have not found foci in the brain parenchyma.

In summary, despite the long-term presence of trace levels of Gd in the brain, there is no evidence of toxicity.

3.2.4.1   ICP-MS analysis of Gd in the brain

Inductively coupled plasma mass spectrometry (ICP-MS) was used to determine Gd levels in the blood and brain of rats at weeks 1 and 20 following 5 weeks of repeat Omniscan and Magnevist (1-week post-dosing time point only) exposure.

There was a roughly dose dependent level of brain Gd present at week 1 post-dosing with Omniscan, with an approximate doubling of the levels seen with double the dose (Figure 4). Levels of Gd in the brains of animals treated with Magnevist were lower than with Omniscan at 1 week post dosing. The high dose Omniscan results are comparable to those reported by others [Robert et al. 2015].
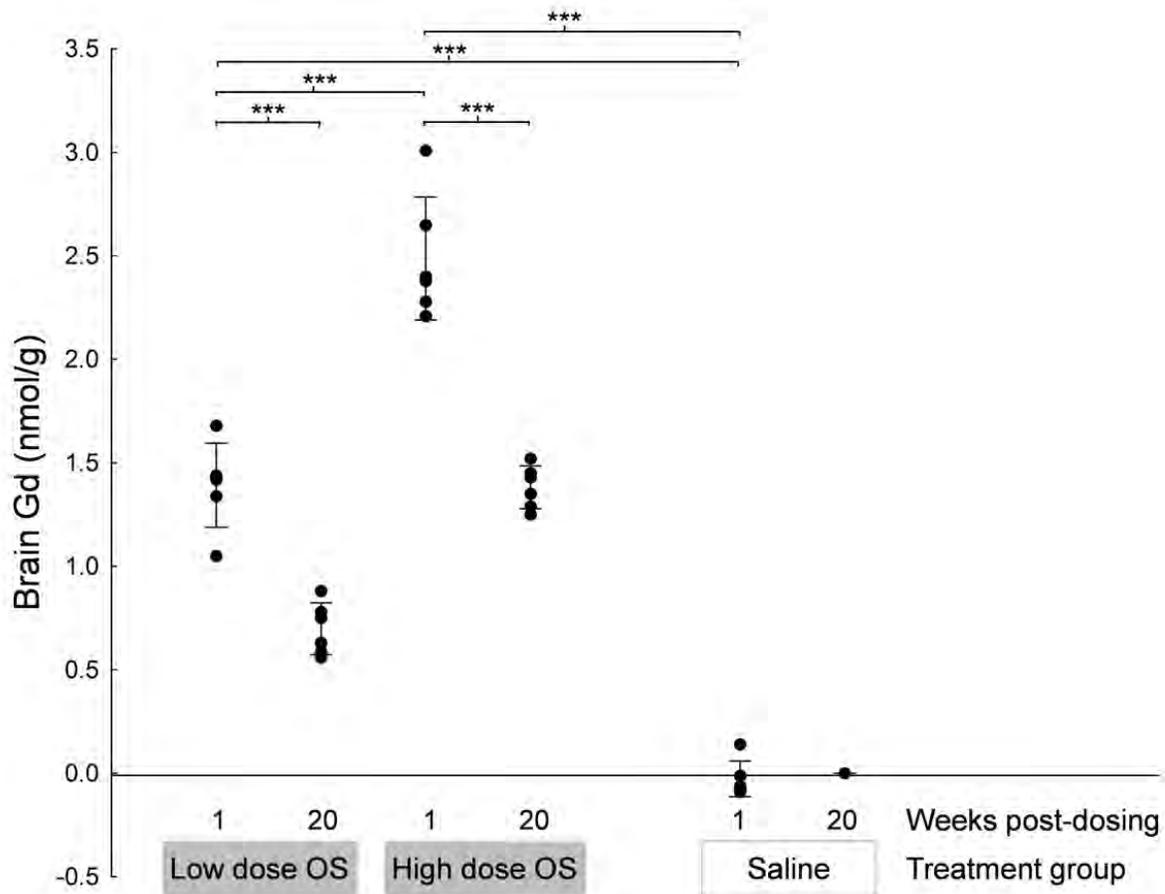
Figure 4   **Gadolinium levels measured in the brain by ICP-MS was dose dependent (compare high and low dose Omniscan groups) and decreases with time (compare 1-week post-dosing with 20-week post dosing levels).** Error bars represent ± 1 standard deviation of the mean. *** indicates p<0.0001 by ANOVA by pairwise comparison.

Importantly the levels of Gd measured at week 20 post-dosing were significantly reduced from those seen at week 1 post-dosing. During this time Gd levels had decreased to approximately half the initial level in both Omniscan treated groups. Extrapolating from just 2 time points predicts that following repeat dose administration, the remaining Gd is cleared from the brain with an elimination half-life in the order of 18 weeks. Comparing the percentage injected dose between the 1 week and 20 week groups demonstrated roughly equivalent retention between doses indicative there is little or no saturation of mechanisms responsible for uptake or elimination from the brain with doses up to12 mmol/kg over a 5-week period (Figure 5).

Figure 5 **Gadolinium measured in the brain as a percentage of injected dose (%ID) shows equivalency with dose indicating that uptake mechanisms are not saturated and equivalency in elimination showing that elimination mechanisms are not saturated.** Error bars represent ± 1 standard deviation of the mean. **indicates $p < 0.001$ by Mann-Whitney U test.

3.2.4.2   Neurohistopathology Assessment

Standard toxicological histopathological assessment of the brains from all groups at week 1, 20 and 50 post-dosing were with normal limits indicating that there is no evidence of any neurotoxicity up to a dose of 12 mmol/kg over a 5-week dosing period.

Tissue sections were taken at 3 standard levels and stained with hematoxylin and eosin according to Registry of Industrial Toxicology Animal-data (RITA) guidelines [Bahnemann et al. 1995]. These were examined by an independent toxicological pathologist blinded to treatment groups against standard toxicological guidelines.

(1)   Cerebrum at the optic chiasm

(2)   Cerebrum at the base of the posterior hypothalamus

(3)   Mid-cerebellum and medulla oblongata

3.2.5   Future Nonclinical Research

GEHC is implementing further programs of nonclinical research to further the understanding of brain Gd (Table 4).

Table 4 GE Healthcare Brain/Tissue Gd Scientific Research Program (Nonclinical)		
Study Type	**Study**	**Objective**
Nonclinical	Rat brain clearance/tissue effects	Investigation of the long-term kinetics of Gd in rat brain and potential effects on neuronal tissue morphology
Nonclinical	Rat brain Gd & behavior	Investigation of the long-term presence of Gd in rat brain follow administration of all major GBCA (linear and macrocyclic) and potential effects on behavior and neurological function
Nonclinical	Rat brain Gd localization	Investigation of the regional distribution and kinetics of Gd in the rat brain following GBCA (linear and macrocyclic) administration
Nonclinical	Gd form methodology	Exploration of potential methods to study Gd chemical form in tissue samples in situ
Nonclinical	Electrophysiology studies in rat brain slices ex vivo	Exploration of potential methods to determine if there are functional effects on axonal and synaptic transmission ex vivo following exposure to GBCA
Nonclinical	Kinetics of Gd retention in multiple rat tissues following a single GBCA dose	To understand how Gd levels in multiple rat tissues change with time over extended periods using the sensitive and direct methodology of ICP-MS

3.2.6   Overall Nonclinical Conclusions

- The presence of Gd in the brain as observed in autopsy samples reported by [McDonald et al. 2015] and [Kanda et al. 2015b] is confirmed in animal models. As in humans, the levels of retained Gd are exceedingly low.

- Data utilizing ICP-MS shows that brain Gd present after GBCA administration occurs after administration of macrocyclic GBCAs, as well as after linear GBCAs. Such studies can

therefore be used for controlled comparative studies across the class as well as studies to better define mechanisms of Gd accumulation and clearance and any potential toxicity.

- Gd tissue levels may be a poor surrogate marker for potential toxicity, as demonstrated by the severe kidney toxicity observed only with the macrocyclic GBCA with the lowest levels of retained Gd in a rat model

- Repeat-dose safety toxicity studies of formulated gadodiamide injection in rats and nonhuman primates did not report neurotoxicity following IV doses of up to 12 times the recommended clinical dose given daily for 28 days.

- No neurotoxicity was observed in studies where the BBB was disrupted in rats and dogs prior to the intravenous administration of gadodiamide injection at a dose of twice the recommended clinical dose.

- Studies in which the brains of rats and mice were directly exposed to high concentrations of Omniscan demonstrated good neurologic tolerance at concentrations of approximately 12 mM. Only after exposure to concentrations of 25 mM and above was neurotoxicity reported. This is 60× higher than the maximum concentration of Gd measured in human autopsy brain samples (0.4 mM).

- In GEHC Study B041015 there was no evidence of inflammation or neurotoxicity despite the presence of Gd in rat brain for up to 50 weeks post-dosing. By 20 weeks Gd levels were diminished by approximately 50% compared with levels 1-week post-dosing.

- GEHC plans additional nonclinical research to further understand brain Gd in relation to different GBCAs, clearance over time, macro/microscopic location, Gd chemical form and evaluation of brain tissue histopathology/ultrastructure.

