CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201277Orig1s000

<u>MEDICAL REVIEW(S)</u>

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 201,277   **Applicant:** Bayer HealthCare   **Stamp Date:** 5-14-10

Drug Name: Gadovist® 1.0 Injection   **NDA/BLA Type:** Original NDA, Standard Review Priority

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			x	
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Protocol Number 308200: Multi-center, double-blind, randomized, parallel group, dose comparison study with corresponding blinded image evaluation following a single intravenous injection of three different doses of gadobutrol 1.0 molar (Gadovist®) in patients with known or highly suspected focal blood brain barrier disturbances and/or abnormality of the central nervous system	x			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

1

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Sample Size: 225 (69-90-70); 229 for safety Arms: 3 (0.03, 0.1, 0.3 mmol/kg) Location in submission: 5.3.5.1 (Report A40524)				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Protocol 310123: A multicenter, randomized, double-blind, crossover, phase 3 study to determine the safety and efficacy of gadobutrol 1.0 molar (Gadovist®) in patients referred for contrast-enhanced MRI of the central nervous system (CNS) (Report A47567) Indication: Gadovist 1.0 Injection is a gadolinium-based contrast agent indicated for intravenous use in diagnostic magnetic resonance imaging (MRI) in adults and children (2 years of age and older) to visualize lesions with disrupted blood brain barrier (BBB) and/or abnormal vascularity of the central nervous system. Pivotal Study #2 Protocol Number 310124: A multicenter, open-label, phase 3 study to determine the safety and efficacy of gadobutrol 1.0 molar (Gadovist®) in patients referred for contrast-enhanced MRI of the central nervous system (CNS) (Report A47570) Indication: Gadovist 1.0 Injection is a gadolinium-based contrast agent indicated for intravenous use in diagnostic magnetic resonance imaging (MRI) in adults and children (2 years of age and older) to visualize lesions with disrupted blood brain barrier (BBB) and/or abnormal vascularity of the central nervous system.	x			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			Study #1 performed under SPA (FDA concurrence 4-17-08); Study #2 identical except without active comparator arm
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner	x			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

2

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	previously requested by the Division?				
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	x			Study 367362 (Report A21381)
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			x	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	x			
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	x			Contained in ISS
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			Section 2.2.3.1
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	x			
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to	x			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	previously by the Division?				
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
34.	Are all datasets to support the critical safety analyses available and complete?	x			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	x			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __x_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

The proposed strength of this diagnostic drug is 1 M (one molar) as compared to other available gadolinium based drugs which are 0.5 M (half molar). This could be a labeling issue.

Barbara A. Stinson, DO	6-24-10
Reviewing Medical Officer	Date

Clinical Team Leader	Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

4

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

/s/

BARBARA A STINSON
04/01/2011

CLINICAL REVIEW

Application Type	201,277
Application Number(s)	SD 1
Priority or Standard	Standard
Submit Date(s)	May 14, 2010
PDUFA Goal Date	March 14, 2011
Division / Office	Division of Medical Imaging Products 0DE IV
Reviewer Name(s)	Barbara A. Stinson, DO
Review Completion Date	January 28, 2011
Established Name	Gadobutrol
(Proposed) Trade Name	Gadovist 1.0 Injection
Therapeutic Class	MRI diagnostic contrast agent
Applicant	Bayer Health Care Pharmaceuticals
Formulation(s)	1.0 mmol Gd/mL
Dosing Regimen	Single use, 0.1 mmol/kg IV
Indication(s)	Gadovist injection (gadobutrol) is a gadolinium-based contrast agent indicated for intravenous use in diagnostic MRI in adults and children (2 years of age and older) to detect and visualize of areas with disrupted blood brain barrier (BBB) and/or abnormal vascularity of the central nervous system (CNS)
Intended Population(s)	Adults and children ages 2 years and older with known or suspected CNS disease

Table of Contents

4

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends approving NDA 201277, pending acceptable revision of proposed trade name and labeling review.

1.2 Risk Benefit Assessment

- The applicant met the primary efficacy endpoints.
- The safety profile is acceptable.
- The benefit/risk assessment favors approval.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

- The applicant should continue the established Global Pharmacovigilance Program (GPV) to ensure that information about all suspected adverse reactions is collected and reported in a global safety database.
- The applicant should ensure enhanced pharmacovigilance and risk minimization for the development of Nephrogenic Systemic Fibrosis (NSF).

1.4 Recommendations for Postmarket Requirements and Commitments

The applicant should continue the ongoing post marketing GRIP study (Safety of Gadobutrol in Renally Impaired Patients) to evaluate the risk of the development of NSF from gadobutrol in patients with impaired renal function.

2 Introduction and Regulatory Background

2.1 Product Information and Product Development

- Gadobutrol Injection (1.0 Molar) is an electrically neutral, macrocyclic paramagnetic gadolinium (Gd) chelate for that causes shortening of relaxation times (T1 and T2) yielding contrast enhancement in magnetic resonance imaging (MRI) scans.
- The non-proprietary (USAN) name is Gadobutrol.
- The proposed trade name is Gadovist 1.0.
- The structural formula reproduced below contains two asymmetric centers in the trihydroxybutyl side chain.
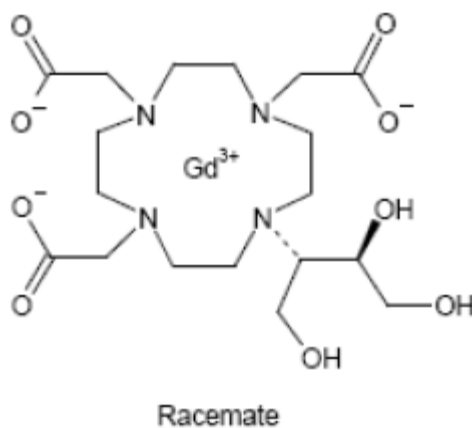
Racemate

- The molecular formula of the racemate, (non-optically active compound) is $C_{18}H_{31}GdN_4O_9$. The molecular mass is 604.72.
- Chemical class: This product is a new molecular entity (NME). It is an electrically neutral gadolinium complex formed by complexation reaction of gadolinium ions (Gd^{3+}) and the ligand Butrol. Butrol is a heterocyclic compound substituted with three molecules acetic acid and a trihydroxybutyl side chain.
- Pharmacological class: The product is a gadolinium-based contrast agent that shortens the T1 and T 2 relaxation times of hydrogen protons which is seen as an increase of signal intensity in T1 weighted imaging sequences.
- Proposed indication: For use in diagnostic magnetic resonance imaging (MRI) [performed] in adults and children (2 years of age and older) to detect and

visualize areas with disrupted blood brain barrier (BBB) and/or abnormal vascularity of the central nervous system (CNS).

- Background and rationale: Contrast-enhanced MRI is the primary method for neurodiagnostic workup for its established role in the detection, localization, and depiction of the intrinsic properties of CNS pathology. Pathology of the brain such as lesions caused by primary or metastatic brain tumors, stroke, and inflammation disrupt the normal blood brain barrier allowing contrast agents to diffuse into these lesions, which increases their detectability on contrast-enhanced (CE) MR sequences. CE-MR is the clinical "gold standard" for detecting and delineating most intracranial and spinal lesions. The primary objective of the two phase 3 pivotal studies that are presented in this NDA was to demonstrate superiority of combined contrast enhanced/unenhanced MRI versus unenhanced MRI for structural characteristics of CNS lesions (contrast enhancement, border delineation, internal morphology) with non-inferiority in detection of the number of lesions so as to provide information for diagnosis and clinical management.

- The proposed dose is 0.1 mmol/kg body weight to be administered by a single injection followed by a 20-mL saline flush, both injections administered by a power injector at a rate of 2mL/sec. It is distributed exclusively within the extracellular fluid and eliminated quickly via the renal system, without any metabolism.

- Calcobutrol sodium, a calcium complex, is an excipient in Gadovist. It functions as a stabilizer by complexing heavy metal ions as Gd^{3+} which may be present in Gadovist.   It is formed by complexation of calcium (Ca^{2+}) ions by the ligand Butrol, the same heterocyclic compound used for the synthesis of Gadobutrol. It is manufactured by Bayer Schering Pharma AG.

- Gadovist solution for injection will be offered as single dose vials, single dose pre-filled glass syringes, and pharmacy bulk pack both as a glass vial and a glass bottle. All sizes of Gadovist will be available with a Radio Frequency Identification (RFID) tag incorporated into the vial/syringe label. The RFID tag will contain the NDC number, lot number, and expiration date.

2.2 Currently Available Treatments for Proposed Indications

There are five extracellular MRI contrast agents in the US approved for use in MRI of the central nervous system (CNS). These have the following indications according to their respective labels.

- **Magnevist** is indicated for use with MRI in adults and pediatric patients (2 years of age and older) to visualize lesions with abnormal vascularity in the brain, spine and associated tissues as well as visualization of lesions with abnormal vascularity of the head and neck and the body (excluding the heart).

- **Omniscan** is indicated for IV use in MRI to visualize lesions with abnormal vascularity in the brain, spine and associated tissues. It is also indicated for IV administration to facilitate the visualization of lesions with abnormal vascularity within the thoracic (non-cardiac), abdominal, pelvic cavities, and the retroperitoneal space. […Pediatric patients 2-16 years…]
- **Multihance** is indicated for IV use in MRI of the CNS in adults and children over 2 years of age to visualize lesions with abnormal blood-brain barrier or abnormal vascularity of the brain, spine and associated tissues.
- **Optimark** is indicated for use in MRI in patients with abnormal blood brain barrier or abnormal vascularity in the brain, spine and associated tissues. It is also indicated for use with MRI to provide contrast enhancement and facilitate visualization of lesions with abnormal vascularity in the liver in patients who are highly suspect for liver structural abnormalities on computed tomography (CT).
- **Prohance** is indicated for use in MRI in adults and children over 2 years of age to visualize lesions with abnormal vascularity in the brain, spine, and associated tissues as well as for use in adults to visualize lesions of the head and neck.

Of these agents, Omniscan, Magnevist, Prohance, and Multihance are approved for use in pediatric patients over age 2.

Prohance is the only other macrocyclic gadolinium-based contrast agent that is approved in the US.

There are two additional US approved gadolinium based contrast agents, Eovist and Ablavar, approved for non-CNS indications.

The other widely used imaging modality for diagnosis of CNS lesions in the brain for the intended population is contrast-enhanced computed tomography. This modality provides limited evaluation of some structures.

2.3 Availability of Proposed Active Ingredient in the United States

The drug product is a new molecular entity and is not currently marketed in this country. The synthesis, purification, and release control of Gadobutrol are performed by Bayer Schering Pharma AG, Bergkamen, Germany.

2.4 Important Safety Issues With Consideration to Related Drugs

In 2006, the Agency issued a Public Health Advisory notice and recommended that the manufacturers of gadolinium containing products send a Dear Healthcare Provider letter regarding the potential development of Nephrogenic Systemic Fibrosis (NSF) that has

been associated with gadolinium containing contrast agents when used in patients with severely impaired renal function (GFR < 30 mL/min/1.73 m^2). Additionally, class labeling changes for these products included the addition of a black box warning and changes to the Warnings section of the label.

Sponsors are required to report all cases of NSF to the Agency on an expedited basis. In addition, sponsors are required to participate in phase 4 postmarketing studies to assess the safety of gadolinium in renally impaired patients. Bayer is currently enrolling patients in their GRIP study (Safety of Gadolinium in Renally-Impaired Patients) to evaluate the safety of gadolinium contrast agents in moderately and severely impaired renal subjects.

In order to satisfy reporting requirements, Bayer has submitted to Gadovist IND 56,410 detailed quarterly reports of NSF with an expert safety statement analyzing all new reports, a review of the literature, and any new non clinical reports.

Bayer reported 8 cases of NSF in association with Gadovist use through the data lock point of January 31, 2010. An additional case (9 cases total) was reported as of the 120 day safety update of 8-31-10 with an additional case reported as of 12-31-10, (10 cases total)**.**

The FDA recently required that some gadolinium-based contrast agents carry new warnings on their labels in addition to the already requird black box warning. Magnevist, Omniscan, and Optimark are now required to be described as inappropriate for use among patients with acute kidney injury or chronic severe kidney disease.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

IND 56,410 for gadobutrol injection was originally submitted by Berlex to the FDA on July 15, 1998. It was subsequently placed on clinical hold by the FDA due to a lack of information on cardiac toxicity. Berlex subsequently submitted a complete response to this clinical hold, submitted a revised phase 2 protocol study, and activated the IND. Berlex made a business decision to place the IND on inactive status and the phase 2 study was cancelled prior to any enrollment. IND 56,410 was subsequently reactivated on December 29, 2003 with a clinical program focused on CNS imaging. Berlex was later acquired by Bayer HealthCare Pharmaceuticals.

On May 24, 2007, a Type C meeting was held between the FDA and Bayer to discuss designs of the phase 3 program. This was followed on August 28, 2007 by an End-of-Phase 2 meeting.

During the course of development, the FDA agreed that in the pediatric population, effectiveness data could be extrapolated from safety and PK data. In addition, the FDA concurred with Bayer's position to defer studies in the 0 to 2 year age group until data in the older age groups became available.

A Special Protocol Assessment (SPA) for the phase 3 study 310123 was submitted on October 4, 2007 then revised and resubmitted, receiving FDA concurrence on April 17, 2008. Subsequently, the final protocol and Amendment #1 were submitted. The phase 3 protocol 310124 (the same clinical study without the active comparator arm) was submitted to the FDA on December 12, 2007, followed by Amendment #1 on October 29, 2008. The pre-NDA meeting between Bayer and the Agency was held on February 4, 2010.

2.6 Other Relevant Background Information

Until recently, Gadovist has not been studied in the United States. However, Gadovist is currently approved for the various uses in 64 countries. Specifically, Gadovist is approved for the indication "Contrast Enhancement in Cranial and Spinal MRI" in doses up to 0.3 mmol/kg body weight (bw) in the European community and in several countries in Eastern Europe and Asia. Studies have been conducted for multiple indications including CNS, whole body, and MRA indications, which involved more than 4500 subjects in phases 2-4. Both 0.5 M and 1.0 M Gadovist have been studied. First approval for both came in Switzerland in 1998. The 0.5 M solution was never marketed.

According to the applicant, an excellent safety profile has been demonstrated in more than 4500 adults enrolled in phase 1 to 4 trials, confirmed by extensive postmarketing experience in more than 5.5 million patients in approved countries.

In addition to developing gadobutrol both in the United States and Japan for "CNS imaging" Bayer is currently performing clinical trials for an indication of Magnetic Resonance Mammography (MRM) and is in the process of developing clinical trials for a Magnetic Resonance Angiography (MRA) indication.

The NDA includes a pediatric pharmacokinetic (PK) study in children 2 to 17 years of age. Bayer has submitted a protocol to IND 56,410 to study children ages 0-23 months.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

DSI was consulted regarding site visits for this NDA. The two phase 3 pivotal studies utilized multiple study centers that enrolled 30 patients or less. The following sites noted in the below table were suggested to DSI for inspection based upon protocol violations and adverse events as reported by the sponsor in the study report. ____(b) (4)____, the core laboratory for the independent blinded read of the images was also recommended for inspection based on the importance of the blinded read results. _____(b) (4)____, which is the site that maintains study files, was also **inspected.**

Table 1: Inspection Sites (Studies 310123, 310124; Core Laboratory; Study Files)

Site # (Name and Address) Chief Investigator	Report # / Protocol #	Number of Subjects	Indication
Site 10006 Hr. Prof. Dr. Rudiger Von Kummer Universitätsklinikum Carl-Gustav Carus Abteilung Neurpradiologie (Haus 59) Fetscherstrasse 74 01307 Dresden, Germany	A47567 310123	27	19 protocol violations
Site 14002 Dr. Elias Melhem University of Pennsylvania Health System 3400 Spruce Street 2nd floor Dulles Building Philadelphia, PA, 19104 USA	A47567 310123	19	68 treatment emergent events
Site 14001	A47570	19	24 treatment emergent events

Dr. Robert Booth UF College of Medicine-C90 655 West Eighth Street Jacksonville, FL, 32209 USA	310124		
Site 14004 Dr. Jae Kim 677 N Wilmot Road Tucson, AZ, 85711 USA	A47570 310124	15	9 treatment emergent events; for comparison to above listed site
(b) (4)			Core lab responsible for independent interpretation of image results; need to assess compliance with blinded read procedures
			Site maintains study files

3.2 Compliance with Good Clinical Practices

The pivotal studies were performed in accordance with acceptable clinical standards, e.g. patients were referred for an MRI contrast-enhanced exam of the CNS based on clinical symptoms or prior imaging exam. All subjects were required to sign an informed consent statement. According to the Sponsor and subject to inspections, as above, the majority of protocol deviations were procedural, relating to dosing, imaging sequences, and timing for example.

As indicated, for one of the phase 3 pivotal trials, the site with the greatest number of protocol violations was placed on the inspection site list. One site with the greatest number of treatment emergent adverse events from each of the main phase 3 clinical trials and a comparator site were also placed on the site inspection list.

DSI inspection at the sites of Drs. Melhem, Booth, Kim and von Kummer revealed that they adhered to the applicable regulations and good clinical practices governing the

conduct of clinical investigations. Studies at these sites appeared to been adequately conducted with data generated by the sites supportive of the indication. Inspection of _____ (b) (4) revealed no regulatory violations and there were no adverse findings regarding the Blinded Image Evaluation. It was noted that Bayer Healthcare had monitoring deficiencies at a single clinical investigator site but that there was no evidence that the monitoring deficiencies were widespread or that the deficiencies should significantly impact the efficacy or safety outcomes of the study. The data from the sponsor appear acceptable for use in support of the NDA.

3.3 Financial Disclosures

Bayer HealthCare Pharmaceuticals submitted a list of all clinical investigators who participated in the clinical studies. For the four considered "covered" clinical studies, approximately 1/3 of investigators (35/102) participating in study 308200 (dose ranging study) had no financial arrangements to disclose pre-study/during the period of study conduct but were unable to be contacted at the end of the study/at the 1 year post study period.

There were two investigators who received significant payments from the sponsor during and/or up to one year after conclusion of study 308200. The financial disclosure report from _____ (b) (6) lists him as a sub-investigator in this clinical study receiving compensation for his services as a consultant to Bayer. His site recruited (b) (6) patients ____ (b) (6) of the total population enrolled) for this study but one was excluded from the efficacy evaluation due to major MRI procedure deviations. _____ (b) (6) _____, also a principal investigator for this protocol during the same time period, was provided compensation by Bayer and Medrad (a wholly owned subsidiary of the Bayer Corporation). His site recruited (b) (6) patients, all of whom were judged to have major MRI procedure deviations thereby excluding them from the Per Protocol Set analysis. In both instances, all efficacy evaluations were based on a blinded independent read. The potential bias based on the pooled safety database of 4549 is felt by this reviewer to be extremely small, (_____ (b) (6) of patients evaluated, respectively).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Gadobutrol is a stable gadolinium complex. It has a macrocyclic configuration with a butrol trialcohol substituent and two "extra" hydroxyl groups to enhance stability. Drug

substance specifications are similar to those of other gadolinium agnets. Synthesis is robust and well defined and the material is well characterized. Thermodynamic stability is very high. Room temperature storage tests that have been performed support a 48 month retest period (expiry).