3.3   PHARMACOVIGILANCE

3.3.1   Summary of Events in Safety Database

3.3.1.1   Methods of Retrieval

Repeated, comprehensive searches of the GE Healthcare's global adverse event database aimed at retrieval of individual case safety reports of increased T1w signal intensity of brain structures, gadolinium detected in brain biopsy specimen findings, possible neurological symptoms, and/or possible lasting symptoms after use of GBCAs. Scope of the searches was broad to increase sensitivity. All retrieved cases were reviewed by a PV Medical Director.

3.3.1.2   Summary of Events in Safety Database

As of 17 July 2017, cumulatively 141 ICSRs have been identified to potentially concern increased T1w signal intensity of brain structures, gadolinium detected in brain biopsy specimen findings, possible neurological symptoms, and/or possible lasting symptoms after use of GBCAs.

One hundred (100) of the 141 ICSRs concerned T1w signal hyperintensity and/or Gd detected in brain specimen. A brief summary is provided in Section 3.3.1.3. Six of the 100 reports additionally included neurological symptoms and/or reported symptoms after use of GBCAs, they are included in Section 3.3.1.4 as well.

Section 3.3.1.4 presents a table of 47 ICSRs concerning possible clinical neurological symptoms and/or lasting symptoms after use of GBCAs. The low specificity of the case retrieval and selection should be borne in mind.

In addition to the 141 ICSRs above, the global safety database includes 63 non-serious individual case reports concerning laboratory findings related to gadolinium. Fifty-six self-reported cases of Gadolinium detected in 24-hour urine collections were derived from a single internet publication [Grimm and Williams 2017]. Identity of the linear and/or macrocyclic GBCAs was not reported or provided upon follow-up. A publication from Japan [Maeda et al. 2017] reported gadolinium in bone tissue in 7 individuals. Presence of Gd in bone tissue has been reported previously by [Gibby et al. 2004]. The publications are not considered to have impact on the safety profile for Omniscan.

3.3.1.3   Imaging Findings and/or Brain Findings

Of the 141 case reports, 100 reported T1w signal hyperintensity in unenhanced MRI of the brain and/or Gd in brain specimens. Eighty cases reported T1 signal hyperintensity, 33 cases reported brain Gd, and 13 cases reported both findings. In 27 of the 33 cases with reported brain Gd, ICP-MS was used; while [Sanyal et al. 2011] and [Xia et al. 2010] used scanning electron microscopy/electron dispersive X-ray spectroscopy (SEM/EDS). In 29 of the 100 reports Omniscan administration was confounded by another identified GBCA, in 38 of 100 reports Omniscan only was used, and in the remaining 33 cases associated with an unspecified GBCA the use of Omniscan cannot be excluded.

T1w signal hyperintensity in unenhanced MRI may have value as a qualitative surrogate marker of gadolinium in the brain, though quantitative methods have not been established, and other pathologies or metals may contribute to findings, especially as the DN and GP accumulate other naturally occurring paramagnetic metals. These signal hyperintensities are subject to the number of doses administered, and are not sensitive to very low levels of Gd as may be detected by ICP-MS in tissue samples. Furthermore, the ability to detect Gd depends upon the sequences and scanner hardware and software used for imaging and image analysis. The 33 cases of Gd in brain specimens were included in publications by [Roberts et al. 2017] [McDonald et al. 2017b], [McDonald et al. 2017c] [Sanyal et al. 2011] [McDonald et al. 2015] [Kanda et al. 2015b] [Xia et al. 2010].

3.3.1.4   Potential Neurological Symptoms

As mentioned above, the GEHC Global Adverse Event Database was searched for case reports of possible neurological symptoms of brain Gd. Possible neurological symptoms and signs are described in Section 3.1.5.

Further to this [Semelka et al. 2016a] described symptoms, mostly from a non-medical website, attributed to Gd retention. He described a syndrome consisting of at least 3 of the following symptoms: central torso pain, headache and clouded mentation, peripheral leg and arm pain, peripheral leg and arm thickening and discoloration, and bone pain. We believe that the method of symptom collection (survey of self-identified patients) resulted in selection bias; included were self-reported symptoms that were not medically confirmed as being associated to Gd presence. We believe that his suggestion of "gadolinium deposition disease" (GDD) as a syndrome is premature, as a firm link between the presence of Gd in the brain is lacking, and both human and animal model investigations do not reveal any basis for toxicity related to the long-term presence of very low levels of Gd. Therefore, there is no plausible mechanistic link between observed trace Gd levels and any clinical syndrome Unlike, for example, NSF). The observation of Gd does not define a disease, or imply toxicity. Nevertheless, the GEHC safety database was searched for possible case reports of the symptoms consistent with Semelka's definition.

Searches of the database for reports with potential neurological symptoms.

Thirty of the potential neurological symptoms of Gd in brain. None of the cases are considered to represent likely symptoms of Gd toxicity in brain as alternative explanations included significant concomitant conditions, medications and /or the transient nature of neurological symptoms despite the long-term lasting presence of Gd in the brain.

Twenty-four case reports are consistent with the symptoms described by Semelka. In 16 of the 24 cases, underlying disease was documented as a likely cause, in additional 5 cases insufficient information about indications of GBCA-enhanced MR scans or underlying disease was provided. Thorough Medical Director review did not reveal a single, well-documented report of "GDD".

The GEHC AE database for non-GBCAs was searched to find patterns that might be consistent with "Gd deposition disease". Iodinated X-ray contrast agents Visipaque (iodixanol) and Omnipaque (iohexol) and the GBCA Omniscan were included in searches of symptoms described by Semelka et al. (central torso pain, headache and clouded mentation, peripheral leg and arm pain, peripheral leg and arm thickening and discoloration, and bone pain). The relative risks of adverse reactions were calculated from adverse event counts and exposure to the three contrast agents, respectively. The relative risks of iodinated contrast media were of the same magnitude as with Omniscan, and that there was no suggestion that there is a preponderance of these types of events due to Omniscan. Any limitations in a spontaneous AE reporting system would apply equally for the iodinated contrast media and for Omniscan.

A published comprehensive risk assessment of GBCAs [Fraum et al. 2017] addressed the survey of Semelka et al. Fraum et al. stated that the survey lacked a control group, that it relied on patient self-reporting (both regarded as significant limitations) and that the results have not been independently verified by other authors; nor were the data verified by medical professionals. Larger controlled studies would be needed to evaluate possible associations between GBCA exposures and specific clinical symptoms.

We identified 6 case reports with lasting symptoms after use of GBCAs in patients with significant underlying disease and chronic renal failure. The reported neurological, musculoskeletal and/or skin symptoms are more likely related to the underlying disease including advanced renal impairment.

In summary, the safety database and all available information have been reviewed for potential neurological symptoms of brain gadolinium like ataxia, disturbances in posture and balance, speech disorders and cognitive effects (see Section 3.1.5). No case report with a consistent pattern of observation has been identified.

Further, the safety database has been searched for symptoms as described by Semelka et al. Adverse reactions were self-reported, not medically confirmed, or most likely explained by significant underlying disease.

3.3.1.5   Pharmacovigilance Conclusion and Recommendations

Review of the GEHC safety database has found no consistent trend or pattern of observations symptoms or signs attributable to Gd retention. GEHC commits to continuing PV to further characterize the potential risk of brain Gd. Any safety signals from these additional PV activities will be evaluated in a timely manner and prioritized. As of 17 July 2017, no data are available to Global Pharmacovigilance that significantly affect the established benefit-risk balance of Omniscan. SUMMARY OF DATA ON GADOLINIUM RETENTION

3.3.2   Summary of Current Knowledge on Gd Presence in Brain

As evident from the data presented above, there is an extensive body of literature providing human evidence of low levels of brain retention of Gd based on indirect (non-invasive MR) and direct (chemical analysis of post-mortem brain tissue), as well as non-clinical evidence. Considerably fewer human data are available regarding Gd retention outside the brain, but convincingly show extracranial as well as intracranial retention. To date the human data are based on retrospective analyses, and therefore there some gaps in knowledge regarding Gd retention which impede a full risk assessment. Prospectively conducted non-clinical (animal) studies have provided helpful data, but have limitations in relevance to human risk assessment. None of the available evidence suggests an actual clinical risk of harm to patients.

Below we summarize what is known about specific aspects of Gd retention, based on the data available to date.

3.3.2.1   Factors Affecting the Probability of Gd Retention

(a)   Medical Conditions

Although there are insufficient data for a full epidemiological assessment of the prevalence of Gd retention, it has been reported predominantly in patients who undergo repeated MR examinations, and thus the population at highest probability is considered to be patients with conditions for which contrast-enhanced MR surveillance (follow-up) is performed. This would include, for example, multiple sclerosis, inflammatory bowel disease, women at high risk of breast cancer, and patients with some types of tumors.

Because most GBCA are excreted predominantly renally, and renal clearance is proportional to GFR, renal impairment reduces the rate of elimination, prolonging retention of the GBCA in the body. Thus, renal impairment is likely a risk factor for Gd retention, although Gd retention has been reported in patients with normal renal function. As mentioned earlier, severe renal impairment is also a risk factor for NSF, and for this reason use of some GBCA (including Omniscan) is contraindicated in patients with severe renal impairment.

(b)   Age

Brain retention of Gd has been reported in both children and adults; it is unknown whether retention probability differs quantitatively by age.

(c)   Sex of Patient

Males and females have been reported to have brain retention of Gd; it is unknown whether retention probability differs quantitatively by sex.

(d)   Race and Ethnicity

Study of the possible association of Gd retention risk with race and ethnicity has not been reported, so it is unknown of race or ethnicity affect retention probability.

(e)   GBCA Dose

Retention probability has been positively associated with the cumulative number of GBCA doses administered. GBCAs are generally dosed based on patient weight; therefore, heavier patients, who may receive higher doses, would be expected to be more likely to show retention, although we are aware of no evidence to support this. At this time, retention appears to occur after 3 or 4 cumulative administrations; however, no reliable threshold can yet be determined.

(f)   GBCA Dose Timing

Although animal studies show that brain Gd levels can decrease ("wash out") over time, at this time there are insufficient human data to recommend a minimum time interval between doses to reduce accumulation.

3.3.2.2   Structure-Activity Relationships

As discussed above, GBCAs have been classified as linear or macrocyclic and as ionic or non-ionic. Table 1 above lists the GBCAs approved in the US, along with their classifications by structure and charge.

The probability of retention appears quantitatively higher for linear GBCA, but only by several times; the difference is too small to be explained by differences in GBCA thermodynamic stability. Early reports of brain T1w hyperintensity suggested an association with only linear GBCAs. It is now known, however, that brain retention also occurs with macrocyclic GBCAs, based on post-mortem studies that, using ICP-MS analysis of brain tissues, found brain Gd following linear (Omniscan, Magnevist, MultiHance, Eovist) and macrocyclic (ProHance, Gadavist) GBCAs [[Kanda et al. 2015b], [McDonald et al. 2015] and [Murata et al. 2015]]). Post-mortem analyses of patients receiving Dotarem and OptiMARK have not been published to our knowledge (Ablavar is no longer marketed in the US, per the FDA Orange Book database).

3.3.2.3   Microscopic Localization of Retained Gd

The microscopic location of Gd appears to be predominantly in the vascular endothelium. It is not clear if Gd in any form has crossed the intact BBB. [Naganawa and Taoka 2016] in a recent International Society for Magnetic Resonance in Medicine (ISMRM) abstract, postulated that GBCA might have permeated from the blood vessels into the cerebrospinal fluid (CSF) and the PVS, which could be a route of GBCA distribution to brain parenchyma in subjects with normal BBB. Firmly establishing the microscopic location of Gd is challenging because mild conditions must be found that separate Gd-containing compartments without disrupting either the biological structures or the Gd-containing chemical species.

3.3.2.4   Chemical Form of Retained Gd

The chemical form of retained Gd is currently unknown because of the inherent difficulty in isolating and identifying the tiny quantities involved. Because retained Gd appears to be MR active, at least for the linear GBCA, this suggests that the Gd remains in a chelated form, i.e., that the Gd^{+3} ion has not been removed from its ligand.

Insoluble Gd was found in brain tumor specimens after single and repeat administrations of Omniscan and/or MultiHance ([Xia et al. 2010]). However, this is unlikely to be a good model for what happens in patients without tumors, because the patients had disrupted BBB function from the tumor, and tumors can contain hypoxic regions, with decreased pH values that may be conducive to Gd+3 release from the chelate. Precipitated Gd was detected in the cerebellum of a

patient with end-stage renal failure and NSF ([Sanyal et al. 2011]); however, the severe blood chemistry abnormalities (including high phosphate levels, which may react to form insoluble Gd phosphate) associated with end-stage renal failure may lead to a different fate of GBCA than in patients without severe renal impairment. It should also be noted that soluble Gd+3 is likely to be toxic, but insoluble Gd is not likely to be, because it is not in solution.

3.3.2.5   Toxicity of Retained Gd

To date, no evidence of toxicity due to retained Gd has been found. No confirmed cases of injury to DN or GP have been identified in comprehensive searches of the GEHC PV database for adverse events possibly related to Gd in the brain. Published studies to date have reported no causally related neurologic signs or symptoms associated with brain Gd that are not otherwise explained by underlying disease. A large study specifically looking for new cases of Parkinsonism following GBCA exposure found no evidence of such a relationship. Publications using survey methodology or websites have described patient-reported symptoms attributed to past GBCA exposure. However, these reports cannot be medically evaluated because of missing epidemiologic information and a lack of control group. Prospectively conducted studies in animal models have found no abnormal neurohistopathology or neurotoxicity.

3.3.3   GEHC Position

Since the initial publication in 2014 reporting high signal intensity (SI) in the DN and/or GP regions on unenhanced T1w magnetic resonance (MR) images after multiple serial administrations of GBCA, the scientific understanding of Gd retention has been evolving. Emerging data using ICP-MS, show that low levels of Gd presence occurs after administration of all GBCAs studied, including both linear and macrocyclic GBCAs. In addition, other clinical MR imaging studies demonstrated the presence of T1 hyperintensities consistent with brain Gd (Stojanov et al) after macrocyclic administration.

To date, GEHC has not identified any validated safety signals or scientific publications in which clinical symptoms were causally related to T1w hyperintensities of the DN or GP, or to Gd presence in the brain detected by ICP-MS.

As stated above, research needs to progress further to help answer some additional questions. These questions include determining which molecular state of Gd is present in the brain, whether there is Gd localization within the brain, whether Gd crosses the BBB, how much Gd clearance from tissue occurs over time, and, most importantly, what the clinical or pathological consequences are, if any, of these findings.

To assess these questions, GEHC is actively evaluating the following scientific areas:

- Studies incorporating larger cohorts to assess histological correlations and clinical implications across the GBCA class

- Studies on the exact location and characterization of the Gd species present in the brain

- Studies with prolonged follow-up after Gd administration, to understand the clearance of Gd from the brain and to assess potential longer-term impact

As the clinical relevance of brain Gd remains uncertain, the current evidence does not support a determination of potential harm, and the patient health benefits of GBCA are clear, GEHC's position is summarized as follows;

- Use of GBCAs remains appropriate when used according to the product Prescribing Information and in line with guidance from the Regulatory authorities.

- At present, no clinical symptoms have been causally associated with Gd in brain with administration of GBCAs.

- Clinical autopsy data using sensitive analytical techniques have shown presence of Gd in the brain with GBCAs, regardless of chemical structure of the chelate or the in vitro stability of the chelate, including macrocyclic chelates. Detected levels have been extremely low, representing exceedingly small fractions of cumulative dose.

- GEHC is actively monitoring the situation and conducting research to add to the understanding of potential risks.

4 SERIOUS IDENTIFIED RISKS OF GBCA

4.1 Acute Hypersensitivity Reactions

4.1.1 Overview of Hypersensitivity Risk with GBCA Use

Hypersensitivity reactions, i.e., allergic reactions, are the most common adverse drug reactions associated with GBCAs.

Severe hypersensitivity reactions have been determined by the FDA to be "hazards that are *serious* or are *otherwise clinically significant* because they have implications for prescribing decisions or for patient management" as indicated by the inclusion of a Warnings section in GBCAs' US package inserts [FDA 2011].

By way of example, in Section 5.3, Hypersensitivity Reactions of the Omniscan US package insert, the Omniscan WARNING states:

Anaphylactoid and anaphylactic reactions, with cardiovascular, respiratory and/or cutaneous manifestations, resulting in death have occurred.

The WARNING requires that healthcare professionals plan for such reactions, going so far as to require certain staffing and equipment for safe use of Omniscan:

> Personnel trained in resuscitation techniques and resuscitation equipment should be present prior to OMNISCAN administration.

The WARNING advises healthcare physicians to take immediate action to address any hypersensitivity reaction:

> If a hypersensitivity reaction occurs, stop Omniscan Injection, and immediately begin appropriate therapy.

Finally, the WARNING identifies a certain subpopulation at likely higher risk for hypersensitivity reactions and advises *additional* monitoring for those patients:

> Observe patients closely, particularly those with a history of drug reactions, asthma, allergy or other hypersensitivity disorders, during and up to several hours after OMNISCAN injection. [1]

While severe hypersensitivity reactions may occur only in a small percentage of GBCA administrations, they must not be disregarded, particularly due to the widespread use of GBCAs, estimated by [ACR Guideline 2016] at 300 million doses worldwide. At this level of administration, approximately 3,000 to 30,000 patients worldwide can be estimated to have suffered serious impact of an anaphylactoid reaction, which are observed at a frequency of 0.001% to 0.0001%. This does not take into account hypersensitivity reactions that are not classified as analphylactiod but still so serious that they require medical treatment. Also, patients with a previous GBCA reaction are at about 8 times higher risk, and patients with asthma and various other allergies may have an increased risk for an allergic-like reaction to GBCA compared to the general population

Acute hypersensitivity reactions can be fatal. In an analysis of the FAERS, [Prince et al. 2011] found that between 2004 and 2009, of 40 GBCA-associated deaths (unrelated to nephrogenic

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[1] For comparison, other GBCAs carry similar warnings, see, e.g., MultiHance US Package Insert Section 5.2:

> Anaphylactic and anaphylactoid reactions have been reported, involving cardiovascular, respiratory, and/or cutaneous manifestation. Some patients experience circulatory collapse and died. In most cases, initial symptoms occurred within minutes of MultiHance administration and resolved with prompt emergency treatment.