It is formulated as as 1.0 M (1 meq/mL) compound as versus 0.5 M formulation of other approved agents. It contains 1 mM (0.001 meq/mL) of calcobutrol to reduce free Gd^{+3} and other excipients to control/adjust the pH. It is terminally sterilized.

Drug product specifications, (identification, physical qualities, assay, and impurities), are adequate to describe and control quality attributes.

It will be marketed as single use vials, single use syringes, and pharmacy bulk pack with compatibility of all container closure components. Stability studies support a 60 month expiry for all dosage forms.

Methods validation is suitable for all specifications and is similar to approved agents. EERs are acceptable on profile with inspection of one German site pending as of November 15, 2010.

There are no outstanding CMC review issues at this time.

4.2 Clinical Microbiology

The drug substance is a sterile, non-preserved solution for injection in single dose containers. It will be supplied in 3 vial configurations, 3 pre-filled syringe configurations, and 2 pharmacy bulk pack configurations. The drug product is   (b) (4). Container closure studies support support the proposed configurations. Studies for hold times to assess bioburden support a 96 hour hold time during manufacturing and a PBP hold time of 24 hours after opening. The conclusion of the microbiology clinical review is that gadobutrol is recommended for approval.

4.3 Preclinical Pharmacology/Toxicology

Safety pharmacology studies perfoprmed in mice showed decreased locomotion, twitching, and decreased respirations which were reversible. In-vitro hERG studies performed showed results comparable to Omniscan, Prohance, and Imeron. Results of safety pharmacology studies performed in dogs were acceptable. Non-clinical toxicology studies performed in rats and dogs showed profiles similar to other approved gadolinium agents. There was a negative ICH battery for genotoxicity. The review for reproductive toxicity is ongoing. Impurities were within acceptable limits.

The pre-clinical considerations for nephrogenic systemic fibrosis, (NSF), were reviewed for various gadolinium agents with consideration to NSF occurrence associated with gadolinium deposition and renal insufficiency. The review noted the propensity for gadolinium deposition in skin and other tissues and reviewed skin gadolinium levels 35 and 364 days after IV administration. At both time periods, skin deposition was greatest for the non-ionic linear gadolinium-based contrast media, (GBCAs), followed by the ionic, linear GBCAs, with relatively small amounts noted for the macrocyclic agents. At day 364, skin deposition for the macrocyclic agents was similar to untreated control or to saline, (slightly higher).

Serum gadolinium values were studied using Omniscan in nephrectomized and non-nephrectomized rats and showed higher gadolinium concentrations at all intervals from 1 to 1440 minutes post injection.

In addition, the role of endogenous cytokines and metals was considered as a possible mechanism in the development of NSF. A study performed using Omniscan revealed elevated levels of cytokines in all organs/tissues after a single IV injection. No specific organ was identified as the source of elevated cytokine expression. Changes in endogenous zinc levels did not affect gadolinium skin deposition elicited by any of the treated gadolinium product.

Preliminary conclusions based on studies of NSF provided by the sponsor were as follows:
1. There is a potential for gadolinium skin deposition in all evaluated gadolinium products.
2. The propensity for skin deposition seems to be higher with linear gadolinium agents.
3. Accumulation of gadolinium in skin and tissues appears to be higher in nephrectomized rats used as a model for renal impairment.
4. Omniscan appears to be the "worst" offender.

The Pharm/Tox review summarized and concluded that the safety and toxicity profiles of gadobutrol were similar to the other approved gadolinium agents and that NDA201277 is recommended for approval.

4.4 Clinical Pharmacology

The applicant conducted 11 PK studies in humans comprised of 8 studies to evaluate safety and PK after single and repeated administratin of gadobutrol. There were also six phase 1 clinical studies in healthy adults, one hase 3 clinical study in subjects with renal impairment, and one phase 1/3 study in pediatric subjects ages 2-17 years to confirm suitability of the proposed 0.1 mmol/kg bw dose in children. PK studies

evaluated the effects of endogenous factors such as age and body weight based on pooled data consisting of all phase 1 studies in healthy adults. A thorough QT study was performed including PK.

The FDA TQT team reviewed the applicant's thorough QT study and concluded the following:
- The effects on QT prolongation are likely to be small and should not have important clnical significance.
- There were no events of clinical importance identified, (for example seizures).
- ECG acquisition and interpretation was acceptable.
- PR and QRS interval changes were not clinically relevant.

The pediatric PK study supported body weight dosing similar to the adult population (0.1 mmol/kg bw).

The applicant conducted a phase 2 dose selection study, (308200), using 0.03, 0.1, and 0.3 mmol/kg bw doses. The 0.1 mmol/kg dose was selected based on average reader categorical visualization score, (CVS), of brain lesions. There was statistically significant improvement in CVS for both the 0.1 and 0.3 mmol/kg bw doses compared to the 0.03 mmol/kg bw dose.

Study 95062 was a dedicated study on renal impairment and dialysability. 32 patients were equally distributed in three groups of different stages of renal impairment as defined by serum creatinine clearance: (1) moderate impairment of creatinine clearance, (clearance <80 and >30 mL/min); (2) severe impairment (clearance <30 mL/min) and; (3) requiring dialysis. Patients randomly received 0.1 or 0.3 mmol/kg bw doses. Total clearance from serum was evaluated for both dose groups. No dose differences were found. The mean elimination half life of gadovist was similar for both dose groups with the better renal function but was prolonged for subjects with the lower creatinine clearance with greater prolongation noted for the higher dose group, the maximum elimination half-lives noted as 23 hours for the 0.1 mmol/kg bw dose and 44.3 hours for the 0.3 mmol.kg bw dose in the group of patients with severe renal impairment.   The overall conclusion was that decreased clearance of gadobutrol was associated with increasing renal impairment. In the group of patients with chronic hemodialysis, it was demonstrated that gadobutrol can be eliminated from the body via dialysis ranging from 98.1% to 98.6% for the 0.1 mmol/kg bw dose and 94.3% to 99.8% for the 0.3 mmol/kg bw dose eliminated after three routine dialysis cycles

No formal drug-drug interaction studies were performed as there is no metabolism of gadobutrol.

The review is ongoing however the conclusion of the Clin/Pharm reviewer was that no issues have been found to date.

4.4.1   Mechanism of Action

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

4.4.2   Pharmacodynamics

Gadobutrol leads to a shortening of the relaxation times of protons in plasma, referred to as relaxivity. Both T1 and T2 relaxivity occur. Both relaxivities display only slight dependence on the strength of the magnetic field.   The T1 shortening effect is dependent on concentration, (1.0 M for gadobutrol), and relaxivity and it is this T1 shortening effect which is associated with improved tissue visualization

4.4.3   Pharmacokinetics

There is rapid distribution of gadobutrol in the extracellular space after injection. The PK is linear. The $t_{1/2}$ (elimination from plasma) of a clinical dose in humans is 1.82 hours. The AUC (area under the curve), increases dose-proportionally. It has low protein binding with >95% noted as unbound. It is not metabolized. Excretion is rapid with >90% of excretion noted to be renal and minimal fecal excretion. There is no known accumulation after repeat dosing.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

In addition to two phase-3, one phase-2, and one pediatric study submitted in support of the proposed indication, the tables below list all studies provided by the applicant that are submitted to this NDA. These additional studies include 17 phase 3 studies (5 studies using 0.5 M gadobutrol, 12 studies using 1.0 M gadobutrol), 12 phase 2 studies, and 7 phase 1 studies. One of the phase 1 studies, a thorough QT/QT$_c$ study, was conducted using 1.0 M gadobutrol. In addition, two special population studies were

conducted, a phase 1 study in the elderly and a phase 3 study in renally impaired subjects, using 1.0 M gadobutrol. One phase 4 supportive study that was submitted was also performed with 1.0 M gadobutrol.

For purposes of consistency with tables presented in the NDA, the study drug, (gadobutrol), has the same designation as the "test product" used for the original clinical trials. SH L 562 BB is the 1.0 M solution currently approved in several countries. SH L 562 AA is the 0.5 M solution that was approved in Switzerland in 1998 but was never marketed.

In addition to a summary of study objectives, a brief statement of efficacy results is included for the four phase 3 studies that the applicant considers as supportive to the NDA indication, (95052, 94054, 309761, and 310864).

Table 2: Tables of Clinical Studies

Study phase Study no. Report no. Blinded reading Number of study centers Location(s)	Study period # Subjects enrolled (clinical indication studies only) # Subjects treated	Study design Type of control	Study and control drugs Dosage and regimen (route: Intravenous)	Study objectives
Study reports and related information of controlled clinical studies pertinent to the claimed indication				
Phase 3 310123 A47567 51 centers US, Europe, Australia, Japan, & S. America	6/08-4/09 402 390 (gadobutrol & comparator) / 391 (gadobutrol)	Randomized double blind, cross-over, comparison	SH L 562 BB (1.0 M); 0.1 mmol/kg Gadoteridol: 0.1 mmol/kg	To demonstrate superiority of the combined unenhanced and gadobutrol-enhanced MRI images compared to unenhanced MRI based on degree of contrast enhancement, assessment of border delineation, and internal morphology of lesions and non-

				inferiority based of lesion number. Secondary objectives to demonstrate non-inferiority of gadobutrol compared to gadoteridol at a dose of 0.1 mmol/kg for the 4 variables; to demonstrate improvement of gadobutrol-enhanced MRI to unenhanced MRI and non-inferiority to gadoteridol-enhanced MRI for exact match of MR diagnosis with the final clinical diagnosis, sensitivity and specificity for normal/abnormal brain tissue based on comparison of T1w contrast-enhanced and T1w unenhanced MR images, sensitivity and specificity for detection of malignant CNS lesions, and confidence in diagnosis; to compare gadobutrol to gadoteridol for T1w MRI image quality in a paired comparison, the number of contrast-enhanced lesions, and quantitative parameters based on signal intensity (SI) measurements
Phase 3 310124	12/07-12/08 343	Randomized open-label,	SH L 562 BB; 0.1 mmol/kg	To demonstrate superiority of the

A4757022 centers US, Asia, & S. America	343	comparison		combined unenhanced and gadobutrol-enhanced MRI images compared to unenhanced MRI based on degree of contrast enhancement, assessment of border delineation, and internal morphology of lesions and non-inferiority based on number of lesions detected. Secondary objectives included improvement for exact match of MR diagnosis compared to final clinical diagnosis, sensitivity and specificity for normal and abnormal brain tissue based on comparison of T1w contrast-enhanced and T1w unenhanced MR images, sensitivity and specificity for detection of malignant CNS lesions, and confidence in diagnosis.
Phase 2 308200 A40524 20 centers US, Colom-bia, Argen-tina, & Brazil	8/05-3/07 229(69-0.03 mmol/kg dose, 90-0.1 mmol/kg dose, 70-0.3 mmol/kg dose) 229 (225-gadobutrol,	Randomized double blind controlled, parallel group, dose-comparison	SH L 562 BB (1.0 M): 0.03, 0.1 or 0.3 mmol/kg Gadoversetamide (0.5M) 0.1 mmol/kg	To determine a safe and effective dose of gadobutrol 1.0 molar based on: 1) the raw number of lesions detected in precontrast and combined precontrast and postcontrast MRI, assessment of border delineation, degree of contrast enhancement,

	227-comparator)			internal morphology of lesions ; and to determine the maximum contrast to noise ration (CNR) between white and gray matter with gadobutrol perfusion MRI. Secondary objectives were to evaluate the proportion of all enhanced lesions detected and matched; to evaluate the proportion of all lesions detected and matched with gadobutrol MRI; to evaluate quantitative and qualitative parameters of perfusion MRI; to evaluate/describe the alteration of perfusion parameters in CNS lesions and in particular that this was associated with different tumor grades of malignancy and to determine the usefulness of these parameters for tumor grade; to evaluate the CNR of lesion/gray matter and lesion/white matter with gadobutrol perfusion MRI; to evaluate diagnosis and confidence in diagnosis.
PK study Phase	9/07-4/08 138 (48-	Open-label	SH L 562 BB (1.0 M): 0.1 mmol/kg	To evaluate the pharmacokinetics of

1/3 310788 A40794 14 centers Europe & Canada	age 2-6, 44- age 7-11, 48-age 12- 17) 138			gadobutrol in the pediatric (age 2-17 years) population, (to define a structural PK model for gadobutrol by using gadolinium plasma concentrations, to characterize the inter- individual variability in the derived PK parameters of gadobutrol in this population, and of appropriate, to evaluate possible covariates influencing the PK of gadobutrol in the pediatric population).
Healthy Subject PK and Initial Tolerability Study Reports				
Phase 1 310865 A 39759 1 center Japan	6/07-10/07 40 (rec'd at least one injection)	Randomized placebo- controlled, single-blind, dose escalation	SH L 562 BB (1.0 M): 0.1, 0.2, 0.3 0r 0.1 + 0.1 mmol/kg; Saline: same volume to SH L 562 BB; 30 minutes between injections	PK, tolerability, and safety parameter study
Phase 1 97113 BOOO 1 center Europe	10/98-2/99 48	Randomized double blind, randomized (only within a dosage level), independent group comparison	SH L BB (1.0 M): 0.3, 0.5, 0.75, 1.0, 1.25, or 1.5 mmol/kg; Saline: same volume to SH L 562 BB	Safety, tolerability, and PK of 0.1 M gadobutrol, dose ranging study, in healthy volunteers
Phase 1 307362 A 21381 1 center US	3/04-6/04 64	Randomized placebo- controlled, 5-period crossover, dose-	SH L 562 BB (1.0 M): 0.1, 0.3 and 0.5 mmol/kg; Saline: 0.5 mL/kg; Moxifloxacin: 400	To evaluate electrocardiographic effects of study drug at various doses especially a potential influence on cardiac

		comparison with a concurrent positive control, double blind for SH L 562 BB and placebo	mg infusion; 4-14 days between each injection	repolarization, primary variable for QT/QTc interval
Phase 1 93016 AS29 1 center Japan	10/92-11/92 32 (24, study drug; 8, saline)	Randomized placebo-controlled, double blind, dose escalation	SH L 562 A (0.5 M): 0.05, 0.1, 0.2, and 0.4 mmol/kg; Saline: same volume to SH L 562 A	Safety, PK, and metabolism of study drug
Phase 1 92001 9746 1 center Europe	3/92-6/92 55 (40, study drug; 15, saline)	Randomized placebo-controlled, double blind, dose escalation	SH L 562 A (0.5 M): 0.04, 0.1, 0.2, 0.3, and 0.4 mmol/kg; Saline: same volume to SH L 562 A	Tolerability and PK versus placebo
Intrinsic Factor PK Study Reports				
Phase 3 95062 B245 1 center Europe	10/96-2/98 32	Open label, randomized	SH L 562 BB (1.0 M): 0.1 or 0.3 mmol/kg	PK, safety, and dialysability in patients with renal failure (creatinine clearance <80 mL/min or on dialysis)
Phase 1 308183 A40982 1 center Europe	8/08-1/09 31 (all healthy volunteers-15, elderly; 16, non-elderly)	Single center, open-label, single dose, parallel group	SH L 562 BB (1.0 M): 0.1 mmol/kg	Safety and PK variables in the elderly popluation
Other Study Reports				
Phase 1				
Phase 1 92010 9748 1 center Europe	6/92-8/92 36 healthy volunteers (24, study drug; 12, saline)	Randomized placebo-controlled, double blind, dose escalation	SH L 562 B (1.0M): 0.3, 0.4, and 0.5 mmol/kg; Saline: same volume to SH L 562 B	Single dose tolerability study in healthy young males; 2 parallel arms with study drug at 3 dose levels and placebo for objective of single dose

				tolerability
Phase 1 96063 B534 2 centers Europe	12/96-3/97 20 healthy volunteers	Open-label, intra- individual comparison	SH L 562 AA (0.5 M) and SH L 562 BB (1.0 M): 0.05, 0.1 or 0.2 mmol/kg (multiple injections); 2-24 hours between doses	Safety and efficacy of MR Angiography using variable dosages, drug concentrations, and injection speeds
Phase 2				
Phase 2 98098 B291 Blinded Read 1 center Europe	10/98-11-98 45 rec'd at least one dose of study drug	Intra-individually controlled, randomized, crossover conc'n	SH L 562 AA (0.5 M) and SH L 562 BB (1.0 M): 0.3 mmol/kg of each concentration; 20 hours to 2 weeks between doses	Using healthy volunteers, to assess technical efficacy of 0.5 and 1.0 M injections in brain perfusion dosed at 0.3 mmol/kg
Phase 2 92095 AC86 Blinded Read (AC86R) 3 centers Europe	1/93-9/93 64	Open-label	SH L 562 A (0.5 M): 0.3 mmol/kg, given as 0.1 dose followed by 0.2 dose 10 minutes later	Primary objective-to assess lesion number; Secondary objectives-to qualitatively evaluation brain lesion (patients with primary cancers outside the CNS)
Phase 2 92096 AC98 3 centers Europe	2/93-10/93 103	Open-label, randomized dose- comparison	SH L 562 A (0.5 M) 0.1, 0.2, or 0.3 mmol/kg	To evaluate safety, tolerance, and efficacy in patients with recurrent herniated disc lesion, primary and secondary bone tumors, or breast lesions; primary evaluation for quantitative lesion enhancement, secondary evaluation for qualitative lesion delineation and visualization parameters
Phase 2 92097	1/93-10/93 47 (2	Open-label	SH L 562 A (0.5 M): 0.1 + 0.1 +	Added dose efficacy in patients with known

AC42 4 centers Europe	patients did not receive protocol dosing but received at least one dose of study drug)		0.1 mmol/kg (total 0.3 mmol/kg)	brain tumor or glioma, evaluation for quantitative and qualitative factors
Phase 2 93017 AS30 2 centers Japan	6/93-9/93 18	Open-label	SH L 562 A (0.5M): 0.1 mmol/kg	Evaluation of brain and spinal cord enhancement in hospitalized patients with known CNS lesions
Phase 2 93018 AS31 4 centers Japan	6/93-10/93 38	Open-label	SH L 562 A (0.5M): 0.1 mmol/kg	Efficacy for lesion detection and delineation (body and extremity enhancement) in hospitalized patients with tumor in the liver, pelvis, or bone and soft tissue
Phase 2 94061 A169 2 centers Europe	1/95-11/95 89	Randomized double blind, dose comparison	SH L 562 A (0.5M): 0.1, 0.2, 0.3, 0.4, or 0.5 mmol/kg	Brain perfusion imaging in patients with unilateral carotid stenosis or unilateral cerebral infarcts, primary objective to evaluate signal intensity, secondary objective to evaluate qualitative parameters
Phase 2 94368 B315 Blinded Read 14 centers Japan	5/94-3/95 114 (58, study drug; 56, reference drug)	Randomized double-blind	SH L 562 A (0.5 M): 0.1 mmol/kg; Gadopentetate dimeglumine (0.5M): 0.1 mmol/kg	Overall objective, to demonstrate improvement by enhancement; primary objective, to compare signal intensity ratios; secondary objective, to demonstrate improvement in diagnostic ability
Phase 2	6/94-3/95	Open-label	SH L 562 AA	Evaluation for the

94369 B314 Blinded read 9 centers Japan	62		(0.5M): Within group comparison with dose escalation (0.1 + 0.1 + 0.1 mmol/kg, total: 0.3 mmol/kg)	numbers of lesions detected in hospitalized patients with known CNS lesions
Phase 2 94383 B313 1 center Japan	11/94-6/95 13	Randomized crossover, conc'n comparison	SH L 562 AA (0.5M) and SH L 562 BB (1.0M), both dosed at .15 mmol/kg, ≥1 day between doses	To evaluate white and gray matter and brain lesions lesions based on the ratio of decreases in peak signal, contrast enhancement effect, and improvement in diagnosis in patients with brain processes such as prior infarct or surgery
Phase 2 97035 B204 Blinded read 2-99 12 centers Europe	2/98-1/99 241	Randomized double blind, dose comparison	SH L 562 BB (1.0M): 0.05, 0.15, or 0.25 mmol/kg	Primary objective, 3 dose effect on renal or iliac arteries compared with DSA for stenosis or pathology; secondary objectives to study signal intensity, visibility, and confidence in recommendation for therapy
Phase 2 30551 A22498 Blinded read 14 centers Europe	3/04-5/06 226	Randomized double-blind, inter-individual parallel group comparison	SH L 562 BB (1.0M): 0.01, 0.025 or 0.05, or or 0.1 mmol/kg: two injections (total: 0.02, 0.05 or 0.1, or 0.2 mmol/kg, one injection after both stress and rest, separated by 10-15 minutes)	Primary objective, first pass study to evaluate 4 increasing doses of gadobutrol for the detection of myocardial perfusion defects at rest and after stress compared to SPECT; secondary, to evaluate qualitative and semi quantitative variables
Phase 3				
Phase	8/07-8-08	Randomized	SH L 562 BB (1.0	Variable doses to

2/3 310864 A41119 Blinded read 20 centers Japan	164	single-blind, controlled, crossover, intra-individual comparison	M): 0.1 + 0.1 mmol/kg (Total: 0.2 mmol/kg) Gadoteridol (0.5 M): 0.1 + 0.1 mmol/kg (Total: 0.2 mmol/kg 13-15 minutes between doses)	study number of lesions and contrast enhancement effect, demonstrating non-inferiority to comparator; demonstrated non-inferiority of gadobutrol to gadoteridol for number of lesions
Phase 3 94052 A179 9 centers Europe	10/94-10/95 305 (155, Gadobutrol; 150 comparator)	Randomized double blind, comparative	SH L 562 AA (0.5 M): 0.1 mmol/kg Gadodiamide 0.1 mmol/kg	To compare efficacy of Gadobutrol with Gadodiaimide in patients with evidence of brain lesions, assessing visualization post contrast comparing pre contrast to post contrast studies; demonstrated improved visualization and characterization of brain lesions post contrast with superiority to non contrast studies
Phase 3 94054 A168 13 centers Europe	9/94-8/95 296	Open-label, non-randomized, dose-comparative intra-individual controlled	SH L 562 BB (1.0 M); 0.1 and 0.2 mmol/kg (total (0.3 mmol/kg, 10 minutes between doses)	Efficacy of cumulative doses as evaluated by signal intensity and lesion visualization parameters, in patients with evidence of brain or spine lesions; demonstrated improved diagnostic confidence after administration of contrast with further improvement in some cases after repeat dosing
Phase 3	11/95-12/98	Open-label	SH L 562 BB (1.0	Determination that

94055 A02140 Blinded read 7 centers Europe	182		M); 0.1 mmol/kg	pre + post contrast images are superior to pre images alone for lesion character, patient management, and diagnostic confidence-studied in patients with evidence of suspected focal liver lesion, tumor lesions of other soft tissues and organs, patients with COPD, or patients with disease of the thoracic aorta
Phase 3 95064 AK76 1 center Europe	1/96-6/96 44	Open-label, non-randomized	SH L 562 BB (1.0 M); 0.3 mmol/kg	To quantify perfusion and evaluate the size of defects by study of the first pass effect of gadobutrol on the brain in patients with unilateral carotid artery stenosis and/or unilateral cerebral infarct by comparing regional cerebral blood to SPECT
Phase 3 95359 B311 Blinded read 16 centers Japan	10/95-9/96 175 (86, gadobutrol; 89, reference drug)	Double blind, parallel comparison	SH L 562 AA (0.5M): 0.1 mmol/kg; Gadopentetate dimeglumine (0.5M): 0.1 mmol/kg	Improvement in diagnostic ability by the contrast enhancement effect in patients with disorders of the liver or pelvis
Phase 3 95361 B312 Blinded read 20 centers Japan	9/95-9-96 195	Double-blind, parallel comparison	SH L 562 AA (0.5M): 0.1 mmol/kg; Gadopentetate dimeglumine (0.5M): 0.1 mmol/kg	Improvement in diagnostic ability by contrast enhancement effect in patients with CNS disease

Phase 3 95362 B309 17 centers Japan	1/96-3/97 134	Open-label	SH L 562 AA (0.5M): 0.5 mmol/kg	To evaluate safety, efficacy, and usefulness of gadobutrol by enhancement effect in patients with diseases of the head and neck, heart, chest, bone/soft tissue or spine
Phase 3 95363 B308 Blinded read 13 centers Japan	1/96-3/97 100	Open-label	SH L 562 AA (0.5M) 0.1 + 0.2 mmol/kg (total 0 mmol/kg)	Efficacy comparison of gadobutrol doses (0.1 and 0.3 mmol/kg) using pre and post contrast images to evaluate the number of lesions in patients with known or suspected brain metastases
Phase 3 95364 B310 5 centers Japan	1/96-3/97 39 (20, 0.05 mmol/kg; 19, 0.1 mmol/kg)	Open-label	SH L 562 AA (0.5M) 0.05 or 0.1 mmol/kg	Improvement in diagnosis by contrast enhancement in patient with known or suspected renal disorder
Phase 3 97099 A04519 Blinded read 10 centers Europe	1/00-1/01 179	Open-label. comparative	SH L 562 BB (1.0M): 7.5 mL for patients <75 kg bw; 10 mL for patients≥75 kg bw	Segmental evaluation For efficacy agreement between contrast enhanced MRA and DSA in patients with suspected or known disease of body arteries
Phase 3 302722, 99011 A02885 Blinded read;10 centers Europe	2/00-10/00 203	Open-label comparative	SH L 562 BB (1.0M): 15 mL for patients <75 kg bw; 20 mL for patients≥75 kg bw	Rate of agreement between MRA and DSA on a segmental basis, with sensitivity/specificity, accuracy, and Confidence in diagnosis for MRA of the pelvic and peripheral arteries
Phase 3	9/00-2/01	Open-label	SH L 562 BB	Quality (visibility) of

304300 A04542 4 centers Europe	53		(1.0M): 7.5 or 15 mL for patients <75 kg bw; 10 or 20 mL for patients≥75 kg bw	contrast-enhanced segments and confidence in diagnosis in MRA studies of body and peripheral arteries in patients with suspected or known arterial vascular disease
Phase 3 304561 A18088 Blinded read 25 cents. Europe	5/02-5/03 466 (233 each treatment)	Single-blind, randomized, inter-individually controlled	SH L 562 BB (1.0M): 0.1 mmol/kg; Gadopentetate dimeglumine (0.5M): 0.1 mmol/kg	Primary, to demonstrate non-inferiority of gadobutrol to comparator regarding classification of benign and malignant lesions,also, for diagnostic efficacy for delineating renal lesions using CT as the standard of truth (with sensitivity, specificity, accuracy)
Phase 3 304562 A13389 Blinded read 25 cents. Europe	7/01-8/02 572 (529 in FAS rec'd one injection of either drug)	Double blind, randomized, inter-individually controlled	SH L 562 BB (1.0M): 0.1 mmol/kg; Gadopentetate dimeglumine (0.5M): 0.1 mmol/kg	To show non-inferiority of gadobutrol to comparator regarding the diagnostic accuracy in lesion classification in contrast-enhanced MRI, to demonstrate the efficacy of gadobutrol for liver MRI and in patients with liver disease by comparison of pre contrast to pre + post contrast images
Phase 3 309761 A40215 5 centers China	9/06-4/07 146 (71, Study drug; 25, comparator)	Single-blind, randomized parallel group comparison	SH L 562 BB (1.0M): 0.1 mmol/kg; Gadopentetate dimeglumine (0.5M): 0.1	To evaluate efficacy of Gadobutrol versus comparator for lesions Of the CNS using primary endpoint as contrast to noise ratio

			mmol/kg	and secondary endpoint as lesion character and confidence in diagnosis; demonstrated non-inferiority of gadobutrol for the primary contrast-to-noise variable and demonstrated similar results for secondary variables of image characteristics
Phase 3 309762 A40727 Blinded read 3 centers China	10/06-10/07 83 (41, study drug followed by comparator; 42, comparator followed by study drug)	Single-blind (keep patients blind), intra-individual, crossover, comparative	SH L 562 BB (1.0M): 0.2 mmol/kg (up to 0.3 mmol/kg); Gadopentetate dimeglumine (0.5M): 0.2 mmol/kg (up to 0.3 mmol/kg)	Efficacy comparison For detection of Vascular lesions using variable drug doses for MRA study, primary objective, to evaluate the number of vessel segments seen of diagnostic quality with secondary objective of diagnostic confidence and comparison
Phase 4				
Phase 4 302600 A12063 5 centers Europe	8/00-9/02 49	Open-label	SH L 562 BB (1.0M): 2 injections (≥3 hours apart) of 12 or 15 mL depending on body weight (approx. 0.2 mmol /kg)	To evaluate the course of stroke by comparing ischemic lesions from several time points and evaluate infarct size 3 months post infarct then compare with neurologic function tests

5.2 Review Strategy

For evaluation of efficacy, this reviewer concentrated on studies termed by the applicant as the four "covered clinical studies":

- **Report A47567 / Phase 3 Study 310123:** "A multicenter, randomized, double-blind, crossover, phase 3 study to determine the safety and efficacy of

gadobutrol 1.0 molar (Gadovist®) in patients referred for contrast-enhanced MRI of the central nervous system (CNS)"

- **Report A47570 / Phase 3 Study 310124:** " A multicenter, open-label, phase 3 study to determine the safety and efficacy of gadobutrol 1.0 molar (Gadovist®) in patients referred for contrast-enhanced MRI of the central nervous system (CNS)"
- **Report A40524 / Phase 2 Study 308200:** " Multi-center, double-blind, randomized, parallel group, dose comparison study with corresponding blinded image evaluation following a single intravenous injection of three different doses of gadobutrol 1.0 molar (Gadovist®) in patients with known or highly suspected focal blood brain barrier disturbances and/or abnormality of the central nervous system"
- **Report 40794 / Pediatric Study 310788:** "Open-label multi-center study of magnetic resonance imaging (MRI) with 0.1 mmol/kg body weight Gadovist (1.0 M) to assess pharmacokinetics, safety and tolerability in children"

The focus of the efficacy review was evaluation of the primary efficacy endpoint to demonstrate superiority of the combined unenhanced and Gadovist enhanced MRI over unenhanced MRI using lesion characteristics (assessment of border delineation, degree of contrast enhancement, and internal morphology of the lesions) and non-inferiority for total number of lesions detected.

In addition, the applicant noted certain secondary variables of the phase 3 studies to be "important." These variables, (sensitivity, specificity, and accuracy for exact match of MR diagnoses and normal/abnormal brain tissue on T1w images) were also considered in detail by this reviewer.

For evaluation of safety, this reviewer included all the information from the 43 clinical trials (313 subjects treated with gadobutrol in phase 1, 68 subjects treated with placebo, 4549 subject treatments with gadobutrol in phases 2-4, and 996 subjects treated in crossover studies).

5.2 Discussion of Individual Studies/Clinical Trials

The main referral lesion types for the CNS protocols were as follows:

- Study 310123: "other" (36.3% of subjects), multiple sclerosis (15.9% of subjects), metastasis (14.9% of subjects), and meningioma (10.9% of subjects)
- Study 310124: "other" (33.8% of subjects), meningioma (14.0% of subjects), multiple sclerosis (9.9% of subjects), pituitary adenoma (6.7% of subjects), and metastasis (6.1% of subjects)

- Study 308200: primary brain tumor, metastasis, multiple sclerosis, and meningeal disease
- Study 310788: Pediatric patients scheduled to undergo Gd-enhanced MRI of brain, spine, liver and/or kidneys or Gd-enhanced MRA; study performed for PK determination (single field-of-view study)

Reviewer's Comment: This reviewer noted that approximately 1/3 of subject referrals, (36.3% for study 310123 and 33.8% for study 310124), were for the "other" diagnosis and that the applicant stated that subjects with "other" or "non assessable" diagnoses by the truth committee were excluded from the secondary efficacy analyses of exact match diagnosis and match for malignant diagnoses. A request was made to the applicant to list the exact diagnoses considered in the "other" category. In addition, for the phase 2 study 308200, a percentage breakdown of referral diagnoses was requested.

The applicant provided a complete listing of all referral diagnoses and all truth committee diagnoses for subjects in the 310123 and 310124 studies referred with the "other" diagnosis. The listings included referrals for a "non assessable" diagnosis.

This reviewer noted the following relative to study 310123:

- There were 146 subjects with referral diagnoses of "other."
- There were 2 subjects with a non-assessable diagnosis in the "other" category.
- Many of the "other" referral diagnoses were symptom based such as headache, back pain, epilepsy, weakness, and trauma. A few were for a specific disease such as amyotrophic lateral sclerosis.
- The overwhelming majority of diagnoses were for one subject only.
- The truth panel diagnoses listed no lesion for 17 subjects and non-assessable for 22 subjects. There was no truth panel diagnosis for one subject with referral of trigeminal neuralgia and for one subject referral diagnosis of subacute infarction.

The following comments are relative to study 310124:

- There were 116 subjects with a referral diagnosis of "other."
- There were 21 subjects with non-assessable as the main referral diagnosis.
- The referral diagnoses in the "other" category were similar to the 310123 study, many symptom based.
- The overwhelming majority of diagnoses were for one subject only.
- The truth panel diagnoses were no lesion for 42 subjects and non-assessable for 25 subjects. One subject with a referral diagnosis of "other" received the same diagnosis by the truth panel.

In general, many of the referral diagnoses were similar although not identical to the truth panel diagnoses, for example one subject with a referral diagnosis of SLE received a truth panel diagnosis of vasculitis.

For analyses of the secondary efficacy endpoints of malignant lesions and exact match diagnoses, subjects who had a standard of truth diagnosis of other or not-assessable were excluded. For both the 310123 and 310124 studies, this exclusion was for approximately 20% of subjects.

Reviewer's conclusion: The "other" diagnoses are acceptable and valid for inclusion into the studies. It is acceptable to exclude subjects with truth panel diagnoses of "other" or no- assessable from the secondary endpoint analyses.

The applicant also provided further clarification of the "other" referral diagnosis for the phase 2 dose selection study 308200. There was no truth panel for this study however the applicant organized the study data according to dose group into benign, malignant, and non-assessable categories, main referral and additional diagnosis listings, and a listing of all subjects referred for the "other" diagnosis and the actual term assigned to this diagnosis

The "other" diagnoses for this study consisted of underlying diseases such as cysticercosis or metastatic disease from unknown primary, medical procedures such as previous radiation therapy, and less common tumors such as medulloblastoma. 45 of the 229 subjects in the safety analysis set were included in the "other" diagnosis listing.

According to the table provided by the applicant, the main referral diagnoses by percentage were as follows: multiple sclerosis, (19.2%), meningioma, (16.2%), metastatic disease, (6.1%), and glial tumor, (low grade 7.0%, high grade 9.6%, and tumor no grade noted 4.4%). 5.7% of referrals were for a non-assessable diagnosis.

Reviewer's conclusion: The referral diagnoses provided in the "other" listing are reasonable to require an MRI study of the CNS. The "other" category for referral diagnoses is acceptable considering that majority of diagnoses are for a single subject. The percentage breakdown of main referral diagnoses is acceptable for the study.

The pivotal phase 3 clinical trials were designed and performed to demonstrate superiority of the combined unenhanced and Gadovist enhanced MRI over unenhanced MRI using lesion characteristics and non-inferiority for total number of lesions detected The efficacy endpoints were based on four variables: degree of contrast enhancement, border delineation, internal morphology, and total number of lesions visualized. During the drug development process, the Division requested a means to assess the clinical utility of the studies. After discussion of possible means to achieve this, the applicant proposed an acceptable standard of truth to consist of all available patient-related information from the time of referral for contrast MRI up to 3 months after the last study

related MRI to be centralized by country/region and then reviewed by 2 experienced physicians in the neuroscience field who were not affiliated with the study, who would reach a final diagnosis by consensus. This would include all pertinent information regarding the patient's referral for diagnosis, medical history summary, clinical laboratory values, histopathology, patient symptomatology, therapy, and imaging results from 3 months prior to study enrollment to 3 months after enrollment (no study related results).   Both studies had similar design elements of subject referral, use of unenhanced and contrast-enhanced images, and MRI sequences. The studies differed in design (randomized, double blind crossover versus open label) and eligibility (normal renal function for the crossover study, moderate renal impairment permitted for the open label study). Both had similar endpoints with the crossover study having an additional secondary endpoint of non-inferiority to the comparator. A prospectively written blinded image evaluation by 3 independent readers was planned in order to facilitate an independent evaluation and a blinded read manual was submitted. Quality control and quality assurance of the MR images and conduct of the blinded readings was done at the image core laboratory, DIGIMA, in Berlin, Germany.

More detailed background on the "covered studies" for the CNS indication is provided in the tables below.