> Prior to MultiHance administration, ensure the availability of personnel trained and medications to treat hypersensitivity reactions.   additionally, consider the risk for hypersensitivity reactions, especially in patients with a history of hypersensitivity reactions or a history of asthma or other allergic disorders. Observe patients for signs and symptoms of a hypersensitivity reaction during and for up to 2 hours after MultiHance administration.

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systemic fibrosis), the death incidence rates were 0.15, 0.19, 0.97, 2.7, and 0.7 per million doses for gadodiamide (Omniscan), gadoversetamide (OptiMARK), gadopentetate dimeglumine (Magnevist), gadobenate dimeglumine (MultiHance), and gadoteridol (ProHance), respectively. The authors stated:

> Because the total number of hypersensitivity reaction deaths (~7 per year in the United States for all GBCAs) far exceeds the number of deaths caused by NSF (near zero now that NSF has been nearly eliminated), allergic reaction risk should be considered in maximizing contrast agent safety.

[Raisch et al. 2014] also analyzed the US FAERS for GBCA-associated AE reports, focusing on anaphylaxis. Importantly, the authors noted that that as a class, the GBCAs have a rate of anaphylaxis reports much higher than the rate for all drugs combined (Table 6).

Prevention of hypersensitivity reactions is far preferable to treatment of manifest reactions, which cannot be relied upon to be successful in clinical practice in all situations. Treatment of acute hypersensitivity reactions can be associated with complications. Per [Dillman et al. 2007], "….*26% of reactions required either medical management, transfer to the emergency department, or hospital admission.*" Appropriate management is not always optimal and results in drug and technical errors [Wang et al. 2008]. It also adds to patient burden if pregnant [Sikka et al. 2016] and increases risk to the fetus.

4.1.2   Omniscan's Low Rate of Hypersensivity Reactions

With this background, it is important to note that multiple studies examining the risk of hypersensitivity reactions associated with various GBCAs have produced strong data that consistently shows that Omniscan carries a comparatively very low risk of hypersensitivity reactions.

A summary of the rates of hypersensitivity reactions reported for each GBCA in these studies is presented in Table 5.

Table 5   Summary of Studies Reporting Differential GBCA-associated AE Rates

Brand Name (Generic)	[Bruder et al. 2011]	[Bruder et al. 2015]	[Jung et al. 2012]	[Murphy et al. 1999]	[Prince et al. 2011]	[Prince et al. 2017]	[Murphy et al. 1996]
MultiHance (gadobenate)	0.47%	0.42%	0.22%		0.12%		
ProHance (gadoteridol)	0.39%	0.19%		0.41%	0.33%		10.4%
Dotarem (gadoterate)	0.25%	0.12%	0.08%				
Eovist (gadoxetate)			0.12%				
Gadovist (gadobutrol)	0.23%	0.10%	0.10%			0.90%	
Magnevist (gadopentetate)	0.20%	0.16%	0.06%	0.07%	0.05%		0.14%
Omniscan (gadodiamide)	0.06%	0.05%	0.01%	0.03%	0.02%		

4.1.2.1   Research using US FAERS Databases

Like [Prince et al. 2011] described above, [Raisch et al. 2014] analyzed the US FAERS for GBCA-associated AE reports, but focused on anaphylaxis. They searched the database beginning with the respective approval date of each GBCA up until August 2012, thus covering from 1988 (the year of the first US approval) to 2012 (nearly 26 years). They calculated the Proportional Reporting Ratio (PRR) overall and for each GBCA, along with 95% confidence intervals (CI); the PRR is the ratio of the fraction of GBCA AE reports that were classified as anaphylaxis divided by the fraction of all drug AE reports that were classified as anaphylaxis. As stated by the authors, the PRR is used to "determine whether reporting rates of specific AEs for specific drugs are disproportionately higher compared to reporting rates for all other drugs combined in voluntary safety reporting databases". They also calculated the Empiric Bayes Geometric Mean (EBGM) values, which are used for the same purpose but stratify by age, gender, and time. All GBCA except 1 (Ablavar [gadofosveset]) had at least 1 report of anaphylaxis in the FAERS database. The PRR for all GBCA combined was 6.16 (95% CI 5.69 – 6.66), indicating that as a class, the GBCA have a rate of anaphylaxis reports that is much higher than the rate for all drugs combined. By GBCA, the PRR ranged from 0.82 (95% CI 0.31 – 2.19) for OptiMARK (gadoversetamide) to 17.54 (95% CI 15.22 – 20.20) for MultiHance (gadobenate dimeglumine) (Table 6). As pointed out by the authors, the utilization rates of the different GBCA are unknown, so differences among the GBCA may be influenced by different utilization rates. However, numerous other studies have found differences in AE rates among the GBCAs (Table 5) even after taking into account utilization rates.

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Table 6   **Summary of Proportional Reporting Ratio (PRR) and Empiric Bayes Geometric Mean (EBGM) Data from Raisch 2014[a]**

US Trade Name	Generic Name	Classification	US Approval Date[b]	Years on Market in US[c]	Number of Anaphylaxis Reports[a]	PRR (95% CI)	EBGM (95% CI)
MultiHance	Gadobenate dimeglumine	Linear ionic	2004 Nov 23	7.8	175	17.54 (15.22-20.20)	17.14 (14.62-19.8)
Dotarem	Gadoterate meglumine	Macrocyclic ionic	2013 Mar 20[d]	-0.6[d]	6	12.80 (5.93-27.68)	9.85 (3.86-20.76)
Gadavist (Gadovist in EU)	Gadobutrol	Macrocyclic non-ionic	2011 Mar 14	1.5	15	8.5 (5.17-14.0)	7.8 (4.51-12.63)
Eovist	Gadoxetate disodium	Linear ionic	2008 Jul 03	4.2	5	7.33 (3.11-17.34)	5.43 (1.76-12.84)
ProHance	Gadoteridol	Macrocyclic non-ionic	1992 Nov 16	19.8	105	5.67 (4.70-6.84)	5.59 (4.59-6.74)
Magnevist	Gadopentetate dimeglumine		1988 Jun 02	24.2	264	4.87 (4.32-5.49)	4.81 (4.25-5.42)
Omniscan	Gadodiamide		1993 Jan 08	19.6	40	3.06 (2.27-4.21)	2.89 (2.12-3.86)
OptiMARK	Gadoversetamide		1999 Dec 08	12.7	4	0.82 (0.31-2.19)	0.94 (0.6-1.39)
Ablavar	Gadofosveset trisodium		2008 Dec 22	3.7	0	n/a	n/a
All GBCA combined	-	-	-	-	614	6.16 (5.69-6.66)	6.06 (5.59 -6.55)

[a] [Raisch et al. 2014]
[b] From FDA drug database:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails
[c] As of 31 Aug 2012, the cut-off date specified by [Raisch et al. 2014]
[d] Note the discrepancy between the approval date for gadoterate (20 Mar 2013) and the cut-off date for the Raisch analysis (31 Aug 2012)

Using the definition of PRR (a / (a + c)) / (b / (b + d)) provided in Appendix 1 of [Raisch et al. 2014], the PRRs reported in Table 3 of [Raisch et al. 2014] were converted to the fraction of all GBCA-reports that were anaphylactic reactions by multiplying each by the factor 100% x (b / (b + d)) using the values of b (37,401) and d (5,462,255) reported in Appendix 1 of [Raisch et al. 2014]. The results are shown in Table 7. As evident from the data, the GBCAs vary widely in their relative risks of anaphylaxis, with 12% of gadobenate (linear, protein-binding GBCA) reports being anaphylaxis, 9% of gadoterate (macrocyclic) reports being anaphylaxis, followed by 6% of gadobutrol (macrocyclic). Note that the lowest percentages are associated with the two non-ionic linear agents, Omniscan (gadodiamide) and OptiMARK (gadoversetamide).