Table 3: Phase 3 Pivotal Studies: Study Number 310123/A47567Study Number 310124/A47570

Parameter	Study 310123	Study 310124
Protocol date/amendments	Original: 3-6-08 (SPA) Amendment 1: 7-24-08 (administrative, corrections, and clarifications)	Original: 10-9-07 Amendment 1: 9-10-08 (revisions in response to comments after SPA review, administrative, and clarifications)
Study dates	6/08-4/09	12/07-12/08
Design and schedule	Phase 3, multicenter, randomized, double-blind, crossover study; 3 blinded readers Four MRIs for each patient: Two Unenhanced MR Image Sets T1W, T2W, FLAIR, with both sets of images sent to the core lab and with an independent external expert reviewing and	Phase 3, multicenter, open-label study; 3 blinded reader Two image sets for each patient: unenhanced MRI and enhanced MRI with gadubutrol (unenhanced MRI consisting of steady-state sequences [T1-weighted, T2-weighted, and FLAIR/STIR], and gadobutrol-enhanced MRI consisting of steady-state sequences T1-weighted)

	• selecting the highest quality images for each of the three sequences • Gadovist® Enhanced MR Image Set consisting of a single steady-state sequence, (T1W) • Gadoteridol Enhanced MR Image Set consisting of a single steady-state sequence, (T1W)	
Inclusion criteria	Referral for contrast-enhanced MRI of the CNS based on clinical symptoms or results from a previous imaging procedure; glomerular filtration rate (GFR) value≥60 mL/min/1.73m^2 derived from a serum creatinine result within 2 weeks prior to study enrollment	Referral for contrast-enhanced MRI of the CNS based on clinical symptoms or results from a previous imaging procedure
Exclusion criteria	Unstable clinical presentation and acute renal insufficiency; patients likely to require a biopsy or any interventional therapeutic procedure from the first study MRI up to 72 hours after the second study MRI; history of severe allergic or anaphylactic reaction	Unstable clinical presentation and acute renal insufficiency; patients likely to require a biopsy or any interventional therapeutic procedure from the first study MRI up to 72 hours after the second study MRI; history of severe allergic or anaphylactic reaction; GFR < 30 mL/min/1.73m^2
Test product dose	Gadobutrol 1.0 molar, 0.1 mmol/kg to be administered by IV single dose at 2mL/sec followed by 20 mL 0.9% saline flush	Gadobutrol 1.0 molar, 0.1 mmol/kg to be administered by IV single dose at 2mL/sec followed by 20 mL 0.9% saline flush
Reference therapy	Prohance® (gadoteridol) 0.5 molar, 0.1 mmol/kg to be administered by IV single dose at 2mL/sec followed by 20 mL 0.9% saline flush	None
Primary objectives	To demonstrate superiority of the combined unenhanced and Gadovist enhanced MRI over	To demonstrate superiority of the combined unenhanced and Gadovist enhanced MRI over

	unenhanced MRI using lesion characteristics and non-inferiority for total number of lesions detected	unenhanced MRI using lesion characteristics and non-inferiority for total number of lesions detected
Secondary objectives; truth standard	To demonstrate non-inferiority of gadobutrol to gadoteridol for the 3 lesion characteristics and for number of lesions; to demonstrate improvement of gadobutrol-enhanced MRI to unenhanced MRI and non-inferiority to gadoteridol-enhanced MRI for final clinical diagnosis as determined by an independent truth committee following evaluation of findings from referral through a 3-month follow-up period, for sensitivity and specificity for normal/abnormal brain tissue based on comparison of the T1-weighted (T1w) contrast-enhanced and T1w unenhanced MR images, and for sensitivity and specificity for the detection of malignant CNS lesions; confidence in diagnosis also assessed	To demonstrate improvement of gadobutrol-enhanced MRI compared for: • Exact match of the MR diagnoses with the final clinical diagnosis • Sensitivity and specificity for normal/abnormal brain tissue based on the comparison of the T1-weighted (T1w) contrast-enhanced and T1w unenhanced MR images • Sensitivity and specificity for the detection of malignant CNS lesions and • Confidence in diagnosis An independent truth committee for evaluation of findings from referral through a 3-month follow-up period
Efficacy variables	Border delineation (4 point scale) Degree of contrast enhancement (4 point scale) Internal morphology of lesions (3 point scale) Total number of lesions detected	Border delineation (4 point scale) Degree of contrast enhancement (4 point scale) Internal morphology of lesions (3 point scale) Total number of lesions detected
Safety evaluation and monitoring	Baseline study period 1 within 24 hours prior to administration of the contrast agent will include history and physical and signing the informed consent; within 1 hour prior to administration of the contrast agent, the patient will	Vital signs, physical examinations to include a detailed examination of the injection site and upper extremities, clinical laboratory parameters, and adverse events (AEs), evaluations to be

have an IV line placed, urine pregnancy test, collection of blood samples for hematology and clinical chemistry, and collection for urinalysis. Immediately prior to MRI, vital signs (blood pressure and heart rate) and AE monitoring to begin with the administration of contrast agent; vital signs again be obtained prior to the patient's removal from the magnet and at 45 minutes after injection of contrast agent 24 hours follow-up physical exam, complete vital signs, and clinical laboratory parameters. Baseline study period 2 for the administration of the second contrast agent must be separated from injection 1 by at least 24 hours and no more than 15 days to include a complete physical examination and vital signs with repeat pregnancy test, placement of an IV line, and blood and urine collections within 1 hour prior to administration of contrast material; patient monitoring during study period 2 similar to study period 1; post-injection follow-up is similar to study period 1 also except that patients also return for a 72-hour follow- up that includes a follow-up creatinine evaluation and AE monitoring When the patient receives the period 2 unenhanced scan, the investigator will check for	performed at baseline up to 72 hours after injection.

	residual contrast agent from study 1 and if present, postpone study by at least 6 hours; post-injection follow-up is similar to study period 1 also except that after this study, patients must also return for a 72-hour follow-up that includes a follow-up creatinine evaluation and AE monitoring.	
Outcome measures/data analysis	Blinded reading consisting of the following parts: • Part I Lesion visualization parameters (3 sessions separated by at least 2 weeks), to include the total number of lesions detected, border delineation, degree of contrast enhancement, internal morphology, diagnosis, and confidence in diagnosis • Part II Normal/abnormal diagnosis for each patient (3 sessions separated by at least 2 weeks) • Part III Image quality (1 session) • Part IV SI measurement: Percentage of enhancement of the lesion and Contrast/Noise (CNR) of the lesion • Part V Number of contrast enhanced lesions and adjudication Investigators perform similar image analyses	Blinded image evaluation performed in a core laboratory by independent experienced radiologists (3) trained in the study design, to consist of 2 parts, each with 2 reading sessions: • Part I Lesion visualization parameters • Part II Normal/abnormal diagnosis
Blinded read	Prospectively defined blinded reading image evaluations and centralized defined in the original protocol; included image quality	Prospectively defined blinded reading image evaluations defined in the original protocol

	assurance, reader selection and training, and reader training; minimum of two week separation between reading sessions to minimize recall bias	
Statistical analysis plan	9/24/09; included in the SPA	10/9/07; included in the original protocol
Primary statistical hypotheses	3 efficacy variables tested for superiority of gadobutrol-enhanced MRI versus unenhanced MRI using paired t-tests, null and alternative hypotheses as follows: H_0: combined unenhanced and gadobutrol mean = unenhanced MRI mean versus H_1: combined unenhanced and gadobutrol mean ≠ unenhanced MRI mean For noninferiority of the number of lesions as follows: H_0: combined unenhanced and gadobutrol mean-unenhanced mean < -0.35 versus H_1: combined unenhanced and gadobutrol mean – unenhanced mean ≥ -0.35	3 efficacy variables tested for superiority of gadobutrol-enhanced MRI versus unenhanced MRI using paired t-tests, null and alternative hypotheses as follows: H_0: combined unenhanced and gadobutrol mean = unenhanced MRI mean versus H_1: combined unenhanced and gadobutrol mean ≠ unenhanced MRI mean For noninferiority of the number of lesions as follows: H_0: combined unenhanced and gadobutrol mean-unenhanced mean < -0.35 versus H_1: combined unenhanced and gadobutrol mean – unenhanced mean ≥ -0.35
Handling of missing data	No imputations for missing data from early termination, missed evaluations, or other; if no scores for normal structures, lesion score mean was used; if no scores for lesions, normal score means were used as the overall mean; images uninterpretable for diagnostic purposes considered nonassessable considered incorrect if a final diagnosis available or excluded from analysis if no standard of truth available	No imputations for missing data from early termination, missed evaluations, or other; if no scores for normal structures, lesion score mean was used; if no scores for lesions, normal score means were used as the overall mean; images uninterpretable for diagnostic purposes considered nonassessable considered incorrect if a final diagnosis available or excluded from analysis if no standard of truth available
Analysis sets	Safety analysis-402 subjects, 399 received gadobutrol, 393	Safety analysis-343 subjects Efficacy analysis (FAS/ITT)*-

received gadoteridol, 390 received both drugs Efficacy analysis (FAS/ITT)*-336 subjects Efficacy analysis (PPS)**-316 subjects	321 subjects Efficacy analysis (PPS)**-314 subjects

Table 4: Phase 2 "Covered" Clinical Study; Study Number 308200/A40524

Parameter	
Protocol date/amendments	3-10-05; amendment 1, 2-21-06, changes referable to patients with brain tumors, additional exclusion criteria, and administrative changes; amendment 2, 2-6-07, administrative changes and additional of increased population with brain tumors; amendment 3, redefinition of CNR 7-3-07
Study dates	8/05-3-07
Design and schedule	Multi-center, double-blind, randomized, controlled, parallel group study with blinded image evaluation following a single intravenous injection of gadobutrol 1.0 molar (Gadovist®); three MRI exams for each subject: unenhanced MRI, gadobutrol-enhanced MRI (perfusion and steady state images), and comparator-enhanced MRI (steady state MRI only); independent radiologist (lesion tracker) matched lesions throughout the different imaging sequences
Inclusion criteria	Subjects with known or highly suspected focal blood brain barrier disturbances and/or abnormality of the central nervous system
Exclusion criteria	Clinically unstable, treated with chemotherapy or radiotherapy for CNS lesions either pre study or likely to be during the course of the study, scheduled to undergo procedure or treatment between the comparator and gadobutrol study that may alter interpretation of findings, history of severe allergic or anaphylactoid reaction
Test product dose	Gadobutrol 1.0 molar, 0.03, 0.1, or 0.3 mmol/kg BW injected IV at a rate of 5 mL/sec followed by a 20 mL 0.9% saline solution flush at the same rate
Reference therapy	OptiMARK (gadoversetaminde) 0.1 mmol/kg injected IV at a rate of 2mL/sec followed by 20 mL 0.9% saline flush at the same rate
Primary objective	To determine a safe and effective dose of gadobutrol 1.0 molar based on: 1) the raw number of lesions detected in precontrast and combined precontrast and postcontrast MRI, assessment of border delineation, degree of contrast enhancement, and internal morphology of lesions ; and 2) the maximum contrast to noise ration (CNR) between white and gray matter with gadobutrol

	perfusion MRI.
Secondary objectives/truth standard	Additional objectives as follows: • To evaluate the proportion of all enhanced lesions detected and matched • To evaluate the proportion of all lesions detected and matched with gadobutrol MRI • To evaluate quantitative and qualitative parameters of perfusion MRI (uncorrected/corrected cerebral blood volume [CBV], cerebral blood flow [CBF]. Time to peak [TTP]. Mean transit time [MTT], permeability factor [PF] • To evaluate/describe the alteration of perfusion parameters in CNS lesions and in particular that this was associated with different tumor grades of malignancy and to determine the usefulness of these parameters for evaluation of tumor grades • To evaluate the CNR of lesion/gray matter and lesion/white matter with gadobutrol perfusion MRI • To evaluate diagnosis and confidence in diagnosis Biopsy with tumor grade whenever possible with patient results to include any histopathology recorded for up to 30 days post study
Efficacy variables	Four primary efficacy variables of raw number of lesions detected in precontrast and combined postcontrast and postcontrast MRI, lesion border delineation (score 1-4), degree of contrast enhancement (score 1-4), and internal morphology of lesions (score 1-3) computed using a composite categorical visualization score (CVS)
Safety evaluation and monitoring	Vital signs, oxygen saturation, 12-lead electrocardiograms, cardiac rhythm, physical examination, clinical laboratory parameters, and adverse events monitoring
Outcome measures/data analysis	3 doses of gadobutrol, thus analysis was on the basis of paired lower-higher dose with the difference in mean score (DCVS) was constructed using t-distribution and 95% confidence interval
Blinded read	2/07-8/07 performed by 3 independent radiologists, pre-specified method in the original protocol
Statistical analysis plan	Contained in original protocol
Primary statistical hypothesis	For the categorical visualization score, the null hypothesis for either pair of consecutive doses is H_0: $\mu1 = \mu2 = p$ and the alternate hypothesis is H_1: $\mu1 \neq \mu2$, where p1 and p2 are the population means for Gadovist® lower dose imaging and higher dose imaging respectively

Handling of missing data	Plan additional subject enrollment to offset subjects that will not complete the study
Analysis sets	Safety-229 Efficacy (FAS/ITT)*-206 subjects Efficacy (PPS)**-173 subjects

Table 5: Pediatric PK "Covered" Clinical Study; Study Number 310788/A47435

Parameter	
Protocol date	9/23/08
Study date	9/07-4/08
Design and schedule	Phase 1/3 open-label, phase 1/3 PK study in children ages 2-17 years
Inclusion and exclusion criteria	Pediatric patients scheduled to undergo Gd-enhanced MRI of brain, spine, liver and/or kidneys, or Gd-enhanced MRA (single field of view)
Test product dose	0.1 mmol/kg
Objectives	To evaluate the pharmacokinetics of gadobutrol in the pediatric population with aims as follows: • To define a structural PK model for gadobutrol by using gadolinium plasma concentrations • To characterize the inter-individual variability in the derived PK parameters of gadobutrol in this population, and • If appropriate, to evaluate possible covariates influencing the PK of gadobutrol in the pediatric population)
Efficacy	4 blood samples obtained (one pre and 3 post injection) to estimate PK parameters such as clearance, area under the concentration versus time curve, and volume of distribution at steady state; results calculated for various covariates such as body weight and estimated glomerular filtration rate
PK analysis	Specified in the protocol
Analysis	Safety-138 subjects Efficacy (FAS/ITT)*-138 subjects Efficacy (PPS)**-135 subjects

*: FAS (Full Analysis Set)/ITT (Intent to Treat):   Analyses of efficacy data performed using data from all subjects on whom images and entries on case report forms were available for unenhanced and combined unenhanced plus contrast-enhanced MRI

**: PPS (Per Protocol Set): Analyses of efficacy data performed using data from those subjects from the FAS who also fulfilled all major provisions of the protocol

6 Review of Efficacy

Efficacy Summary

Two phase 3 clinical studies, a phase 2 dose ranging study, and a pediatric study were performed to support a CNS indication for Gadovist and indentified by the applicane as the "covered" studies:

- Study 310123 was a two period crossover phase 3 study with Gadobutrol and Prohance, (336 subjects in Full Analysis Set [FAS])
- Study 310124 was an identical study as a single arm Gadobutrol study, (321 subjects in FAS).
- Study 308200 was a phase 2 two period cross-over study with Gadobutrol and Optimark, (68 subjects in FAS).
- Study 310788 was a single arm Gadobutrol Pediatric PK study, (138 subjects ages 2-17 in FAS).

Three of the "covered" studies in adults (310123, 310124 and 308200) were termed by the applicant as "US IND studies". The applicant also identified four additional studies for the proposed indication, termed as "supportive", which were selected on the basis of the same body region as used in the three US IND studies (MRI of the CNS) and reasonable sample size.   The applicant noted that all four of these supportive studies demonstrated that gadobutrol-enhanced images were superior to unenhanced images with regard to clinically relevant imaging parameters.   Supportive studies included three phase 3 studies and a phase 2/3 study as follows:

- Study 94052 performed with 0.5 M Gadobutrol and Omniscan, a parallel arm study performed to assess visualization of brain lesions comparing lesion number and characteristics on pre contrast images to post contrast images, (153 subjects in FAS)
- Study 94054 performed with 1.0 M Gadobutrol, an open-label study using variable doses of Gadobutrol to study signal intensity and lesion visualization parameters of CNS lesions (291 subjects in FAS)
- Study 309761, a parallel group comparison using 1.0 M Gadobutrol and Magnevist to study contrast to noise ratio and lesion characteristics in subjects with known or suspected CNS lesions, (70 subjects in FAS)
- Study 310864, a phase 2/3 crossover study using Prohance to study contrast enhancement, border delineation, and number of lesions in patients with known or suspected brain metastases, (157 subjects in FAS)

Further details regarding the efficacy results of these studies are included in the sources of clinical data, section 5.1, tables of clinical studies, Table 2.

The two US phase 3 IND studies (310123 and 310124) are the main focus of the evaluations designed to demonstrate efficacy of gadobutrol 1.0 M at a dose of 0.1 mmol/kg body weight (BW) for the CNS indication. The results of the US phase 2 study (308200) which was designed to determine a safe and effective dose of gadobutrol 1.0 M for the CNS indication were combined for pooled efficacy analyses.

All 3 studies were similar in terms of study population and design having the following similarities:
- Study population: enrollment of male and female subjects ≥ 18 years of age referred for contrast-enhanced MRI of the CNS
- Gadobutrol regimen: all subjects in the phase 3 studies and approximately 1/3 of subjects in the phase 2 study received gadobutrol 1.0 M at the targeted dose of 0.1 mmol/kg BW by single i.v. injection at a rate of either 2 or 5 mL/second, followed by a 20 mL 0.9% saline flush at the same rate as the contrast agent
- MRI (minimum images obtained): Unenhanced MR image set obtained before the gadobutrol administration, consisting of at least the steady-state sequences T1w, T2w, and Fluid-Attenuated Inversion Recovery (FLAIR)
- Gadobutrol-enhanced MR image set obtained after the gadobutrol consisting of at least the steady-state sequences T1w
- Blinded reading: the unenhanced MR image set and the combined unenhanced   and gadobutrol-enhanced MR image set were evaluated by three independent blinded readers.

For all three above mentioned US IND studies, the primary efficacy evaluations were based on the following four visualization variables, with the scoring system for each as indicated below in parentheses:

- Degree of contrast enhancement (1=none, 2=moderate, 3=good, 4=excellent)
- Assessment of border delineation (1=none, 2=moderate, 3=good, 4=excellent)
- Internal morphology of lesions (1=poor, 2=moderate, 3=good)
- Number of lesions detected.

As a second variable, the two phase 3 studies analyzed exact match of the MR diagnoses with the final clinical diagnosis for accuracy, sensitivity, and specificity for malignancy determination and diagnosis and for the MR images to demonstrate the presence of normal/abnormal tissue based on a comparison of the T1w images.

The pediatric study was primarily to assess the pharmacokinetics of the proposed 0.1 mmol/kg BW dose in pediatric patients 2-17 years of age.

For all 3 US IND studies, evaluation of the efficacy variables was performed as a prospectively planned evaluation in a centralized manner. This was done by independent radiologists (blinded readers) who were trained for efficacy evaluations to standardize the reading and to minimize variability among the readers.

For both of the phase 3 studies, the four primary efficacy variables identified above were assessed for superiority or non-inferiority of the combined image set (i.e. unenhanced plus contrast-enhanced compared to the unenhanced image set) as follows:

- Superiority: Degree of contrast enhancement, assessment of border delineation, internal morphology of lesions
- Non-inferiority: Number of lesions detected

The primary efficacy analyses of these four visualization variables were done using the average of the score values of the three blinded readers. Statistical tests for superiority were two-sided, using the 0.05 level of significance. Statistical tests for non-inferiority were one-sided tests using the 0.025 level of significance. In study 310123, a crossover study, all efficacy variables were also evaluated for gadoteridol and a non-inferiority analysis was used as a secondary efficacy variable.

For the phase 2 study, the primary efficacy analysis of the same four primary efficacy variables was done using a composite score, the Categorical Visualization Score (CVS). An additional primary efficacy variable, contrast-to-noise ratio (CNR) in perfusion imaging was also analyzed. Statistical tests were two-sided at the 0.05-level of significance.

On a post-hoc basis, a supplemental analysis of efficacy data pooled from the three studies was conducted. Two efficacy data pools (E1 and E2) were created for the purpose of analyses. Pool E1 consisted of 725 subjects from all three studies with average reader results used for the processing. Pool E2 consisted of 657 subjects from the two phase 3 studies with data pooling done on the majority reader values.

For study 310123, for both gadobutrol and gadoteridol, the blinded readers' evaluations demonstrated statistically significant superiority of the combined unenhanced/contrast-enhanced MRI to unenhanced MRI for contrast enhancement, border delineation, and internal morphology of lesions. Non-inferiority for number of lesions detected was also demonstrated for both compounds. As a secondary efficacy endpoint, non-inferiority of gadobutrol to gadoteridol for all four variables was demonstrated.

The blinded readers' evaluations were similar for study 310124, demonstrating statistically significant superiority for the 3 primary variables and non-inferiority for the number of lesions.

Efficacy analyses of study 308200 supported a statistically significant improvement in the average reader score for contrast enhancement, border delineation, and internal morphology in favor of the 0.1 mmol/kg dose.

Results of the post hoc efficacy analysis of the E1 pool are consistent with the individual studies and support a statistically significant difference in favor of the combined unenhanced/enhanced image set for contrast enhancement, border delineation, and internal morphology. For the number of lesions, the mean difference between the unenhanced and combined image sets was in favor of the combined image set although, for this variable, the 95% confidence intervals did include the value "0". The post hoc analysis of the E2 pool for the two secondary variables of presence/absence of malignancy and exact match of MR diagnoses with the final clinical diagnosis provided the same picture as seen for the individual studies and was supportive of improved sensitivity and accuracy for presence/absence of malignancy and improved accuracy of MR diagnoses versus final clinical diagnosis. Specificity for presence/absence of malignancy was unchanged between the image sets.

Statistical analyses for primary, secondary, and post hoc analyses are discussed in the sections 6.1.4-6.1.10.

6.1 Indication

For diagnostic magnetic resonance imaging; *Gadobutrol Injection is a gadolinium-based contrast agent indicated for intravenous use in diagnostic magnetic resonance imaging (MRI) in adults and children (2 years of age and older) to visualize lesions with disrupted blood brain barrier and/or abnormal vascularity in the brain, spine, and associated tissues.*

6.1.1   Methods

In support of the indication to visualize CNS lesions, the sponsor performed two phase 3 studies and one phase 2 study in an adult population and one pediatric PK study in children age 2-17 years.

6.1.2   Demographics

The study population for efficacy includes 725 subjects from 3 US IND studies. The patient populations that were enrolled in these studies reflect the proposed indicated patient population, (subjects likely to undergo a contrast-enhanced MRI of the CNS in routine clinical practice.) Subjects were eligible for inclusion if they were referred for contrast-enhanced MRI of the CNS, either brain or spine, based on symptomatology or prior diagnostic testing. Only subjects with normal renal function were eligible for inclusion in the phase 3 crossover study (310123). Subjects with mild to moderate renal

impairment were eligible for inclusion in the non-comparator phase 3 study (310124). Subject renal function was not assessed by eGFR for the phase 2 study (308200) reflective of the date of the original protocol (submitted 3-05, amended 2-06 in response to Division comments) and study enrollment period (8-27-05 to 8-15-07). The table below, reproduced from the NDA submission (text table 6, Summary of Clinical Efficacy, page 34), summarizes the demographics of the 3 US IND studies.

Table 6: US IND Studies: Demographics*

		Study 308200 68[a] (100.0%)	Study 310123 336 (100.0%)	Study 310124 321 (100.0%)	Total 725 (100.0%)
Sex	Male	27 (39.7%)	144 (42.9%)	135 (42.1%)	306 (42.2%)
	Female	41 (60.3%)	192 (57.1%)	186 (57.9%)	419 (57.8%)
Age	18 to < 45 years	30 (44.1%)	122 (36.3%)	139 (43.3%)	291 (40.1%)
	45 to < 65 years	30 (44.1%)	139 (41.4%)	136 (42.4%)	305 (42.1%)
	65 to < 80 years	8 (11.8%)	70 (20.8%)	44 (13.7%)	122 (16.8%)
	≥ 80 years	0	5 (1.5%)	2 (0.6%)	7 (1.0%)
Race	Caucasian	34 (50.0%)	192 (57.1%)	61 (19.0%)	287 (39.6%)
	Black	5 (7.4%)	21 (6.3%)	8 (2.5%)	34 (4.7%)
	Hispanic	4 (5.9%)	25 (7.4%)	82 (25.5%)	111 (15.3%)
	Asian	1 (1.5%)	97 (28.9%)	152 (47.4%)	250 (34.5%)
	Other	24 (35.3%)*	1 (0.3%)	18 (5.6%)	43 (5.9%)
Weight	< 60 kg	10 (14.7%)	106 (31.5%)	99 (30.8%)	215 (29.7%)
	60 kg to < 90 kg	48 (70.6%)	163 (48.5%)	192 (59.8%)	403 (55.6%)
	≥ 90 kg	10 (14.7%)	67 (19.9%)	30 (9.3%)	107 (14.8%)
Region	Europe	0	101 (30.1%)	0	101 (13.9%)
	USA/Canada	22 (32.4%)	107 (31.8%)	52 (16.2%)	181 (25.0%)
	South/Central America	46 (67.6%)	27 (8.0%)	119 (37.1%)	192 (26.5%)
	Asia	0	94 (28.0%)	150 (46.7%)	244 (33.7%)
	Australia	0	7 (2.1%)	0	7 (1.0%)

* "Other" includes South American, Latino-American, Native American, and Aborigine American
** Number and percentage of studies based on Full Analysis Set
a Correct number of subjects assigned to this group, reported elsewhere in the NDA as 69

Using the above table, the demographics may be summated as follows:
- Slightly more females (overall 57.8%) than males (42.2%) were included
- 82.2% of subjects were between the age of 18 and <65 years, 17.8% of the subjects were 65 years of age or older
- Overall, Caucasians and Asians accounted for the highest proportions of the pooled study population (39.6% and 34.5% frequency respectively); racial distribution in the studies reflected recruitment sites
- Most subjects weighed 60 kg to < 90 kg (55.6%) or less than 60 kg (29.7%)
- Ethnicity reflected the study region.

The patient populations enrolled in these studies are reflective of the proposed indicated patient population.

6.1.3   Subject Disposition

Table 7: Subject Disposition (4 "covered" studies)

Parameter	Study Report A47567 Protocol 310123	Study Report A47570 Protocol 310124	Study Report A40524 Protocol 308200	Study Report A40794 Protocol 310788
Total # patients	402	343	229 (3 dose + comparator study)	3 groups total 140, ages 2-6 years (48), 7-11 years (44), 12-17 years (48)
Drop outs	22 (5.5%)	7(.2%)	12(4.8%)	2 (1.5%) (received no study drug)
Lost to follow up	1 (0.2%)	1(.03%)	1 (0.4%) after both drugs	0
Completed study	380	336	217	138(46, 44, 48)
Total protocol deviations/Major/Minor	103 (25.6%) with at least one deviation/47 (11.7%) major/73 (18.2%) minor	43 (12.6%) with at least one deviation /9 (2.6%) major/36 (10.5%) minor	Gadobutrol group only, 208 (90.8%) with at least one deviation/45 (19.7%) major/204 (89.1%) minor	12 (9%)/ 3 major (2.2%)/ 1 minor (.7%)/ 8 PK deviations (6%)/5 major (3.7%/3 minor (2.2%); subjects with major protocol or PK violations excluded
Safety population	399	343	229 (225 gadobutrol, 227 comparator)	138
Full analysis set	336	321	206	138 (46, 44, 48); PK analysis (45, 39, 46)
Per protocol set	316	314	173	135 (45, 42,

				48); PK set 130 (45, 39, 46)

For study 310123, 44 of the major protocol deviations were procedural and 65 of the minor protocol deviations were procedural. The deviation listing reflects either the gadobutrol or gadoteridol study with the procedural deviations reflecting MRI sequencing or doses. For study 310124, the protocol deviations were also mainly procedural. Four out of the nine, (4/9), major protocol deviations for this study related to dosing. Similarly, for study 308200, most protocol deviations were procedural. For example, 26 (11.4% of subjects) major protocol deviations were procedural. Subjects with incorrect dosing were excluded from the PPS efficacy analysis. 195 (85.2%) subjects in that study had minor protocol deviations that were procedural such as incorrect sequences and missed visits. For the pediatric study, there were 12 PK and protocol violations listed, 8 major and 4 minor. Major PK deviations included implausible profiles. Major protocol violations included missing data. All 8 of these subjects were eliminated from the data handling. For the 4 subjects with minor deviations, 2 received alternate data handling, data from one was retained, and the baseline record was disabled for the fourth with planned data analyses both with and without this subject.

Table 8 summarizes subject disposition for the two phase 3 pivotal trials with a breakdown of subject discontinuations.

Table 8: Subject Disposition Phase 3 Studies

Parameter	Study 310123 # of Subjects	Study 310124 # of Subjects
Enrolled	419	347
Randomized and/or Received study drug	402	343
Completed study	380	336
Discontinued study	39	11
…Prior to any study drug	17	4
…Consent withdrawal	6	2
…Protocol	7	4

deviation/ failed inclusion criteria		
…Adverse event	4	0
…Lost to f/u	1	1
…Other	4	0

Analyses of efficacy data were performed using data from all subjects on whom images and entries on case report forms were available for unenhanced and combined unenhanced plus contrast-enhanced MRI, (FAS). Additional efficacy analyses were performed using data from those subjects from the FAS who also fulfilled all major provisions of the protocol, (PPS), with subjects excluded for the following reasons: administration of a contrast dose that was < 90% or > 110% of that which was assigned, an obvious error in the MRI procedure occurred, or pertinent images for the subject were damaged or lost. The primary efficacy analysis for studies 310123 and 310124 was performed using both the FAS and the PPS. For both studies, analyses of the 3 lesion character variables (contrast enhancement, border delineation, and internal morphology) for the average reader, as well as for the 3 individual readers demonstrated a statistically significant change in scores from the unenhanced to the combined images (P<0.001) using the FAS with the sponsor noting " similar" results for the PPS.

Both FAS and PPS analyses were performed with the primary efficacy analysis for study 308200 based on the per protocol set (PPS). PPS for this study included all subjects with valid images who received ± 10% of the intended dose of study drug and had no major protocol or MRI procedure deviation.   Subjects with major protocol violations, (mostly procedural such as missing images or treatment deviations or incorrect or missing doses of study drug) were excluded from the primary efficacy analysis for this study.

As previously noted, 8 subjects in the pediatric study were excluded for either major protocol or PK deviation with exclusions relating to missing information or to an implausible profile.

6.1.4   Analysis of Primary Endpoint(s)

For all three of the US IND studies, the primary efficacy evaluations were based on the the following four visualization variables assessed on the unenhanced and combined unenhanced and enhanced MRI:

- Degree of contrast enhancement (scores: 1 = none, 2 = moderate, 3 = good, 4 = excellent)
- Assessment of border delineation (scores: 1 = none, 2 = moderate, 3 = good, 4 = excellent)
- Internal morphology of lesions (scores: 1 = poor, 2 = moderate, 3 = good)
- Number of lesions detected

An overview of the efficacy variables assessed in the phase 3 studies (310123 and 310124), reproduced from the NDA Summary of Clinical Efficacy, page 13, is presented in Table 9 below. Most of the variables were evaluated by both site investigators and blinded readers. In study 310123, the crossover study performed using gadobutrol and gadoteridol, the same variables were assessed separately for both of the compounds.

Table 9: Efficacy Variables Recorded in Phase 3 Studies 310123 & 310124*

		Unenhanced		Combined (unenhanced and contrast-enhanced)		T1w-contrast-enhanced
		Investigator	Blinded read	Investigator	Blinded read	Blinded read
Degree of contrast enhancement [a]	Lesions		•	•	•	
	Normal structures [b]		•	•	•	
Assessment of border delineation	Lesions	•	•	•	•	
	Normal structures [b]	•	•	•	•	
Internal morphology	Lesions	•	•	•	•	
	Normal structures [b]	•	•	•	•	
Total number of lesions detected		•	•	•	•	
Exact match (MR diagnoses vs. final diagnosis)		•	•	•	•	
Normal/abnormal brain tissue					• [c]	
Malignant CNS lesions (derived)		•	•	•	•	
Confidence in diagnosis		•	•	•	•	
Number of contrast-enhanced lesions [d]						•
Image quality [d]						•
Signal intensity measurement [d]					• [e]	

Bold type: Primary efficacy variables
Contrast: Gadobutrol (study 310124) or gadobutrol and gadoteridol (study 310123)
a: The degree of contrast enhancement was recorded for normal brain structures such as the pituitary gland; that normal structure was not scored in cases of a lesion within the normal area
b: Normal structures were scored only if the whole brain was scanned
c: Ratio determined for unenhanced and T1w contrast-enhanced only
d: The number of contrast-enhanced lesions on the T1w study, image quality, and signal intensity measurement was evaluated only for Study 310123
e: Signal intensity measurement (measured by the blinded reader) was measured separately for the unenhanced and contrast-enhanced MRI and for the unenhanced MRI was measured only once according to the evaluation of the other variables

*: Table reproduced from NDA 201277, Summary of Clinical Efficacy, page 13

For the 2 pivotal phase 3 US studies as well as the phase 2 US study, diagnostic efficacy was evaluated by prospectively planned evaluations of the images in a centralized manner.

Conduct of the Blinded Read (Pivotal phase 3 studies):

A prospectively planned blinded image evaluation was performed in a core laboratory by independent experienced radiologists trained in the study design. The readers were experienced radiologists not associated with the study with no knowledge of the details of the study. Readers were responsible for the 5 parts (11 sessions) of the conduct of the blinded read as noted below. DIGIMA was responsible for the image preparation and blinded reading planning and conduct. Site set up, image quality control, reader training, the blinded read, collection of data, and archiving was all performed by DIGIMA. The manual included reader training and procedures for replacement readers and procedures to be carried out with regards to randomization and blinded reads to minimize recall bias and to insure that only a single image set for any patient was read in the same session. The blinded reading consisted of the following parts:

- Part I   Lesion visualization parameters (3 sessions separated by at least 2 weeks), to include the total number of lesions detected, border delineation, degree of contrast enhancement, internal morphology, diagnosis, and confidence in diagnosis
- Part II   Normal/abnormal diagnosis for each patient (3 sessions separated by at least 2 weeks)
- Part III Image quality (1 session)
- Part IV   Signal intensity (SI) measurement: Percentage of enhancement of the lesion and Contrast/Noise (CNR) of the lesion
- Part V   Number of contrast enhanced lesions and adjudication

The same 3 readers could conduct the first 3 sessions of Part I, 3 sessions of Part II, and the single session of Part III or Part III sessions could be conducted by 3 independent readers not involved with any other part.   Part IV was performed by one reader not involved in any other part in one session. Part V was performed by 2 independent readers not involved in any other part in 1 session generating a consensus read with an additional session (session 11) by another independent reader also not involved in any other part if adjudication was necessary. Readers received training in the protocol, operation of the work station, and the eCRF prior to the reading sessions and refresher training was available prior to each reading session. The blinded reading sessions took place in parallel with the conduct of the clinical trial. Each image set received separate randomization numbers for each session. The primary efficacy analyses of the 4 primary efficacy variables and analysis of the secondary efficacy variables was done for both the blinded readers and the investigators as noted in the table above.

Primary Efficacy Analysis (Pivotal Phase 3 Studies):

The primary objective of these studies was to demonstrate superiority of the combined unenhanced and gadobutrol-enhanced MRI compared to unenhanced MRI for:

- Degree of contrast enhancement

- Assessment of border delineation and
- Internal morphology of lesions

And to demonstrate non-inferiority for:
- Number of lesions detected.

The individual results for the three blinded readers were combined into one single value using the average reader data for the ordinal variables, (lesion characteristics and total number of lesions detected) and the majority reader data for the binary variables, (secondary endpoints of sensitivity/specificity for the presence/absence of malignancy and exact match of the MR diagnoses with the final clinical diagnosis).

Analysis for each of the 4 efficacy variable parameters was performed using the mean of the values for the three blinded readers (blinded reader average). This dataset was generated based on the average scores for both lesions and normal structures, calculated separately initially then calculated as an overall mean to reflect the mean of the lesion score and the normal structures. The lesion characterization variables (contrast enhancement, border delineation, and internal morphology) were tested for the superiority of gadobutrol-enhanced MRI versus unenhanced MRI using paired t-tests which were two-sided using the 0.05 level of significance. Null and alternative hypotheses were as follows:

H_0: combined unenhanced and gadobutrol mean = unenhanced MRI mean versus
H_1: combined unenhanced and gadobutrol mean ≠ unenhanced MRI mean

Non-inferiority of the number of lesions detected was assessed using confidence intervals based on the t-distribution, using a non-inferiority margin of 0.35. A one-sided test conducted at the 0.025 level of significance would be a statistically equivalent procedure. The null and alternative hypotheses for non-inferiority were as follows:

H_0: combined unenhanced and gadobutrol mean-unenhanced mean < -0.35 versus
H_1: combined unenhanced and gadobutrol mean – unenhanced mean ≥ -0.35

All efficacy values for study 310123 were evaluated in similar fashion for both gadobutrol and gadoteridol with non-inferiority of gadobutrol to gadoteridol as a secondary analysis.
.
Efficacy analyses were performed for the full analysis set (FAS) and for the per protocol set (PPS). The FAS was comprised of data from all subjects for whom images and entries on case report forms were available for unenhanced and combined unenhanced and gadobutrol-enhanced MRI, excluding the sample subjects used for determination of quality assurance at an investigative site. The PPS was comprised of all subjects who also fulfilled all major provisions of the protocol with subjects excluded for administration of a dose of contrast agent that was <90% or >110% of that which was assigned, an

obvious error in the MRI procedure, or damage or loss of the pertinent images for the subject. For study 310123, there was a difference of 20 subjects between the FAS and the PPS, N = 336 and N = 316 respectively. For study 310124, there was a difference of 7 subjects with N = 321 for the FAS and N = 314 for the PPS. Results of the efficacy analyses performed for both the FAS and PPS were similar.

For both the 310123 and 310124 studies, the changes in scores from pre-contrast to post contrast were found to be statistically significant for the average reader as well as for all 3 individual readers (P<0.0001 in all cases) for the three lesion characteristic variables. For study 310124, the number of lesions detected by the average reader increased post contrast within the pre-specified non-inferiority margin, (testing a non-inferiority margin of 0.35 such that 95% 2-sided confidence interval for the mean difference of the score must have excluded the value of -0.35). For this study 310124, although non-inferiority for the number of lesions was met for the average reader and for readers number one and three it was not met for reader two where mean change in lesion number was -0.17 and where there was a difference in number of lesions detected when compared to the other two readers. For study 310123, non-inferiority for the number of lesions was met for the average reader as well as for all three individual blinded readers when a non-parametric analysis was performed. Tables 9 and 10 below summarize average scores for the primary efficacy visuzlization variables and total lesion number for each reader and for the average reader. The point scores were derived from a combination of normal brain structures and lesions. The number of lesions used for analysis, presented in tables as total numbers, was considered as a mean number of lesions for the statistical analysis. Further discussion of results contained in the tables follows the tables.