Table 7   Percentages of GBCA Adverse Reactions Reported to FDA that Were Anaphylactic

US Trade Name	Generic Name	PRR[a]	Percentage of AEs that were anaphylaxis[b]
MultiHance	Gadobenate	17.54	12%
Dotarem	Gadoterate	12.80	9%
Gadavist (Gadovist in EU)	Gadobutrol	8.50	6%
Eovist	Gadoxetate	7.33	5%
ProHance	Gadoteridol	5.67	4%
Magnevist	Gadopentetate	4.87	3%
Omniscan	Gadodiamide	3.06	2%
OptiMARK	Gadoversetamide	0.82	1%

[a] From [Raisch et al. 2014]
[b] Calculated by multiplying PRR by the factor b / (b + d) (37,401 / (37,401 + 5,462,255))

(a)   The "Weber Effect" Did Not Impact the FAERS Analyses

Importantly, an analysis of the [Raisch et al. 2014] data show that the so-called "Weber effect" [Weber 1984], which posits that AE reporting is highest shortly after a regulatory authority approves a drug and it is relatively unfamiliar to healthcare professionals, was unlikely to have had any impact on the Raisch or Prince et al. 2017 (unpublished manuscript accepted by Radiology) analyses. A plot (Figure 6) of anaphylaxis reports by year for all GBCA combined and for gadobenate, gadopentetate, and gadoteridol, i.e., the 3 products with the highest numbers of reports shows peaks for all GBCA reports at years 1999, 2003, 2007, 2009, and 2011. Examination of the curves for gadobenate, gadoteridol, and gadopentetate shows that the first two peaks are likely due to the observed peaks in gadopentetate reports, and the latter 3 are likely due to peaks in gadobenate reports. These data are inconsistent with a Weber effect.
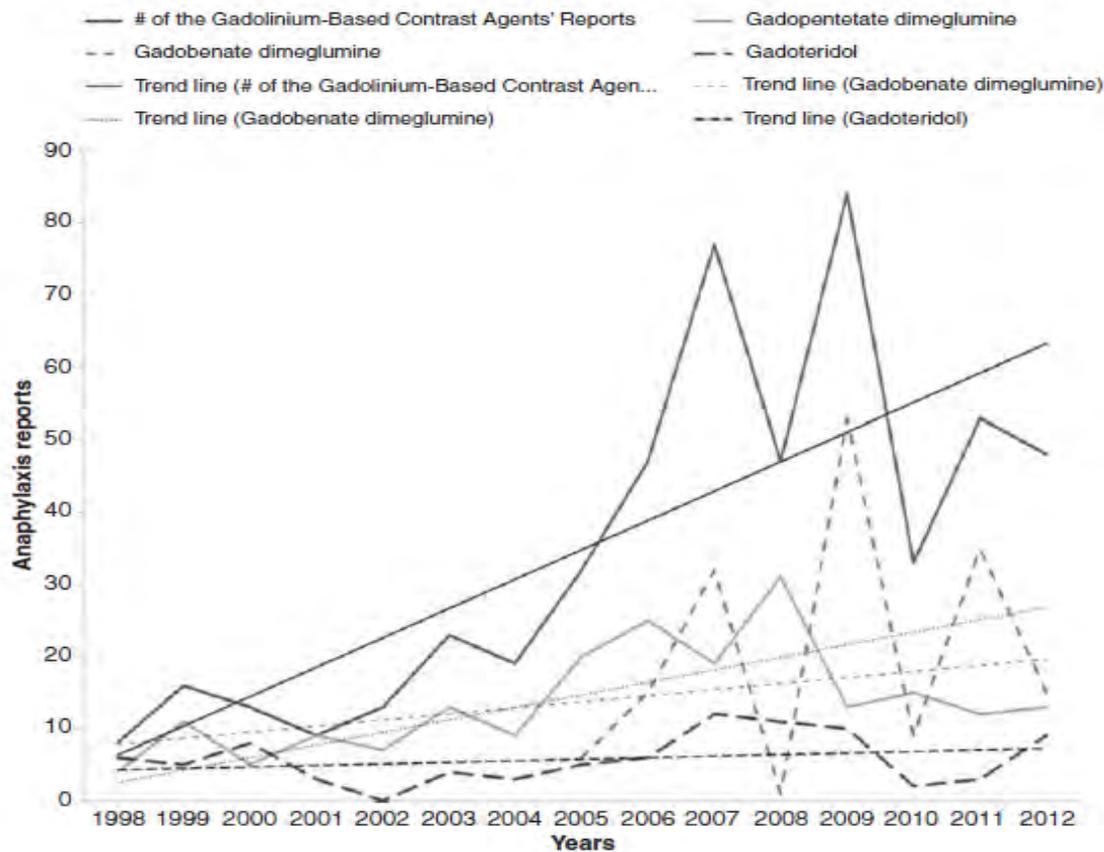
Figure 6   Anaphylaxis reports to FDA FAERS Database by Year and GBCA [Raisch et al. 2014]

However, to confirm this, we compared the US approval years with Figure 6 where possible, and found:

- no peaks in 2001/2002 (2 years after gadoversetamide's December 1999 approval)

- a peak in 2007 (2 years after gadobenate approval; however, additional peaks in 2009 and 2011 are inconsistent with a Weber effect)

- no peak in 2010 (2 years after gadoxetate approval)

- a peak in 2011 (2 years after gadofosveset approval) that appears mainly due to gadobenate

Overall, the Raisch data do not show evidence of a Weber effect.

Moreover, if a Weber effect did affect adverse drug reaction (ADR) reporting, it should apply *equally* to all GBCAs; there is no reasonable basis for assuming that independent healthcare

professionals would randomly differ in ADR reporting behavior. An independent analysis of 334,984 ADR reports for 62 drugs in the FAERS database concluded, regarding the Weber effect, "We did not find evidence of such a general trend in 62 drugs, therefore assertions that modern FAERS data are unreliable due to the 'Weber effect' appear unfounded." [Hoffman et al. 2014].

4.1.2.2   Case Reports of Hypersensitivity Reactions to GBCAs

A literature search conducted by GEHC found no case reports of fatal hypersensitivity reactions to Omniscan (gadodiamide). Fatal case reports were, however, published involving ProHance (gadoteridol) [Takahashi et al. 2015] and Magnevist (gadopentetate) [Jordan and Mintz 1995]. A more recent publication attributed one death to Gadovist (gadobutrol) [Prince et al. 2017]. For context, the analysis of the FDA FAERS database by [Prince et al. 2011] found deaths rates (deaths/million doses) of 2.7 for gadobenate, 0.97 for gadopentetate, 0.70 for gadoteridol, 0.19 for gadoversetamide, 0.15 for gadodiamide, and 0 for gadoxetate.

[Raisch et al. 2014] also reported the number of case reports of GBCA-associated anaphylaxis found in a literature search. Of 14 case reports found, 4 were associated with Magnevist (gadopentetate), 4 with MultiHance (gadobenate), 4 with Dotarem (gadoterate), and 2 with ProHance (gadoteridol). None was associated with Omniscan (gadodiamide), consistent with a literature search GEHC conducted.

4.1.2.3   Meta-analysis of Studies on GBCA Hypersensitivity Reactions

Differential rates of acute hypersensitivity reactions among GBCAs have been confirmed by a recent meta-analysis presented at the 2017 ISMRM meeting [Behzadi et al. 2017]. Ten papers covering a total of 749,647 GBCA administrations (of which 1,034 administrations were reported to have immediate adverse reactions) were analyzed. Gadodiamide (Omniscan; nonionic linear) had the lowest overall rate of immediate adverse reactions (1.8/10000); other GBCAs gave rates up to 50 times higher. The authors concluded that the properties of protein binding, ionicity and macrocyclic structure increase the rate of immediate adverse reactions.

4.1.3   Implications of Differences Among GBCAs in Rates of Acute Hypersensitivity Reaction

In patients with a prior allergic reaction to a GBCA, asthma and various other risk factors, Omniscan provides physicians a reasonable choice for minimizing the well-known and severe risk of acute hypersensitivity reactions and deaths across all its indications. Omniscan's lower ADR rate may also reduce use of healthcare resources currently consumed in treating ADRs (additional personnel time, labs, and medications), repeat examinations, and may reduce the potential delay of workflow or discharge of an affected patient.

In conclusion, based on published robust scientific data, acute hypersensitivity reactions are a potentially serious risk to patients, and should therefore be included in any complete assessment of benefits and risks of GBCA.

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4.2   Nephrogenic Systemic Fibrosis

NSF, a serious condition associated with the use of GBCA in patients with severe renal impairment, has largely been eliminated through appropriate pharmacovigilance measures, specifically, Contraindications and Warnings in the approved products' labeling and education of prescribers. As previously stated, there have been no medically confirmed reports of NSF associated with a post-September 2008 administration of Omniscan

5   POTENTIAL MEASURES TO MINIMIZE RISK

Any concerns arising from the findings of trace amounts of retained Gd can be appropriately addressed using labeling changes and other educational tools.

Although the currently available evidence from the Gd retention does not establish tissue toxicity or clinical adverse effects from long-term retained Gd, proposed labeling changes would include text in appropriate sections of the US package insert that states:

- GBCAs should only be used when diagnostic information is essential and not available with unenhanced MRI.

- The lowest effective dose should be used in conducting enhanced scans.

- A risk-benefit assessment should be conducted when considering administering repeated doses.

- Trace amounts of Gd have been observed following multiple GBCA administrations and may be higher with linear GBCAs than with macrocyclics; the potential clinical significance of this finding is unknown.

Health Canada, TGA in Australia, and Medsafe in New Zealand are currently implementing similar label changes for GBCAs.

GEHC also proposes to communicate information that Gd may be retained in order to reinforce the public communications FDA has already made and the other available public information previously available on this topic. Additionally, consideration should be given to labeling that indicates all GBCAs are not to be administered intrathecally.

As low levels of Gd are seen after use of all GBCAs and none has shown any clinical consequences, labeling changes and educational activities, should be implemented largely consistently across the entire class of GBCAs.

6 GEHC SCIENTIFIC RESEARCH PROGRAM ON GADOLINIUM RETENTION

GEHC continues ongoing research and work with external partners to further investigate Gd retention. The program is intended to delineate further the understanding of a wide-variety of issues in relation to GBCA class, including confirming absence of clinical impact of any Gd retention, clearance kinetics, distribution, and chemical form of retained Gd (Table 8).