Table 10: Study 310123 Summary of Contrast Enhancement-Blinded Readers Combined Unenhanced/Gadobutrol-Enhanced vs. Unenhanced, (FAS, N = 336)

Reader and Number of Subjects[a]	Degree of Contrast Enhancement	Assessment of Border Delineation	Internal Morphology of Lesions	Total Number of Lesions Detected
Reader 1 N = 314	Unenhanced 0.94 Combined 2.21 Difference 1.26[b]	Unenhanced 2.03 Combined 2.70 Difference 0.67[b]	Unenhanced 1.16 Combined 1.78 Difference 0.62[b]	Unenhanced N = 2490 Combined N = 2622 Difference N = 132[c]
Reader 2 N = 314	Unenhanced 1.01 Combined 2.60	Unenhanced 2.19 Combined 2.91	Unenhanced 1.46 Combined 2.28	Unenhanced N = 3383 Combined N =

				3234 Difference N = -149[c]
	Difference 1.59[b]	Difference 0.72[b]	Difference 0.82[b]	
Reader 3 N = 312	Unenhanced 0.96 Combined 2.02	Unenhanced 1.73 Combined 2.16	Unenhanced 1.34 Combined 1.76	Unenhanced N= 2267 Combined N = 2456
	Difference 1.06[b]	Difference 0.43[b]	Difference 0.41[b]	Difference N = 189[c]
Average N = 316	Unenhanced 0.97 Combined 2.26	Unenhanced 1.98 Combined 2.58	Unenhanced 1.32 Combined 1.93	Unenhanced N = 2713 Combined N = 2771
	Difference 1.20[b]	Difference 0.60[b]	Difference 0.61[b]	Difference N = 57[c]

a: Zero-filled averaging was used when different numbers of lesions were detected by different modalities in order for the averages to be based on the same number of scores such that complete tables reflecting minimum, maximum, and median scores as well as mean may have zero scores; the number of subjects differ between blinded readers because a subject was not counted if the blinded reader did not see any lesions

b: **P-Value for these was statistically significant at p<0.0001**

c: Reader 2 had a higher mean number of lesions for both the unenhanced and combined modalities (10.07 and 9.63 respectively as versus 7.41 and 7.80 for reader 1 and 6.75 and 7.31 for reader 3) with standard deviation for the difference between the two lesion counts measured as 12.38 for reader 2 as versus 5.51 for reader 1 and 4.07 for reader 3; the lower limit of the confidence interval for number of lesions, -0.439, did not meet the pre-specified noninferiority margin of -0.35 thus nonparametric analysis was performed

Reviewers Comments:
1. *The number of subjects analyzed by each reader is less than the number of subjects in the FAS, presumed secondary to subjects where no lesions were detected. The sponsor should confirm this and note the number of subjects for which all 3 blinded readers did not see any lesions.*
2. *Non-inferiority for the number of lesions was achieved by a non-parametric analysis, (i.e. non-inferiority was not demonstrated by direct analysis of the number of lesions). This reviewer considers a non-parametric analysis showing the number of lesions overall detected on post contrast and combined images are increased from the pre-contrast set is acceptable.*

Table 11: Study 310124 Summary of Contrast Enhancement-Blinded Readers Combined Unenhanced/Gadobutrol-Enhanced vs. Unenhanced, (FAS, N = 321)

Reader and Number of Subjects[a]	Degree of Contrast Enhancement	Assessment of Border Delineation	Internal Morphology of Lesions	Total Number of Lesions Detected
Reader 1	Unenhanced	Unenhanced	Unenhanced	Unenhanced

N = 301	0.94 Combined 2.96 Difference 2.03[b]	2.17 Combined 3.01 Difference 0.85[b]	1.87 Combined 2.40 Difference 0.53[b]	N = 726 Combined N = 939 Difference N = 213[c]
Reader 2 N = 301	Unenhanced 0.93 Combined 2.87 Difference 1.94[b]	Unenhanced 1.98 Combined 3.15 Difference 1.17[b]	Unenhanced 1.38 Combined 2.46 Difference 1.08[b]	Unenhanced N = 1210 Combined N = 1157 Difference N = -53[c]
Reader 3 N = 309	Unenhanced 0.93 Combined 2.86 Difference 1.93[b]	Unenhanced 1.64 Combined 2.76 Difference 1.12[b]	Unenhanced 1.49 Combined 2.25 Difference 0.77[b]	Unenhanced N = 615 Combined N = 760 Difference N = 145[c]
Average N = 311	Unenhanced 0.93 Combined 2.86 Difference 1.94[b]	Unenhanced 1.92 Combined 2.94 Difference 1.02[b]	Unenhanced 1.57 Combined 2.35 Difference 0.78[b]	Unenhanced N = 850 Combined N = 952 Difference N = 102[c]

a: Zero-filled averaging was used when different numbers of lesions were detected by different modalities in order for the averages to be based on the same number of scores such that complete tables reflecting minimum, maximum, and median scores as well as mean may have zero scores; the number of subjects differ between blinded readers because a subject was not counted if the blinded reader did not see any lesions (for this study all 3 blinded readers did not see 10 lesions)

b: **P-Value for these was statistically significant at p<0.0001**

c: Reader number 2 had a mean change in lesion number of -0.17 as versus readers 1 and 3 with changes of 0.66 and 0.45 respectively and the mean number of unenhanced lesions detected for reader 2 was 3.77 as compared to 2.26 and 1.92 for readers 1 and 3; the average assessment, however, was 0.32 with 95% confidence intervals of (-0.70, 0.704), thus this satisfied the prespecified noninferiority margin of -0.35

Reviewer's Comment: The above table is reflective of original analyses. According to the applicant there was incorrect use of the "other" diagnosis when analysis of the secondary variables was performed. A blinded reader re-read of the images in question was performed, introducing inconsistencies due to lesion numbers in primary analysis data. The repeat analyses confirm efficacy for the 4 primary variables, p-value<0.0001.

As seen in Table 10, for study 310123 analysis revealed mean contrast enhancement average reader score to increase from 0.97 pre-contrast to 2.26 post contrast, mean border delineation to increase from 1.98 precontrast to 2.58 post contrast (both on a 4 point scale), and mean internal morphology to increase from 1.32 pre-contrast to 1.93 post contrast on a 3 point scale with some variability noted across the readers. For the

mean number of lesions, (table reflects total lesion number), there was a high level of variability across the three readers with reader 2 having a higher mean number of lesions for both unenhanced and combined modalities and more variability within assessments than for reader 1 or reader 3. As such, the mean increase from the unenhanced to the combined images was 0.17 lesions with a 95% confidence interval of (-0.439, 0.780). Thus, the lower limit of the confidence interval was lower than the pre-specified non-inferiority margin of -0.35.

Based on the observed data, a nonparametric analysis was performed where the lesion counts were replaced by a categorical variable, (lesion numbers replaced by comparing the number of lesions detected by the two modalities). For the average reader, the number of lesions detected for the two modalities was equal for 20.8 % of subjects, higher for combined unenhanced/gadobutrol-enhanced in 44.0% of subjects, and higher for unenhanced in 35.1 % of subjects. Using this nonparametric analysis, the difference between combined unenhanced/gadobutrol-enhanced and unenhanced was 8.9% with a 95% confidence interval of (-0.5%, 18.4%), which is within the pre-specified non-inferiority margin for the categorical variables. Non-inferiority was then demonstrated for all 3 blinded readers as well.

Analysis of study 310124 revealed mean contrast enhancement average reader score to increase from 0.93 pre-contrast to 2.86 post contrast, mean border delineation to increase from 1.92 pre=contrast to 2.94 post contrast (both on a 4 point scale), and mean internal morphology to increase from 1.57 pre-contrast to 2.35 post contrast on a 3 point scale with mean changes across the 3 readers more variable than for the other two features. The mean number of lesions, (table reflects total lesion number), increased from 2.65 pre-contrast to 2.97 post contrast with individual reader non-inferiority for this variable also demonstrated by readers 1 and 3.

Reviewer's comment: This reviewer and the statistical reviewer both noted that the average number of lesions was greater for study 310123 than for study 310124 (on combined image sets, greater than 8 compared to nearly 3). This reviewer attributed the differences to referring diagnoses, namely 2.5 times the number referred for metastases and 40% more referred for multiple sclerosis. The applicant provided further explanation that "white matter spots" (Unidentified Bright Objects) that are commonly seen in MRI scans in patients over 65 years of age might be contributory and that the 310123 study had 23.4% of subjects in this age group compared to 14.3% in the 310124 study. The applicant concluded that there was no definitive reason for the difference in lesion. This is acceptable as this variable did not impact other endpoints.

Primary Efficacy Analysis (Phase 2 Dose Comparison Study)

Table 12 below reproduced from the NDA 201277 presents an overview of the primary and secondary efficacy variables of study 308200 where BR represents evaluation by

blinded readers/centralized procedure and INV represents image evaluation by the investigator.

Table 12: Overview of Efficacy Variables Study 308200*

Variables	Unenhanced MRI		Combined unenhanced and gadobutrol-enhanced MRI		Combined unenhanced and comparator-enhanced MRI		Gadobutrol perfusion MRI
	INV	BR	INV	BR	INV	BR	BR
Primary efficacy variables:							
Raw number of lesions detected	✓	✓	✓	✓	✓	✓	
Assessment of border delineation	✓	✓	✓	✓	✓	✓	
Degree of contrast enhancement			✓	✓	✓	✓	
Internal morphology	✓	✓	✓	✓	✓	✓	
Maximum CNR (between gray/white matter)							✓
Secondary efficacy variables:							
Detection of all matched lesions	✓	✓	✓	✓	✓	✓	
Detection of contrast-enhanced matched lesions			✓	✓	✓	✓	
Diagnosis/Confidence in diagnosis	✓	✓	✓	✓	✓	✓	
CNR of lesion/gray and lesion/white matter							✓
Perfusion values							✓
Quality of perfusion maps							✓
Artifacts in perfusion maps							✓
Estimation of tumor grades							✓
Lesion tracking	✓	✓	✓	✓	✓	✓	✓

*: Reproduced from NDA 201277 clinical study report Number A40524, page 37

The primary objective of the study was to determine a safe and effective dose of gadobutrol 1.0 molar based on:
- The raw number of lesions detected in pre-contrast and combined pre-contrast and post contrast MRI
- Assessment of border delineation, (1 = none, 2 = moderate, 3 = good, 4 = excellent)
- Degree of contrast enhancement, (1 = no enhancement, 2 = moderate enhancement, 3 = good enhancement, 4 = excellent enhancement), and

- Internal morphology, (1 = poor, 2 = moderate, 3 = good) of lesions

and on the maximum contrast to noise ration (CNR) between white and gray matter with gadobutrol perfusion MRI.

The four primary efficacy variables of raw number of lesions detected in pre-contrast and combined pre-contrast and post contrast MRI, lesion border delineation, degree of contrast enhancement, and internal morphology of lesions were computed using a composite categorical visualization score (CVS). As there were 3 doses of gadobutrol, analysis was on the basis of paired lower-higher dose. Analyses performed for the variables were all two-tailed and at the 0.05 level of significance. The difference in mean score (DCVS) was constructed using t-distribution and a two-sided 95% confidence interval.

Both FAS and PPS analyses were performed with the primary efficacy analysis for study 308200 based on the per protocol set (PPS). PPS for this study included all subjects with valid images who received ± 10% of the intended dose of study drug and had no major protocol or MRI procedure deviation.   Subjects with major protocol violations, (mostly procedural such as missing images or treatment deviations or incorrect or missing doses of study drug) were excluded from the primary efficacy analysis for this study. For the combined 3 dose study, there were 206 subjects in the FAS set and 173 subjects in the PPS. 69 and 56 subjects, respectively, in these categories received the 0.1 mmol/kg dose which is proposed for licensure.

For the average reader, the lowest CVS value (1.43) was obtained for the 0.03 mmol/kg dose group and the highest CVS value (2.02) was obtained for the 0.1 mmol/kg (standard) group. The difference between these dose groups was statistically significant, (p = 0.003), in favor of the higher dose. The 0.3 mmol/kg dose showed no further increase in CVS compared to the 0.1 mmol/kg dose. Scores for 2 of the 3 individual blinded readers were similar to average reader scores. Increasing the dose of gadobutrol did not significantly increase the number of lesions detected between the unenhanced and enhanced MRI. Statistically significant differences between the 0.03 and 0.1 mmol/kg dose groups were observed for every reader for contrast enhancement and for 2 of 3 readers for border delineation and internal morphology. Analysis was on the basis of paired lower-higher dose.

Analysis of the CNR in perfusion imaging was by dose group and descriptive statistics. Mean CNR values were higher for the 0.1 (27.0) and 0.3 (22.2) mmol/kg dose groups compared to the 0.03 mmol/kg dose group (9.42). There was no statistically significant difference between the 0.03 and 0.1 mmol/kg dose groups or between the 0.1 and 0.3 mmol/kg dose groups. Results of the FAS (N=206 subjects) analysis of the primary visualization variables were similar to those of the PPS (N=173 subjects). CVS value for the 0.1 mmol/kg set was 1.90, for the 0.03 mmol/kg dose group was 1.33. There

was no difference observed with comparison to the higher 0.3 mmol/kg dose group (2.00). CNR results for the FAS were also similar to those for the PPS and did not show any statistically significant difference among the 3 gadobutrol doses.

Table 13 below which is a summary of the average reader categorical visualization score (CVS) for all subjects in the per protocol set reflects the 3 doses of gadobutrol used for the study. For the average reader, the lowest CVS value (1.43) was obtained for the 0.03 mmol/kg dose group and the highest CVS value (2.02) was obtained for the 0.1 mmol/kg group. The difference in CVS between these two groups was statistically significant, (p = 0.003), in favor of the 0.1 mmol/kg dose group. CVS values reached a plateau with the 0.1 mmol/kg dose group, i.e. there was no increase in CVS from the 0.1 mmol/kg dose to the 0.3 mmol/kg dose and no statistical significance to the actual difference, (p = 0.844).

Table 13: Average Reader Categorical Visualization Score (CVS)-Per Protocol Set

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

*: T-test P-value = 0.844 comparing CVS values between the 0.1 mmol/kg dose and the 0.3 mmol/kg dose and is not statistically significant; T-test P-value = 0.003 comparing the CVS values between the 0.03 mmol/kg dose and the 0.1 mmol/kg dose is statistically significant
**: Standard Deviation (StD)

Reviewer's Comment: Average reader data in the table does not indicate a score difference between the groups for any of the three doses. An Informatiion Request (IR) was sent to the applicant for clarification of the scoring process with the following (acceptable) response as text taken from the protocol: "These 4 primary visualization efficacy variables will be condensed to a composite score called "Categorical

Visualization Score" (CVS) based on the assessment of each of the three blinded readers. Considering each of the 4 variables as a category, the CVS for each patient will be calculated as

CVS =   (number of categories with increase over pre-contrast)
*   – (number of categories with decrease over pre-contrast).*

For the category "contrast enhancement", the pre-contrast value will be set to "1 = No = lesion is not enhanced" to evaluate the CVS.

The possible outcomes of the CVS for a single patient and each reader will be in the range of –3 to +4. Then the CVS will be averaged across the 3 blinded readers, producing one mean CVS per patient."

Using a similar dose comparison scheme, the additional primary efficacy endpoint of contrast to noise ratio (CNR) between white-gray matter derived from signal intensity measurements was computed with results in Table 14 below.

Table 14: Summary of Contrast to Noise Ratio (CNR) Between White-Gray Matter Derived from Signal Intensity Measurements (Per Protocol Set)

Dose (mmol/kg)	Number of Subjects	Mean* StD**	Dose Difference (Lower, Upper)***
0.3	55	22.2 15.2	Difference between 0.1 mmol/kg and 0.3 mmol/kg = 4.7421 (-15.86, 25.347)
0.1	56	27.0 75.6	Difference between 0.03 mmol/kg and 0.1 mmol/kg = 17.54 (-37.11, 2.022)
0.03	60	9.42 11.4	

*:   For each subject, mean of the CNR's for 6 maps was used
**: StD = Standard Deviation
***: Confidence intervals for the difference between the two mean CNR values are asymptotic based on T-distribution

Analysis of the CNR in perfusion imaging was by dose group and descriptive statistics. Mean CNR values were higher for the 0.1 (27.0) and 0.3 (22.2) mmol/kg dose groups compared to the 0.03 mmol/kg dose group (9.42). There was no statistically significant

difference between the 0.03 and 0.1 mmol/kg dose groups or between the 0.1 and 0.3 mmol/kg dose groups.

6.1.5   Analysis of Secondary Endpoints(s)

The secondary efficacy objectives of the 310123 crossover study were as follows:

- To demonstrate non-inferiority of gadobutrol compared to the 0.1 mmol/kg approved dose of gadoteridol for all 4 visualization parameters
- To demonstrate improvement of gadobutrol-enhanced MRI to unenhanced MRI and non-inferiority to gadoteridol-enhanced MRI for: exact match of the MR diagnoses with the final clinical diagnosis, sensitivity and specificity for normal/abnormal brain tissue based on the comparison of the T-1 weighted (T1w) contrast-enhanced and T1w unenhanced images, sensitivity and specificity for the detection of malignant CNS lesions, and confidence in diagnosis.
- To compare gadobutrol to gadoteridol for: T1w image quality in a paired comparison, the number of contrast-enhanced lesions (confirm, using adjudication, differences in the number of contrast-enhanced lesions on T1w images), and quantitative parameters based on signal intensity (SI) measurements.

Secondary objectives of the 310124 open-label study were to demonstrate improvement of gadobutrol-enhanced MRI to unenhanced MRI for:

- Exact match of MR diagnoses compared to final clinical diagnoses.
- Sensitivity and specificity for normal and abnormal brain tissue based on comparison of T1w contrast-enhanced and T1w unenhanced MR images.
- Sensitivity and specificity for detection of malignant CNS lesions.
- Confidence in diagnosis.

The secondary efficacy variables for the 310123 crossover study that were evaluated are listed below. The 310124 study considered only the first four variables on this list. Most of the primary and secondary variables were also assessed by the investigators and were considered as secondary analyses.

- Exact match of the MR diagnoses with the final clinical diagnosis
- Assessment of normal (specificity) and abnormal (sensitivity) brain tissue
- Assessment of malignant CNS lesions
- Confidence in diagnosis
- SI measurements

- Number of contrast-enhanced lesions and
- Image quality.

From the list of the above variables, the applicant considered the following three variables analyzed for the two US phase 3 studies as the important secondary variables:

- Exact match of the MR diagnoses with the final clinical diagnosis, using a pre-defined list of malignant diagnoses (analyzed for accuracy)
- Determination of malignancy (analyzed for sensitivity, specificity, and accuracy)
- Normal/abnormal brain tissue (independent assessment based on a comparison of the T1w images only)

Analyses of these secondary endpoint variables will be discussed in greater detail. Results to include tables of anlyses of these three secondary variables will be discussed individually but presented concurrently, discussion of each variable for the 310123 study to include comparison with gadoteridol followed by discussion of the same variable for the 310124 study. For analyses, the majority reader data was used for the binary variables i.e. the secondary endpoints of sensitivity/specificity for the presence/absence of malignancy and exact match of the MR diagnoses with the final clinical diagnosis, and normal/abnormal tissue.   These secondary efficacy variables were calculated for contrast enhanced MRI, (gadobutrol as well as gadoteridol), and unenhanced MRI and Mcnemar's test for the difference in these proportions was used for the analyses. The signal intensity measurements that were calculated for the gadobutrol and gadoteridol comparison were summarized by MRI modality (study type) using descriptive statistics and confidence intervals.

For some cases in study 310124, blinded reader diagnoses were re- evaluated. The tables presented in this review reflect the re-read diagnoses. In the process of data analysis, the applicant noted use of the "other" diagnosis for image findings citing aneurysm clips as an example. To address this issue, the applicant re-trained the blinded readers, the investigators, and the truth committee members, keeping the process blinded for the blinded readers. Inconsistencies in data were introduced by this process, namely in the no lesion category for the number of lesions. Additional analyses were then performed for the primary efficacy variables reflecting a change in the number of lesions with results continuing to demonstrate superiority for contrast enhancement, border delineation, and internal morphology and non-inferiority for the number of lesions on the combined image set, (P<0.0001).