Table 8	GE Healthcare Gd Retention Scientific Research Program	
Study Type	**Study**	**Objective**
Clinical	Database Mining/Neurological Signs	Exploration of large, linked databases for feasibility of studying potential effect of GBCA on patient neurological function
Clinical	Mayo Aging Study GBCA Neuro Analysis	Long-term prospective multicenter controlled study of data from the Mayo Clinic Study of Aging (MCSA) to investigate potential effect of GBCA exposure on neurological function and cognitive impairment in patients
Clinical	Breast cancer study	Feasibility assessment of prospective study investigating neurological function in patient population that receives frequent, regular GBCA for screening of non-neurological disease
Clinical/ Nonclinical	Human brain autopsy	Investigation of the amount and regional distribution Gd in the human brain using quantitative and imaging technology in specific areas of the brain, together with tissue morphology
Nonclinical	Rat brain clearance/tissue effects	Investigation of the long-term kinetics of Gd in rat brain and potential effects on neuronal tissue morphology
Nonclinical	Rat brain Gd & behavior	Investigation of the long-term presence of Gd in rat brain follow administration of all major GBCA (linear and macrocyclic) and potential effects on behavior and neurological function
Nonclinical	Rat brain Gd localization	Investigation of the regional distribution and kinetics of Gd in the rat brain following GBCA (linear and macrocyclic) administration
Nonclinical	Gd form methodology	Exploration of potential methods to study Gd chemical form in tissue samples in situ
Nonclinical	Electrophysiology studies in rat brain slices ex vivo	Exploration of potential methods to determine if there are functional effects on axonal and synaptic transmission ex vivo following exposure to GBCA
Nonclinical	Kinetics of Gd retention in multiple rat tissues following a single GBCA dose	To understand how Gd levels in multiple rat tissues change with time over extended periods using the sensitive and direct methodology of ICP-MS

7   CONCLUSION

In summary, trace amounts of Gd have been observed in human and animal tissues following administration of both linear and macrocyclic GBCAs. Nonetheless, no evidence correlates such trace amounts of Gd to harm in patients.

Thus, the benefit risk balance for Omniscan remains positive. The benefits of Omniscan in image enhancement are well-accepted. With regard to the risks, the data show that Omniscan offers very low incidence of hypersensitivity reactions, a serious adverse reaction causally-associated with GBCA administration.

While GEHC does not believe that the detection of trace amounts of Gd following GBCA administration changes the benefit risk balance for GBCAs, in an abundance of caution GEHC has proposed label changes and additional research to better understand the finding of Gd retention.

GEHC appreciates the opportunity for this discussion and remains committed to further collaboration with scientific, medical and regulatory community.

8 APPENDICES

8.1 Study Synopses of Gd Retention in Brain [Appendix A]

Adult MR Studies

[Kanda et al. 2014] retrospectively compared 19 patients who had undergone ≥6 CEMR examinations with 16 patients who had undergone ≥6 unenhanced MR examinations. A fixed dose (7.5 mmol) of Magnevist or Omniscan was used for every patient, who each had eGFR>60 mL/min/1.73m^2. T1 signal intensity (SI) in the DN and GP was correlated with the number of previous administrations of GBCA. The SI ratios (DN to pons and GP to thalamus) were significantly higher in patients who had undergone CEMR examinations than patients who had undergone unenhanced examinations (P <0.001 for both ratios), with no correlation between renal function and GP/DN SI. No clinical sequelae were reported.

[Errante et al. 2014] retrospectively explored the association between previous Omniscan-enhanced MRI examinations and DN T1w on 75 unenhanced images obtained in patients with normal renal function who had either MS or brain metastases. Values for patients with <6 enhanced MRI scans were compared with values for patients with ≥6 enhanced MRI scans. Increased SI was linearly and dose-dependently related to the number of past Gd-enhanced MRI scans. There were no clinical correlates with increased SI in the DN.

[Quattrocchi et al. 2015] retrospectively studied 46 patients with normal renal function who underwent routine follow-up with Omniscan-enhanced MRI for meningioma. DN T1 SI significantly increased between the first and last MRI in patients with a history of ≥6 enhanced MRI scans (p <0.01), but not in those with 1 to 5 enhanced MRI scans (p = 0.74). No clinical findings were reported.

[Ramalho et al. 2015] determined the level of association between the number of previous enhanced MRI examinations and high SI in the GP and DN in 23 patients who received Omniscan (3 to 11 doses, mean 5.0 doses) and 46 patients who received MultiHance (3 to 11 doses, mean 4.6 doses); all had normal liver and kidney function. SI ratios for DN and GP and the relative percentage change (R_{change}) between the first and last examination for each patient were calculated. A significant increase in T1 signal in DN and GP was associated with multiple Omniscan-enhanced studies but not with multiple MultiHance–enhanced studies. However, there was a significant trend toward an increase in rate of change (Rchange) for DN SI ratio (p = 0.013) in the MultiHance–treated patients, suggesting that MultiHance could lead to the presence of Gd in these structures. No clinical sequelae to the increased SI were reported.

[Huang et al. 2015], in a 2015 International Society for Magnetic Resonance in Medicine (ISMRM) abstract, reported signal changes in DN after Magnevist, Omniscan, MultiHance (linear GBCAs) and Gadavist (macrocyclic). Each of the 25 subjects in each GBCA group had at least 6 GBCA-enhanced MRIs. Subjects who received more than 1 GBCA were excluded. The MR

examinations of the brain included MRIs at the initial and final time points. Seven of the 25 Omniscan subjects had a lowest eGFR of <30. Huang observed a progressive increase in DN signal after serial administrations of Magnevist, Omniscan and MultiHance, whereas no appreciable increase in DN signal was seen after administrations of the Gadavist. Additionally, Huang reported a decrease in T1 intensity with Magnevist after 6 months that became undetectable after 22 months from the last administration, which may correspond to "washout" of brain Gd. This study was later published as [Cao et al. 2016a], however, the Omniscan and MultiHance results were not included. No clinical symptoms/signs were reported.

[Radbruch et al. 2015a] compared two ionic GBCAs (gadopentetate dimeglumine (Magnevist); linear and gadoterate meglumine (Dotarem); macrocyclic) for associated changes in DN and GP signal intensity-ratio (SIRs) between earliest and latest MR images. Images from 100 patients (50 in each contrast group) who had each received ≥6 doses of GBCA were analyzed. There were significant increases in SIR in the DN and GP of the gadopentetate patients but no significant increases in the gadoterate group.

[Radbruch et al. 2015b] compared earliest and latest MR images for changes in DN and GP SIRs for 30 patients who had each received at least 5 doses of gadobutrol (Gadavist; macrocyclic non-ionic); the mean cumulative dose was 54.1 ± 30.4 mL. The authors reported finding no signal increases.

[Zhang et al. 2016] and [Zhang et al. 2017] evaluated 16 patients who had each received 35 to 88 (mean 47) administrations of linear GBCA (Magnevist, Omniscan and MultiHance). They found increased T1 signal on unenhanced images in the DN (100%), GP (100%), cerebral peduncles (100%), substantia nigra (88%), red nucleus (88%), colliculi (81%), posterior thalamus (75%), superior cerebellar peduncle (56%), internal capsule (50%), head of caudate nucleus (31%), body of caudate nucleus (25%), whole thalamus (25%), pons (13%), anterior commissure (13%), posterior brain stem (6%), pituitary gland (6%), mammillary body (6%) and putamen (6%), identifying additional regions of increased signal after GBCA. The authors did not report whether one type of GBCA per patient was used or whether the data was confounded by multiple GBCA use. Despite 35-88 GBCA administrations, none of the patients had any clinical sequelae attributed to the elevated brain signals. The author wrote *"since these findings are not associated with any known adverse effects in spite of hundreds of millions of linear GBCA administrations worldwide, there does not appear to be any clinical significance."*

[Cao et al. 2016b] compared 25 patients on chronic hemodialysis (HD) who received GBCA (Omniscan, Magnevist, and Omniscan; average 1.8 GBCAs) to 3 groups of control patients (HD without GBCA; normal renal function plus GBCA; normal renal function without GBCA). The authors did not report the type of GBCA per patient. The HD group who had received GBCAs had T1w SI in the DN that was 3 times stronger than in controls with near normal renal function; all had undergone the same number of GBCA administrations. Dialysis patients at Cornell were all examined by a nurse or nephrologist at the dialysis clinic 3 times per week. A review of these notes from 30 days before and 30 days after each GBCA exposure showed that there were 91

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clinical issues, 64 issues before the GBCA MRI and 27 post GBCA MRI. Seven neurological issues described during the 30 days after GBCA administration, migraine headache, loss of consciousness, memory loss, falling, light-headedness, and ataxia, were also present before the GBCA procedure. None of these patients showed evidence of NSF. Cao wrote "*to date, no reports have identified any clinical impact from this DN signal intensity increase. Because dialysis patients have a substantially greater effect on the DN per GBCA injection, these are the patients in whom we are most likely to find a clinical effect if any exists*". No clinical effects could be identified in the nephrologist/nurse notes of the dialysis patients. There was a trend toward increased choroid plexus SI after GBCA exposures adding support to a hypothesis that Gd may reach the brain parenchyma via the CSF.