For study 310123, all 3 blinded readers demonstrated a higher accuracy of diagnosis (an exact match to the standard of truth diagnosis) on the combined unenhanced/gadobutrol-enhanced images as compared to the unenhanced image set and the improvement was statistically significant for 2 of the 3 blinded readers as well as for the majority reader, (P = 0.0796 for reader 1, P = 0.0422 for reader 2, and P =

0.0006 for reader 3). The improvement in accuracy rates ranged from 4.5% for reader 1 to 8.6% for reader 3. The majority reader assessment was statistically significant for accuracy improving by 6.2% from unenhanced to combined unenhanced/enhanced, 95% CI [1.7%, 10.8%], P-Value 0.0082. For the comparison with gadoteridol, all three readers demonstrated similar accuracy of diagnosis for the two contrast agents and using the pre-specified non-inferiority margin of -10%. Non-inferiority of gadobutrol to gadoteridol was demonstrated for all three readers and for the majority reader (majority read difference was -0.4%, 95% CI [-3.8%, 2.9%]).

Table 15: Blinded Reader Accuracy for Exact Match Diagnosis, Unenhanced Images, Combined Unenhanced/Gadobutrol Images, & Gadoteridol Enhanced Images; Full Analysis Set (N = 336)

Reader	Number of Subjects	Unenhanced Accuracy	Unenhanced + Enhanced Accuracy (Gadobutrol)	Difference	Gadoteridol Unenhanced + Enhanced Accuracy	Gadobutrol-Gadoteridol Unenhanced + Enhanced Accuracy
1	292	51.7%	56.2%	4.5%	58.6%	-2.4%
2	292	43.5%	49.0%	5.5%	47.3%	1.7%
3	292	45.9%	54.5%	8.6%	53.1%	1.4%
Majority	225* 229**	58.2%	64.4% 65.1%	6.2%	65.5%	-0.4%

* N = 225 for gadobutrol study, 67 subjects excluded from majority read because the blinded readers provided three different diagnoses due to standard of truth diagnoses; for the individual reader analyses, 44 subjects were excluded due to standard of truth diagnoses of not assessable or other
** N = 229 for gadoteridol study, truth panel diagnoses of other and non-assessable are excluded and cases are excluded when there is no majority reader diagnosis

For study 310124, all 3 blinded readers demonstrated a higher accuracy of diagnosis (an exact match to the standard of truth diagnosis) on the combined unenhanced/gadobutrol-enhanced images as compared to the unenhanced image set, (P = 0.0321 for reader 1, P = 0.0046 for reader 2, and P = 0.0094 for reader 3) with improvement in accuracy rates ranging from 5.7% to 8.0%. The improvement was statistically significant as well as for the majority reader, (P = 0.0002), improving by 9.4%. Using results from the original reads based on analysis of 205 subjects, the majority reader also demonstrated a statistically significant improvement in exact match diagnosis comparing unenhanced images to the combined enhanced/gadobutrol-enhanced study with a p-value<0.0027.

Table 16: Blinded Reader Accuracy for Exact Match Diagnosis, Unenhanced Images vs Combined Unenhanced/Gadobutrol Images, Full Analysis Set (N = 321) Based on Re-Read Results

Reader	Number of Subjects	Unenhanced Accuracy	Unenhanced + Enhanced Accuracy (Gadobutrol)	Difference	95% CI and P-Value
1	261*	51.7%	56.2%	4.5%	(0.5%, 11.0%); 0.0321
2	261*	43.5%	49.0%	5.5%	(2.6%, 13.5%); 0.0046
3	261*	45.9%	54.5%	8.6%	(1.8%, 12.0%); 0.0094
Majority	224**	51.8%	61.2%	9.4%	(4.7%, 14.1%); 0.0002

* N = 261 secondary to subject exclusion if the standard of truth diagnosis provided by the blinded reader was "not assessable" or "other"
* N = 224 for the majority reader assessment due to exclusion of 37 subjects for whom the 3 blinded readers provided 3 different diagnoses

For study 310123, the blinded readers provided their assessment of whether the T1w images were normal or abnormal and the assessments were compared to the standard of truth diagnoses. Sensitivity, specificity, and accuracy were calculated for each reader and for the majority reader. For all 3 blinded readers accuracy and sensitivity were statistically significantly higher for the gadobutrol-enhanced images as compared to the unenhanced image set. Improvements in accuracy are noted in Table 16 below. Improvements in sensitivity for readers 1, 2, 3, and the majority reader were 12.1%, 14.1%, 15.0%, and 13.6% respectively. Specificity analysis was limited due to inclusion of only 61 subjects but showed a slight increase in value for 2 of the three readers, a decrease for the third reader, and no loss in specificity for the majority reader. For the comparison with gadoteridol, all three readers and the majority demonstrated similar accuracy, sensitivity, and specificity rates. For accuracy and sensitivity of diagnosis for the two contrast agents and using the pre-specified non-inferiority margin of -10%, non-inferiority of gadobutrol to gadoteridol was demonstrated for all three readers and for the majority reader. For specificity, due to the lower sample sizes, the confidence intervals were slightly below 10% for all 3 readers and for the majority reader, (-11.1%, -10.8%, -10.1%, -10.1%).

Table 17: Blinded Reader Accuracy of Detection of T1w Normal/Abnormal Brain Tissue Unenhanced Images vs Gadobutrol-Enhanced & Gadoteridol-Enhanced Images; Full Analysis Set (N = 336)

Reader	Number of Subjects	Unenhanced Accuracy	Unenhanced + Enhanced Accuracy (Gadobutrol)	Difference	Gadoteridol Unenhanced + Enhanced Accuracy	Gadobutrol-Gadoteridol Unenhanced + Enhanced Accuracy
1	267	65.5%	76.0%	10.5%	77.2%	-1.1%
2	267	64.8%	76.4%	11.6%	78.7%	-0.4%
3	267	68.9%	78.3%	9.4%	77.2%	0.0%
Majority	267	66.7%	77.2%	10.5%	77.2%	0.0%

Reviewer's Comment: Specificity and accuracy of T1w normal/abnormal brain tissue was slightly greater than the pre-specified -10% non-inferiority margin of gadobutrol to gadoteridol and for the comparison of unenhanced images to the gadobutrol enhanced set there was no change in specificity for the majority reader, both due to the small sample size.

For study 310124, the blinded readers provided their assessment of whether the T1w images were normal or abnormal and the assessments were compared to the standard of truth diagnoses. Sensitivity, specificity, and accuracy were calculated for each reader and for the majority reader. For readers 1 and 2 and the majority reader assessment, accuracy and sensitivity were statistically significantly higher of on the combined gadobutrol-enhanced images as compared to the unenhanced image set. The improvements in accuracy for readers 1, 2, and the majority reader were 5.4%, 6.7%, and 5.0% respectively as noted Table 18 below. Improvements in sensitivity for readers 1, 2, and the majority reader were 9.0, 9.5%, and 8.5% respectively. Although accuracy and sensitivity also improved for reader 3, the increases were not statistically significant. Specificity analysis was limited due to inclusion of only 40 subjects since 199 of the 239 subjects available for the analysis had standard of truth assessments of abnormal brain tissue and showed a decrease in specificity on the enhanced images for all 3 readers as well as for the majority reader.

Table 18: Blinded Reader Accuracy of Detection of T1w Normal/Abnormal Brain Tissue Unenhanced vs Gadobutrol-Enhanced Images; Full Analysis Set (N = 321)

Reader	Number of Subjects	Unenhanced Accuracy	Unenhanced + Enhanced Accuracy (Gadobutrol)	Difference
1	239	74.5%	79.9%	5.4%
2	239	73.2%	79.9%	6.7%

3	239	75.7%	77.4%	1.7%	
Majority	239	74.9%	79.9%	5.0%	

For study 310123, sensitivity, specificity, and accuracy for malignant diagnoses compared to the standard of truth demonstrated statistically significant increases in sensitivity from unenhanced to combined unenhanced/gadobutrol enhanced image sets with no loss in specificity, and thus an increase in the accuracy which was statistically significant for the three blinded readers and the majority reader. Results of the accuracy analyses are displayed in Table 19. The increases noted for sensitivity from unenhanced to combined unenhanced/enhanced ranged from 11.8% to 17.2% for the 3 blinded readers with majority reader increase of 19.4%, all of which were statistically significant increases. Specificity values were essentially unchanged from unenhanced to combined unenhanced/enhanced for all 3 readers and for the majority reader. As such, the increase in accuracy values, although statistically significant for both the 3 blinded readers and the majority reader (P = 0.0006 for the majority reader), were not as great as the increases in sensitivity. For the gadobutrol vs gadoteridol comparison, non-inferiority of gadobutrol to gadoteridol was proven for this variable for sensitivity, specificity, and accuracy for all 3 blinded readers and for the majority reader.

Table 19: Summary of Accuracy of Malignant Lesions, Unenhanced, Unenhanced + Gadobutrol, and Unenhanced + Gadoteridol; Full Analysis Set (N = 336)

Reader	Number of Subjects	Unenhanced Accuracy	Unenhanced + Enhanced Accuracy (Gadobutrol)	Difference	Unenhanced + Gadoteridol Enhanced Accuracy	Accuracy Differ. Gadobut.- Gadoter. Enhance
1	292*	82.9%	87.0%	4.1%	86.0%	1.0%
2	292*	78.1%	86.0%	11.6%	83.6%	2.4%
3	292*	81.2%	86.6%	9.4%	86.3%	0.3%
Majority	292*	81.2%	87.7%	10.5%	85.6%	2.1%

*: 71 subjects excluded due to standard of truth diagnoses of not assessable or other

Similar to study 310123, for study 310124, sensitivity, specificity, and accuracy for malignant diagnoses were compared to the standard of truth with all diagnoses assessed as malignant, not malignant, or when not assessable or other, as not assessable. 60 subjects were excluded from the majority read for malignancy due to a standard of truth diagnosis of other or not assessable. All 3 readers and the majority reader demonstrated statistically significant increases in sensitivity from unenhanced to combined unenhanced/gadobutrol- enhanced image sets with no loss in specificity, and thus an increase in the accuracy which was not statistically significant for the three blinded readers but was for the majority reader, (p-value 0.0093). Results of the

accuracy analyses are displayed in Table 20. The increase noted for sensitivity from unenhanced to combined unenhanced/ gadobutrol-enhanced was 15.9% for all 3 blinded readers with majority reader increase of 20.6%, all of which were statistically significant increases.

Table 20: Summary of Accuracy of Malignant Lesions, Unenhanced vs Unenhanced/ Gadobutrol-Enhanced-Full Analysis Set (N = 321)

Reader	Number of Subjects	Unenhanced Accuracy	Unenhanced + Enhanced Accuracy (Gadobutrol)	Difference
1	261*	84.3%	87.4%	4.1%
2	261*	81.6%	85.1%	8.1%
3	261*	83.9%	87.0%	6.9%
Majority	261*	82.4%	87.3%	8.7%

*: 60 subjects excluded due to standard of truth diagnoses of not assessable or other

In addition to the above analyses for exact match diagnosis, determination of malignancy, and T1w normal/abnormal brain tissue, secondary analysis for the comparator study (310123) was also performed for each of the 4 visualization parameters for determination of non-inferiority of gadobutrol versus gadoteridol. This was evaluated using confidence intervals based on the t-distribution. A noninferiority margin of 0.35 was used in each case.

Analysis of the four visualization parameters for gadoteridol revealed similar scores to the gadobutrol parameters for the contrast enhancdement, border delineation, and internal morphology. Results were similar for both the average reader as well as the 3 individual readers. The non-inferiority of gadobutrol to gadoteridol was proven for each of these three parameters. As was the case for gadobutrol, the variability of reader 2 was higher, thus the difference between gadobutrol and gadoteridol for this variable using the 95% confidence interval was (-0.601, 0.622) as versus the prespecified non-inferiority margin of -0.35.

Nonparametric analysis was performed as for the gadobutrol alone yielding an 8.3% difference between gadobutrol and gadoteridol with 95% confidence interval of (0.9%, 17.6%). This result then is within the prespecified 10% non-inferiority margin. Non-inferiority was demonstrated for all 3 blinded readers as well.

All 3 blinded readers demonstrated a similar accuracy of diagnosis for the two contrast agents and using the pre-specified non-inferiority margin of -10%, non-inferiority of gadobutrol to gadoteridol was demonstrated for all three readers and the majority reader.

Table 21: Gadobutrol vs Gadoteridol Comparison of Primary Efficacy Variables

Reader	Image Set (Combined)	No. of Subjects	Mean Contrast Enhancement	Mean Border Delineation	Mean Internal Morphology
1	Gadobutrol	314	2.22	2.72	1.80
1	Gadoteridol	314	2.17	2.69	1.78
1	Difference	314	0.05	0.04	0.01
2	Gadobutrol	313	2.67	2.97	2.32
2	Gadoteridol	313	2.60	2.90	2.28
2	Difference	313	0.06	0.07	0.04
3	Gadobutrol	312	1.98	2.13	1.73
3	Gadoteridol	312	1.95	2.12	1.70
3	Difference	312	0.03	0.01	0.03
Average	Gadobutrol	315	2.28	2.60	1.94
Average	Gadoteridol	315	2.24	2.56	1.91
Average	Difference	315	0.04	0.04	0.03

Non-inferiority, (-0.35) of gadobutrol to gadoteridol was proven for the three lesion visualization parameters, for all 3 blinded readers and for the average reader:

- Mean score average reader contrast enhancement: 95% confidence intervals for the difference in scores (.004, 0.078)
- Mean score average reader border delineation: 95% confidence intervals for the difference in scores (-0.009, 0.082)
- Mean score average reader internal morphology: 95% confidence intervals for the difference in scores, (-0.006, 0.059)

The mean number of lesions, the fourth efficacy variable, was 8.25 for gadobutrol and 8.24 for gadoteridol. However, as mentioned in section 6.1.4 the variability for reader 2 was higher than for the other two readers which resulted in higher than expected variability for the average reader which upon analysis yielded 95% confidence intervals of (-0.601, 0.622). When a nonparametric analysis was performed for this variable, for the average reader the number of lesions detected was equal for the two modalities for 25.0% of subjects, higher for gadobutrol in 41.7% of subjects, and higher for gadoteridol in 33.3% of subjects. Using this analysis, the difference between gadobutrol and gadoteridol was 8.3% with a 95% confidence interval of (-0.9%, 17.6%), thus meeting the pre-specified non-inferiority margin of -10% for the categorical variables for the average reader as well as for all three blinded readers.

Reviewer's Comment: For study 310124, analyses of the exact match determination and malignant vs non-malignant diagnosis are the result of repeat analyses using blinder readers re-revaluations of "other" diagnoses. According to the applicant, when

analysis was initiated, the "other" diagnosis was incorrectly used. Blinded readers, investigators, and the truth committee were re-trained on the use of this diagnosis and images with this diagnosis were re-read, maintaining the blind for the blinded readers. The submission contains tables of results from both analyses. In general, overall findings are similar.

Secondary objectives of the phase 2 study 308200 included the following:
- To evaluate the proportion of all enhanced lesions detected and matched.
- To evaluate the proportion of all lesions detected and matched with gadobutrol MRI.
- To evaluate quantitative and qualitative parameters of perfusion MRI.
- To evaluate/describe the alteration of perfusion parameters in CNS lesions and in particular that this was associated with different tumor grades of malignancy and to determine the usefulness of these parameters for evaluation of tumor grades.
- To evaluate the CNR of lesion/gray matter and lesion/white matter with gadobutrol perfusion MRI.
- To evaluate diagnosis and confidence in diagnosis.

Each subject in this study received three MRI exams, (unenhanced MRI, gadobutrol-enhanced MRI [perfusion and steady state images], and comparator-enhanced MRI [steady state MRI only]). Blinded readers evaluated the contrast to noise ratio (CNR) in white and gray matter and the blood volume, time, and permeability factors for purposes of the secondary analyses. Factors were compared to histopathology where applicable. An independent radiologist (lesion tracker) matched lesions throughout the different imaging sequences. The results of the analyses of secondary variables provided variable support of the results of the primary efficacy analysis.

For one of the blinded readers, there was a statistically significant difference between the low and standard dose (p = 0.03) and between the standard and high doses (p = 0.02) in favor of the 0.1 mmol/kg dose with respect to accuracy comparison of low-standard gadobutrol doses (0.03 mmol/kg and 0.1 mmol/kg) and the accuracy comparison of the standard-high gadobutrol doses (0.1 mmol/kg and 0.3 mmol/kg) using detection of all matched lesions. For the other 2 blinded readers, there was no significant difference in detection accuracy between either dose pair.

Accuracy comparison of the low-standard gadobutrol dose compared to the standard-high gadobutrol dose using detection of enhanced matched lesions was also tested. Two of the three blinded readers (readers 1 and 3 for the low-standard dose and readers 1 and 2 for the standard-high dose) demonstrated a statistically significant difference between the low and standard doses (p = 0.02) and between the standard and high doses (p = 0.02 and p = 0.04) in favor of the standard (0.01mmol/kg) dose.

Perfusion maps were generated for the gadobutrol-enhanced images only. Quality of the maps was assessed by 3 blinded readers and presented by dose group using summary statistics and distribution frequencies. Overall, there was little difference among the three dose groups. Dose patterns were variable. Evaluation of the summary of perfusion map artifacts demonstrated no obvious pattern with regard to dose group and the type of artifacts noted.

To correlate the information obtained by perfusion imaging/maps for lesions, blinded readers gave their estimation of the tumor grade on a 4 point scale. This information was collected separately for each of the perfusion variables/maps, i.e with MRI tumor grade a consensus of 6 perfusion maps. For purposes of identifying the location of the lesion(s), the unenhanced T2-weighted images were simultaneously displayed. There was little difference between the 0.03 and 0.1 mmol/kg dose groups with regard to percent agreement between tumor grade and biopsy results, (40.0% to 60.0% for 0.03 mmol/kg and 42.9% to 57.1% for 0.1 mmol/kg). The percent agreement in the 0.03 mmol/kg dose was lower, (30.0% to 40.0%).

The six perfusion imaging maps were also used for evaluation of contrast to noise ratio (CNR) for lesion/gray matter and lesion/white matter. Mean CNR values generated for each dose level demonstrated a statistically significant difference in mean values for the CNR of white matter for the 0.03 mmol/kg group and for the 0.01 mmol/kg group. There was no statistically significant difference between the 0.1 and 0.3 mmol/kg doses and there was no difference between dose pairs for gray matter.
The comparison of the correct diagnosis following gadobutrol-enhanced and unenhanced MRI was summarized for the 3 blinded readers and the average reader. For the average reader, the percent agreement between gadobutrol enhancement and the final diagnosis was 54.2%, 57.1%, and 62.3% for the 0.3, 0.1, and 0.03 mmol/kg dose groups, respectively compared with 53.6%, 45.8%, and 51.9%, respectively for the unenhanced images. The greatest improvement in making the correct diagnosis was for the 0.1 mmol/kg dose group, (11.3%).

Diagnostic confidence was similar across all dose groups with results from individual readers consistent with the average reader.

6.1.6   Other Endpoints

- Confidence in Diagnosis (310123 & 310124): On a 4-point scale, there was a statistically significant increase (P<0.0001) for the average reader comparison between the unenhanced and combined unenhanced/enhanced diagnoses
- Image Quality (310123): Mean scores on a 5-point scale, (gadobutrol image was worse to gadobutrol image was better) demonstrated values statistically different from 0 value or no change (P< 0.0001 for each reader) indicating readers found

the gadobutrol images to be of significantly higher quality than the unenhanced images
- Contrast-Enhanced Lesions (310123): Assessment of the number of contrast-enhanced lesions seen with gadobutrol and gadoteridol done by two additional readers, show the mean number of lesions was 1.73 for both gadobutrol and gadoteridol (95% CI [0.117, 0.111])
- Signal Intensity (310123): Contrast to noise ratio determined by an additional blinded reader demonstrated consistent values between gadobutrol and gadoteridol with lesion enhancement 80.1% for gadobutrol and 77.7% for gadoteridol and CNR 38.0 for gadobutrol and 36.4 for gadoterodol

Results of investigators' analyses were generally similar to those of the blinded readers.