[Ramalho et al. 2016a] compared two MR sequences (T1w spin echo [SE] and 3D magnetization-prepared rapid acquisition of gradient echo [MPRAGE]) for their ability to quantify changes in DN SIR in 18 patients previously exposed to multiple doses of gadodiamide (Omniscan; linear non-ionic). Although the changes in SIR from earliest to latest MR images were not significantly different for the two sequences, the actual SIR values were significantly different, so the two sequences cannot be used interchangeably; studies evaluating changes in SIR over time (or number of Gd doses) should compare data acquired using the same sequence.

[Ramalho et al. 2016b] studied 2 groups of patients (62 total) who had 3 to 11 administrations of MultiHance. One group (Group 1) had additionally received 3 to 11 prior doses of Omniscan, while group 2 had exposures to only MultiHance. Group 1 showed a significant increase in baseline and follow-up T1w hyperintensity compared to group 2. Gender, age, and dosing intervals did not have significant influence on relative change. The small sample size was suggested as the reason for the non-statistically significant trend in rate of change. Additional limitations included the potential confounding effect of variations between the 2 groups in age, sex, dosing intervals, and underlying disease processes. Importantly, patients in Group 1 had more total GBCA doses than Group 2, and there was no crossover Group that were exposed to MultiHance first and then Omniscan. Firm conclusions about the results in this study cannot be made.

[Barbieri et al. 2016] reported on 3 patients with impaired renal function and vascular calcification (2 with confirmed NSF) whose unenhanced T1w MRIs showed high SI in the DN and the GP after they had been exposed to relatively low doses of linear GBCAs (0.27, 0.45, and 0.68 mmol/kg). All 3 patients had received multiple GBCAs, including a macrocyclic. Signal ratios between DN and pons and between GP and thalamus were comparable with previously reported measurements in subjects without renal impairment. It was reported that all 3 analyzed patients suffered from transient signs of neurological disorders of undetermined cause; no further details were provided. These symptoms could potentially be explained by their underlying diseases. Barbieri et al. concluded that after several enhanced MRI scans, the amount of Gd in the brain does not differ significantly between patients with and without impaired renal function. None of these cases gave information on any potential influence of the underlying diagnosis on accumulation of Gd.

[Radbruch et al. 2016] retrospectively looked for changes in DN-pons SIR in T1w MR images from 36 patients who had received serial doses of gadopentetate dimeglumine (Magnevist; linear ionic) and subsequently received serial doses of macrocyclic GBCAs gadobutrol (Gadavist; macrocyclic non-ionic) and gadoterate meglumine (Dotarem; macrocyclic ionic). Change in SIR was calculated by subtracting the earliest image's SIR from the latest image's SIR for each of the 3 periods of GBCA administration. They reported SIR to increase following gadopentetate, but to decrease following gadobutrol and gadoterate, which they interpreted as suggesting washout or precipitation of Gd.

[Vatnehol et al. 2016] analyzed the quantitative T1 values (qT1) and the normalized native T1 signal intensity (nSI) for the GP and the DN in patients with 3 to 13 double dose injections of Gadovist at 0.2 mmol/kg. Using T1 relaxometry and T1-SI measurements normalized to thalamus and pons values, they found evidence of subtle, but significant dose-dependent Gd-retention in the investigated brain areas after repeated administration of macrocyclic agent, Gadovist ($p<0.02$).

Earlier studies with MultiHance, [Weberling et al. 2015] and [Ramalho et al. 2015], showed that MultiHance trended to increase in T1w SI though not statistically significantly. However, four recent studies showed that MultiHance also results in detectable brain Gd.

[Metting et al. 2016] assessed for increased T1 signal after multiple doses of MultiHance in five patients with MS and intra-cranial neoplasms, and looked for group differences possibly related to BBB derangements, to see if regions of increased vascular permeability in MS patients may be more susceptible to Gd retention than any permeability changes observed in patients with only local BBB derangement. Patients with 5 consecutive administrations of MultiHance were included. There was a significant increase of DN SI in intra-cranial neoplasm patients per year and a strong trend per units GBCA, which was not seen for MS patients. No difference between groups was found in the GP and white matter. The authors did not report any clinical symptoms.

[Tedeschi et al. 2016] measured relaxation rates in the DN of 74 patients with relapsing-remitting multiple sclerosis and reported a significant association between R1 (1/T1) and with the number of GBCA administrations ($p<0.001$). In a subgroup analysis of patients (n = 35) with known GBCA subtype, the effect on R1 appeared mainly related to linear GBCA.

[Tanaka et al. 2016] compared the effects of linear GBCA on the retention in the cerebellar DN of 21 patients with multiple sclerosis (MS) and 6 with neuromyelitis optica spectrum disorder (NMOsd) who were given at least 10 doses of Gd. The results suggested that MS patients given at least 10 doses of conventional linear Gd exhibited a large amount of Gd accumulation in the cerebellar DN, but the ratio of patients with accumulation of Gd was significantly lower in the NMOsd group, making the mechanism for Gd accumulation unclear. The products administered were not specified. No new cerebellar symptoms or progression of cerebellar symptoms was seen in any patients.

[Marsecano et al. 2017] reported a moderate linear increase of T1 signal intensity in the dentate nucleus in patients with multiple sclerosis that received serial administration of either Dotarem (81

patients) or Gadovist (77 patients) with an average 7.6 ± 1.5 GBCA administrations. Although significance was not reached, a positive trend between SI and dose was reported. We note though, that significance was set at 0.01 and not the commonly used higher value of 0.05. In addition, the authors provided images with visible signal intensity change in the dentate nucleus.

[Bjornerud et al. 2017] reported a dose-dependent signal enhancement in the dentate nucleus in patients with high grade glioma on unenhanced T1w MR images following a high number of macrocyclic GBCA (Gadovist) injections mean (SD): 21.9 (10.9). Visual dentate nucleus enhancement was radiologically observed in three patients having received at least 37 injections. In addition, a significant linear correlation was detected between the number of contrast injections and the relative signal intensity change of the dentate nucleus between first and last scan as well as averaged across all post-baseline examinations. This study used data from a prospectively designed therapeutic trial in which MR imaging was required as part of the protocol, and, as such strictly controlled uniformity across all MR-parameters. Many of the other studies in the published literature could not control or standardize MR imaging parameters as they were chosen from uncontrolled diagnostic scans used in day-to-day clinical patient management. Furthermore, in Bjornerud's study, strict exclusion criteria were used, including a requirement for no lifetime history of exposure to linear or any other unspecified GBCAs, as well as excluding any patient with exposure to any Mn-based agents. The single 3T scanner optimized signal acquisition by its high-field strength and was not hampered by inter-scanner variability. An 8-channel and subsequently 32-channel coil increased signal detection and all images were optimized to detect brain T1w hyperintensity.

[Stojanov et al. 2016] reported T1 signal increase in the dentate nucleus and globus pallidus in 58 patients with relapsing remitting multiple sclerosis after multiple administrations of Gadovist (4.74 ± 0.72). There was a significant correlation between signal intensity increase and number of administrations for the dentate nucleus only. This study was cited as having important limitations when first published due to lack of visual signal intensity in the reference figures. However, quantitative measurements have greater sensitivity to detect signal intensity changes before visual appearance. Indeed, the positive association between signal intensity and dose may well be detecting the lower threshold limit in detection for Gadovist which would become more prominent with additional doses. A higher field-strength scanner (the author used a 1.5 T scanner) would further increase sensitivity to signal change. Finally, it is important to note that a spin-echo sequence that had high sensitivity to differences in tissue T1 was used. Subsequent clinical studies have confirmed Stojanov's findings, and we note that the brain Gd levels detected were after only 4-5 doses of Gadavist, and therefore similar to the number of doses that lead to T1w signals from linear agents.

[Moreno Negrete et al. 2017] reported brain hyperintensities in a retrospective cohort of 139 patients with localized melanoma with an average of 8 administrations of Gadovist at 0.1mmol/kg dose. T1 hyperintensities in the dentate nucleus was observed in 41% of patients at last scan by qualitative assessment. These investigators used a spin-echo sequence which has high sensitivity to T1-related changes.

[Kang et al. 2017] observed a significant association between T1 shortening in the globus pallidus with multiple administrations of Gadovist in a group of 46 patients using a sensitive T1 quantitative mapping technique (multi-dynamic, multi-echo sequence). This sequence is optimized for quantifying T1 changes which results in robust reproducibility. Furthermore, T1 relaxometry is a more sensitive technique than current clinical sequences as it quantitatively measures actual tissue T1, and is not dependent on observer characterization of signal. T1 relaxometry is a quantitative technique that should be used in the next generation of studies in this field.

In a retrospective cohort of patients exposed to therapeutic doses of ionizing radiation, [Adin et al. 2015] investigated the possible associations between GBCA exposure, a hyperintense appearance of the DN on T1w MR images, the cumulative number of CE MR images, amount of Gd administration, dosage of ionizing radiation, and various selected patient demographics. One hundred and eighty-four (184) subjects were included for DN analysis. Among them, 103 patients had hyperintense DN on pre-contrast T1w MR images. The GBCA used in patients included in this study was almost exclusively gadopentetate dimeglumine, but other GBCAs were also used in small proportions (gadodiamide, gadobenate dimeglumine, gadoteridol, gadoversetamide, gadobutrol). The average number of Gd-enhanced MR imaging studies that had been performed was significantly lower for the group with normal DN than for the group with hyperintense DN. After $\geq$4 GBCA-enhanced MRI scans and a total dose of 77 mL of GBCA, there was a significant increase in the likelihood of developing hyperdense DN. Every doubling of the number of GBCA-enhanced MRI scans was associated with 1.51 times higher odds of hyperintense DN (95% CI, 1.14 –2.01; P = 0.004). Every doubling of the total GBCA volume was associated with 1.33 times higher odds of hyperintense DN (95% CI, 1.02–1.73; P = 0.038). In 113 of 137 individuals who were included for subset analysis, every CE-MRI study was performed using a Magnevist (gadopentetate dimeglumine) injection. In all except 1 of the remaining cases (n=23), at least 1 different Gd molecule including Magnevist was injected during the follow-up. The Fisher exact test showed no statistically significant difference between gadopentetate dimeglumine and other GBCAs. Analyses of multiple sequential MR images with long follow-up periods revealed that once a hyperdense DN was evident, it was most likely to remain as long as 139 months after onset. On the other hand, no significant difference was observed between hyperintense and normal DN groups in terms of exposed radiation dose, serum creatinine and calcium/phosphate levels, patient demographics, history of chemotherapy, and strength of the scanner. CT scans of patients demonstrating hyperintense DN were also reviewed by using the same methodology. No DN abnormalities were found on the corresponding CT scans of patients with hyperintense DN (n=44). No DN abnormalities were found in 53 healthy volunteers who were recruited as a control group. The authors concluded that repeat performance of GBCA-enhanced studies likely contributes to a long-standing hyperintense appearance of DN on pre-contrast T1w-MR images. The study did not investigate the clinical consequences of hyperintense DN.

[Bae et al. 2017] retrospectively studied 122 patients who underwent double-dose GBCA-enhanced magnetic resonance imaging to determine the relationship between number of GBCA administrations and T1 signal intensity in the GP and DN. Of the 122 patients, 6 (4.9%) received only linear GBCAs (15-30 administrations each; mean 20.8), 44 (36.1%) received only

macrocyclic GBCAs (14-51 administrations each; mean 26.1) and 72 (59.0%) received both (12-65 administrations each; mean 31.5). A significant association for the DN was found with linear GBCA (gadodiamide and gadopentetate dimeglumine) but not for the macrocyclics; no association was found for the GP.

[Eisele et al. 2016] analyzed the DN of 279 unenhanced T1w images from 41 RRMS patients (mean 38 years old; 33 women) who had each received at least 6 enhanced MRI examinations using the macrocyclic gadoterate meglumine (Dotarem) and found no signal increases.

[Schlemm et al. 2017] determined T1w signal intensity ratios (SIR) for the DN in 265 consecutive MR images from 97 MS patients and reported finding T1w hyperintensity in those who received only gadopentetate (Magnevist) but not in those who received only gadobutrol (Gadavist), with a significant positive linear relationship between the SIR and the number of gadopentetate doses.

[Radbruch et al. 2017a] retrospectively determined DN SIRs in 33 patients who each received $\geq$20 consecutive doses of the macrocyclic GBCAs gadoterate meglumine (ionic; Dotarem) and gadobutrol (non-ionic; Gadavist). Dosing was: mean $\pm$ SD: 23.03 $\pm$ 4.20 administrations; mean cumulative dose 491.21 $\pm$ 87.04 mL; mean inter-dose interval 12.09 $\pm$ 2.16 weeks. The authors reported finding no significant increase in DN SIRs.

[Kahn et al. 2017] determined T1 SIRs for the DN and GP in 91 patients who had received 1-37 doses of the linear ionic GBCA gadoxetate disodium (Eovist), compared to 52 GBCA-naïve controls. DN and GP SIRs were significantly higher in the GBCA group vs. the control group. SIR was significantly associated with the number of GBCA administrations for the DN but not the GP.

[Ichikawa et al. 2017] retrospectively analyzed T1w MR images for DN SIR in 132 patients who had received the linear ionic GBCA gadoxetate disodium (Eovist) or the linear non-ionic GBCA gadodiamide (Omniscan). Each patient was classified as belonging to 1 of 4 analysis groups: 1) 5 or more doses of gadoxetic acid ("gadoxetic acid $\geq$5 administrations" group); 2) only 1 administration of gadoxetic acid ("gadoxetic acid 1 administration" group); 3) no GBCA or chronic liver disease (CLD; "no GBCA administration and no CLD" group); and 4) 5 or more doses of gadodiamide ("gadodiamide $\geq$5 administrations" group). Compared to the "no GBCA administration and no CLD" group, SIR was significantly higher for the "gadodiamide $\geq$5 administrations" group only. However, the authors point out that despite equal numbers of administrations for the 2 GBCA groups, the amount of Gd contained in each dose of gadoxetate was only a quarter of that contained in each dose of gadodiamide.

[Kuno et al. 2017] analyzed MR images from 35 patients (9 who had received gadopentetate dimeglumine (Magnevist; linear ionic), and 26 who had not) for T1 and T2 relaxation times. Gd exposure was associated with significantly shorter T1 values of grey matter. T1 was significantly correlated with cumulative Gd dose in whole brain, GP, DN, and thalamus. T2 was significantly correlated with cumulative Gd dose in whole brain, DN, and thalamus. There was no significant correlation between T1 of white matter and cumulative Gd dose.

These reports were important in raising the possibility of Gd retention in the brain, and prompted others to perform direct quantification of brain Gd using more sensitive methods such as ICP-MS. None of these reports indicated any level of patient harm in association with the hyperintensity.

Pediatric MR Studies

The majority of reports of T1w hyperintensity have been in adults, but an increasing number of reports in children are being published. As in adults, the hyperintensity was reported in patients who had received multiple doses of GBCAs.

[Kinner et al. 2016] reviewed MRI images of 76 children, who each underwent between 4- 20 MultiHance-enhanced MRI's. Sixteen patients had posterior fossa tumor, treated with radiation and/or chemotherapy, and the remainder were unconfounded with such treatment. Twelve (75%; 10 to 20 injections each) of the 16 patients from the first group had deep grey hyperintensities (DN and GP) while only 2 (3%; 16 and 20 injections) of the 60 control patients were positive. Statistical analysis showed a statistical significant change in signal ratio for the number of scans. There was a significant difference in average change in ratio over time between the 2 groups (p<0.001). No obvious patterns of clinical deficits were observed in children with hyperintensities. The authors concluded that there is a correlation between number of CE-MRIs and T1w signal hyperintensity of the deep brain nuclei in children, and that radiation and/or chemotherapy for posterior fossa tumors accelerates the appearance of the apparently asymptomatic hyperintensity. The authors reported that to date, there have not been any reported adverse clinical effects directly attributable to retained Gd.

[Hu et al. 2016] analyzed DN and GP signal intensity in the unenhanced MR images from children aged 0.9 to 14.4 years of age (at first MR), who had each received 5-37 doses of gadopentetate dimeglumine (Magnevist). Between the earliest and latest MR images, signal increased a mean of 18.6%±12.7% (range: 0.5% to 47.5%) in the DN and 12.4%±7.4% (range: -1.2% to 33.7%) in the GP. Signal intensity was also higher in GBCA patients than in controls (P<0.01). Signal intensity increase was not statistically significantly associated with cumulative number or volume of GBCA dose, age or time interval between the earliest and latest MRIs.

[Flood et al. 2017] investigated the effect of Gd exposure on the brain in 40 pediatric patients (age 6 months to 18 years) with a history of ≥3 (mean 4.8 exams/patient) MR exams using Magnevist and age-matched contrast-naïve controls. GBCA exposure was associated with statistically significantly increased SI ratios within the GP and DN. This study did not report clinical symptoms related to linear GBCA exposure in young children, though T1w SI was observed after an average of about 5 doses per patient.

[Radbruch et al. 2017b] retrospectively studied the effect of ≥5 serial doses of macrocyclic ionic gadoterate meglumine (Dotarem) (mean 8.6 ± 3.9 doses; mean cumulative dose 32.07 mmol ± 17.62; mean inter-dose interval 16.7 ± 7.9 weeks) on DN intensity in 41 children aged 3 to 17 years, and reported finding no significant change in SIR.

[Roberts et al. 2016a] investigated the association between DN SIR and prior exposure to gadopentetate dimeglumine (Magnevist; linear ionic) in children. Of 280 children at their institution who had each received ≥5 doses of GBCA, 58 had documented use of gadopentetate dimeglumine. After excluding patients with posterior fossa pathology or radiation, 16 patients (aged 2 months to 14 years at first exposure) were available for analysis. DN SIR were significantly associated with number of prior GBCA doses.

[Espagnet et al. 2017] investigated the effect of macrocyclic Gd exposure on the brain in 50 pediatric patients (age 2 to 18 years) with a history of ≥6 (mean 10 exams/patient). MR exams using macrocyclic ionic gadoterate meglumine (Dotarem) and age-matched contrast-naïve controls. GBCA exposure was associated with statistically significantly increased SI ratios within the GP and DN.

These reports indicate that T1w hyperintensity also occurs in children, with both linear and macrocyclic agents in a dose dependent manner. As in adults, none of these reports indicated any harm in association with the hyperintensity.

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