Comparison and Analyses of Results Across Studies and in Subpopulations:

Key demographic variables for the two US phase 3 studies and for the US phase 2 study are summarized in the table below.

Table 22:   US IND Studies; Demographic Variables

		Study 308200 N = 68	Study 310123 N = 336	Study 310124 N = 321	Total N = 725
Sex	Male Female	27 (39.7%) 41 (60.3%)	144 (42.9%) 192 (57.1%)	135 (42.1%) 186 (57.9%)	306 (42.2%) 419 (57.8%)
Age	18- <45 years 45- <65 years 60- 80 years ≥ 80 years	30 (44.1%) 40 (44.1%) 8 (11.8%) 0	122 (36.3%) 139 (41.4%) 70 (20.8%) 5 (1.5%)	139 (43.3%) 136 (42.4%) 44 (13.7%) 2 (0.6%)	291 (40.1%) 305 (42.1%) 122 (16.8%) 7 (1.0%)
Race	Caucasian Black Hispanic Asian Other*	34 (50.0%) 5 (7.4%) 4 (5.9%0 1 (1.5%) 24 (35.3%)	192 (57.1%0 21 (6.3%) 25 (7.4%) 97 (28.95) 1 (0.3%)	61 (19.0%0 8 (2.5%0 82 (25.5%) 152 (47.4%) 18 (5.6%)	287 (39.6%) 34 (4.7%0 111 (15.3%) 250 (34.3%) 43 (5.9%)
Weight	<60 kg 60 kg – 90 kg	10 (14.7%) 48 (70.6%0	106 (31.5%0 163 (48.5%)	99 (30.8%) 192 (59.8%)	215 (29.7%)

	≥90 kg	10 (14.7%)	67 (19.9%)	30 (9.3%)	403 (55.6%) 107 (14.8%)
Region	Europe US/Canada S/Cen Amer. Asia Australia	0 22 (32.4%) 46 (67.6%) 0 0	101 (30.0%) 107 (31.8%) 27 (8.0%) 94 (28.0%) 7 (2.1%)	0 52 (16.2%) 119 (37.1%) 150 (46.7%) 0	101 (13.9%) 181 (25.0%) 192 (26.5%) 244 (33.7%) 7 (1.0%)

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

Adequate comparability of the three US IND studies can be concluded with regards to their subjects'demographics.

- For all 3 studies, slightly more females than males were included.
- 82.2% of subjects were between 18 and <65 years and 17.8% were age 65 or olde with a similar pattern for each individual study.
- The racial distribution of subjects was compatible with the region of study recruitment.

The data from the efficacy pool E1 (consisting of study 308200, study 310123, and study 310124 subjects as per the above demographic table) were used to perform subgroup analyses for the four primary efficacy variables (contrast enhancement, border delineation, internal morphology, and number of lesions). Subgroup analyses were performed for sex, age (as per the above table), and race. Additional subgroup analyses were performed for malignancy, (with malignant diagnosis and without malignant diagnosis), and for lesion type, (with primary brain tumor and without primary brain tumor). The subgroup analyses did not reveal any clinically relevant pattern.

Analysis of Clinical Information Relevant to Dosing Recommendations

Information relevant for dosing recommendations of gadobutrol 1.0 M originates from the following studies:

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

- Study 95062 which assessed the pharmacokinetics of gadobutrol 1.0 M in renally impaired patients and demonstrated that renal impairment does not affect the pharmacokinetics of gadobutrol 1.0 M after injection of doses up to 0.3 mmol/kg.
- Study 310788 that assessed the pharmacokinetics of gadobutrol 1.0 M in pediatric patients and demonstrated that BW-adjusted dose proposed for adults is also appropriate for pediatric patients aged 2 to 17 years.

Special Populations

Safety and pharmacokinetics of gadobutrol after a single i.v. bolus administration of 0.1 mmol/kg bw was studied in a group of healthy volunteers (males and females ages 18 to 45 years) and in elderly male and female subjects ≥65 years, study 308183, report A40982). Results of previous pharmacokinetic analysis have indicated that the pharmacokinetics are dose-proportional for gadobutrol injection and that they can be described by an open two-compartment model. Following injection, the compound is distributed predominantly in the extra cellular space. Renal clearance is almost identical to total clearance according to glomerular filtration rate. The terminal half-life in plasma is 1.7-2 hours. About 98% of the dose is excreted renally. There are no metabolic products or biotransformations. Gadobutrol has neglibible plasma protein binding and has no effect on zinc or iron metabolism. The purpose of this study was to evaluate the influence of age and gender on the pharmacokinetics of gadobutrol at the routinely administered clinical dose (0.1 mmol/kg body weight) in order to complete the clinical pharmacology information for the package insert of gadobutrol. Additional determination of urine zinc and other metals in 24-hour urine was performed to complete safety data with regard to the complex stability of gadobutrol.

Following i.v.bolus injection of 0.1 mmol/kg gadobutrol, plasma concentrations of gadobutrol decreased rapidly with urinary excretion almost completed 12 hours after injection. The study found no notable differences between the groups. Studies of plasma clearance for the groups noted a moderate effect for the volunteer's age with clearance reduced by approximately 25% and 35% in elderly men and women respectively as compared with non-elderly subjects paralleled with an increase in systemic exposure, (33% and 58% respectively). Gender had no effect on total clearance but there was a slightly higher area under the plasma concentration time curve (AUC) for elderly women.

The applicant provided summary information regarding hepatic impairment based on previous pharmacokinetic studies using a single intravenous dose of gadobutrol in healthy volunteers. This included noting the following points:
- Pharmacokinetics of gadobutrol were linear in the dose range studied to include the proposed dose with serum concentrations and AUC increased dose-proportionally within the range.
- Gadobutrol distributed predominantly in the extracellular space.

- Renal clearance was attributed mainly to glomerular filtration, similar to creatinine clearance, with urinary elimination almost complete 12 hours after administration.
- Fecal excretion was measured in only one study in which it was 0.03-0.06% of the injected dose.
- Gadobutrol is not metabolized as demonstrated by the lack of gadolinium containing compounds in the plasma.
- A hepatic impairment study was not conducted (as agreed upon by the Division prior to submission of the NDA). Safety results based on liver function tests revealed no difference in safety between subjects with or without abnormal liver function test values.

Study 95062 (report B245) was a dedicated study on renal impairment and dialysability. 32 patients were equally distributed in three groups of different stages of renal impairment as defined by serum creatinine clearance: (1) moderate impairment of creatinine clearance, (clearance <80 and >30 mL/min); (2) severe impairment (clearance <30 mL/min) and; (3) requiring dialysis. Patients randomly received 0.1 or 0.3 mmol/kg bw doses. Sampling times were 6 hours, 24 hours, 48 hours, and 72 hours for all groups with additional sampling at 96 hours and 120 hours for group 3. No dose differences were found.

Four out of 21 patients in groups 1 and 2 demonstrated clinically relevant changes in creatinine clearance which for 2 cases represented a worsening of renal function. None of the changes were considered related to gadobutrol administration, but rather to the underlying diseases or to other causes. Glomerular filtration markers (creatinine, cystatin C, and β2-microglobulin) demonstrated a clinically significant increase in creatinine for one patient but no changes in the markers otherwise. There were no clinically relevant changes in urinary total protein or in microglobulin.One patient had a clinically significant change in α1-microglobulin and N-acetyl-β-D-glucosaminidase attributed to the patient's significant disease.

The conclusion, thus, was that there was no influence of gadobutrol on renal function in patients with moderate or severe chronic renal impairment. Decreased clearance of gadobutrol was associated with increasing renal impairment. In the group of patients with severe renal impairment, the maximum elimination half-lives were 23 hours for the 0.1 mmol/kg bw dose and 44.3 hours for the 0.3 mmol.kg bw dose. In patients with mild renal impairment, regardless of dose, the recovery of gadobutrol in urine was complete within 72 hours. In patients with severe renal impairment, recovery was not complete within the study period of 120 hours. In the group of patients with chronic hemodialysis, it was demonstrated that gadobutrol can be eliminated from the body via dialysis with more than 95% of the dose eliminated after three routine dialysis cycles.

The conclusion from the study of renally impaired patients was that while elimination was prolonged, no dosage adjustments were necessary.

Reviewer's Comment: Although more than 94% of gadobutrol dose may be eliminated after 3 dialysis sessions, recovery of gadobutrol in the urine of patients with severe renal impairment was incomplete within the study period of 120 hours. The applicant did not indicate any effect on efficacy in this patient group. Therefore, although efficacious, gadobutrol should be used with caution in renally impaired patients

Pediatric Patients

Study 310788 in pediatric patients, ages 2-17 years, was a PK study that confirmed similar pharmacokinetics in the pediatric population as in the adult population and concluded that the 0.1mmol/kg bw dose was appropriate for this population. This study is further discussd below, in section 6.1.10.

Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence of efficacy and/or tolerance effects are not applicable to gadobutrol, a single dose imaging compound.

6.1.10   Additional Efficacy Issues/Analyses

<u>Pooled Efficacy Analyses</u>

Pooled efficacy analyses (post hoc analyses) were performed using two data pools. The first data pool, designated E1 was comprised of all FAS subjects in the phase 3 pivotal studies, (310123 and 310124) and all FAS subjects in the phase 2 "covered" study, (308200).

Efficacy Pool E1 (Studies 308200, 310123, and 310124) was used to analyze the four primary efficacy variables, (contrast enhancement, border delineation, internal morphology, and number of lesions), on a post hoc basis. Since the results of the individual studies were consistent with each other, the results for the pooled analyses are reflective of the findings from the individual studies.

For contrast enhancement, border delineation, and internal morphology, the combined unenhanced/enhancd image set showed higher scores for the variables than the unenhanced image set alone. The 95% confidence intervals for the difference between both values did not include the value zero, thus demonstrating a statistically significant treatment effect. For the number of lesions, the mean difference was in favor of the combined image set although the 95% confidence intervals did include the value zero. The results of this pooled analysis are presented in Table 23.

Table 23: Pooled Analyses (Pool E1): Primary Efficacy Variables

	Number of Subjects	Image Set	Mean and Standard Deviation	95% CI Limits
Contrast Enhancement	695	Unenhanced Combined Difference	0.99 0.00 2.47 0.02 1.51 0.03	 1.465, 1.563
Border Delineation	695	Unenhanced Combined Difference	1.98 0.01 2.70 0.02 0.74 0.02	 0.696, 0.785
Internal Morphology	695	Unenhanced Combined Difference	1.14 0.01 2.08 0.02 0.68 0.02	 0.647, 0.718
Number of Lesions	725	Unenhanced Combined Difference	3.87 0.30 4.46 0.31 0.21 0.14	 -0.062, 0.482

Efficacy Pool E2 (Studies 310123 and 310123) was created for purposes of a post hoc analysis of the two secondary efficacy variables "sensitivity and specificity for the presence/absence of a malignancy" and "exact match of the MR diagnoses with the final clinical diagnosis."   As was the case for the primary variables, the results from the individual phase 3 studies were also consistent with each other with regard to these two secondary efficacy variables. Thus, results of the pooled analysis as summarized in Table 24 for the blinded readers' majority read provided results similar to the individual studies. As for the individual studies, sensitivity for the presence/absence of malignancy substantially increased from the unenhanced to the combined image set resulting in a statistically significant effect and there was little change in the specificity between image sets. As a result, the accuracy value increased but to a lesser extent nonetheless demonstrating a statistically significant effect. The majority read for exact match of the MR diagnoses with the final clinical diagnosis was also statistically significant when the unenhanced image set was compared to the combined image set.

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**Table 24: Pooled Analyses (E2): Secondary Efficacy Variables-
Presence/Absence of a Malignancy and Exact Match of The MR Diagnoses With
The Final Clinical Diagnosis**

		Unenhanced	Combined Unenhanced + Gadobutrol-Enhanced	Differ-ence	95% CI Limit
Presence/Absence of a Malignancy	Sensitivity Specificity Accuracy	51.3% 93.7% 81.7%	71.2% 94.0% 87.5%	19.9% 0.3% 3.2%	12.7, 27.1 -1.8, 2.3 3.2, 8.4
Exact Match of MR Diagnoses vs Final Clinical Diagnosis		55.0%	62.8%	7.8%	4.5, 11.1

Pediatric PK Study (Protocol 310788/Study Report A43735)

This was an open-label multi-center study of magnetic resonance imaging (MRI) with 0.1 mmol/kg gadobutrol to assess pharmacokinetics, safety, and tolerability in children. Studies were performed at 14 centers in 4 countries. Subjects were referred for MRI of the brain, spine, liver, or kidneys or for MRA. There were 138 subjects in the FAS (46 subjects ages 2-6 years, 44 patients ages 7-11 years, and 48 patients ages 12-17 years). The PPS group consisted of 135 subjects (45, 42, and 48 subjects respectively). There were 130 subjects in the final PK analysis (45, 39, and 46 subjects). Gadobutrol 0.1 mmol/kg BW was administered at a flow rate of 0.8 to 3 mL/sec and was followed by a saline flush of at least 10mL at the same injection rate.

The clinical investigator assessed the images for quality and impact on patient management. Overall image quality post contrast administration was assessed as good or excellent for 97 % of subjects, (100% for the 2-6 years and 7-11 years groups and 93.85 for the 12-17 years group). Images of 53.6% of the 138 subjects in the FAS demonstrated a pathology on the pre-contrast, (unenhanced), images. 55.8% demonstrated a pathology on post contrast, (enhanced), images. There were 119 lesions seen on pre-contrast images and 122 lesions seen on post contrast images. Most lesions were present on both image sets. Some lesions were visible on post contrast images only. Some lesions present on pre-contrast images could be excluded after contrast administration. There were no differences noted for age.

Contrast enhancement following gadobutrol administration was judged to be good or excellent in 55, (45.1%) of the 122 lesions. For 4.9% of the lesions, contrast enhancement was moderate and no contrast enhancement was seen in 45.9% of the lesions due to the nature of the lesions. For 4.1% of lesions, this assessment was not applicable. The overall conclusion based on contrast enhancement of lesions was that there was a good efficacy of gadobutrol, based on the spectrum of diseases which included lesions for which contrast enhancement was not expected.

Diagnostic confidence improved in 91.3% of subjects. For this set of subjects, improvement was good or excellent for 64.3%, moderate for 33.3%, and minimal for 2.4%.   There were no differences noted for age.

The investigator assessed internal morphology (lesion characterization) on a 4-point scale, (good, moderate, poor, or not applicable).   For the majority of lesions, characterization was assessed as good, (78.2% pre-contrast and 80.3% post contrast). One subject in the 12-17 years old group had an increase in the number of lesions poorly characterized post contrast, felt to be secondary to the diagnosis of aspergillus infection.

MR diagnosis was compared to the final diagnosis which was obtained within 4 weeks after the MR procedure on the basis of all available information. 98.6% of subjects' diagnoses were in agreement. The results of the MR examination led either to the confirmation of or a better specification of the referral diagnosis or allowed the exclusion of certain pathology and thus positively influenced patient management.

As noted above, there was a positive influence on patient management for 98.6% of subjects. For 86.2% of subjects, no change in patient management was necessary. Management was changed due to the MR diagnosis for 13.0% of the subjects, i.e. alteration of therapy or follow-up schedules were changed.

The primary objective of the PK study was to evaluate the pharmacokinetics of gadobutrol in the pediatric population aged 2-17 years. The aims of the population PK analysis were: to define a structural PK model for gadobutrol by using gadolinium plasma concentrations; to characterize the inter-individual variabiiity in the derived PK parameters of gadobutrol in this specific population; and, if appropriate, to evaluate possible covariates influencing the PK of gadobutrol in the pediatric population. A total of 4 blood samples were taken from each patient-1 pre contrast injection and 3 post injection. Body weight was used as the major covariate to scale the PK parameters, total body clearance and central volume of distribution. In addition to body weight, estimated glomerular filtration rate normalized to 1.73 m^2 body surface area, had a significant impact on gadobutrol clearance. Age was not found to be an additional independent parameter affecting the pharmacokinetics of gadobutrol in the pediatric population.

The conclusion from the PK study was that in the pediatric population, the pharmacokinetics of gadobutrol were best described using a two-compartment model with elimination from the central compartment. PK parameters such as total body clearance, area under the curve, and volume of distribution at a steady state increased with increasing body weight and thus, on average, with age. The observed differences in pharmacokinetic parameters among children aged 2 to 6 years compared to adolescents 12 to 17 years are minor due to the non-linear relationship between weight and clearance. Based on the final population PK model, applying differences in body weight showed minor differences in median gadolinium plasma concentrations within 20 and 30 minutes, respectively. Thus, comparable plasma gadolinium concentrations within the time window relevant for MRI are predicted to be achieved with body weight-based dosing in the pediatric population aged 2 to 17 years.

Overall reviewer comment regarding efficacy:

 When unenhanced images were compared to combined unenhanced + gadobutrol-enhanced images, the applicant met the primary endpoint of superiority of the combined image set for 3 vizualization variables, (contrast enhancement, border delineation, and internal morphology) and non-inferiority for the number of lesions as based on a pre-specified statistical analysis plan. The applicant also met the pre-specified secondary endpoints of non-inferiority to a comparator, (gadoteridol) and met the secondary endpoints of increased accuracy of exact match for MR diagnoses and increased accuracy for diagnosis of presence/absence of malignancy, and determination of normal/abnormal brain tissue thus confirming clinical utility of this product in the intended patient population. The PK study confirmed comparable dose of gadobutrol according to body weight in the pediatric population ages 2-17 years.

7 Review of Safety

Safety Summary

The Integrated Summary of Safety presented by the applicant considered all phase 1-4 studies in which subjects received gadobutrol as an 0.5 M or 1.0 M concentration IV injection, placebo, (normal saline), or one of four comparator gadolinium based contrast agents. The total number of studies, the number of subjects enrolled and treated, and the number of subject treatments considered in the summary is reflected in Table 25. Safety analyses were performed for two pools: the S1 pool which consisted of all phase one studies with administration of gadobutrol and placebo and the S2 pool which consisted of all phase 2-4 studies to include the crossover studies.

Table 25: Number of Studies, Subjects Enrolled, Subject Treatments by Phase

Study Phase	Number of Studies	Subjects Enrolled and Treated	Subject Treatments*
All gadobutrol studies	9	313	313
Placebo-controlled studies	6	262	262
Total phase 1	**9**	**313**	**313**
Gadobutrol			
Phase 2	13	1326	1326
Phase 3	20	3174	3174
Phase 4	1	49	49
Total	**34**	**4549**	**4549**
Gadobutrol/Comparator			
Phase 2	13	1333	1715
Phase 3	20	4163	4629
Phase 4	1	49	49
Total	**34**	**5545**	**6393**

* Number reflects subjects from 4 crossover studies analyzed by period

Phase 1
In nine phase 1 studies, a total of 313 subjects received gadobutrol, either 0.5 M or 1.0 M, at doses between ≤0.11 and >1.51 mmol/kg bw. The trials originated in Europe, (N = 196 subjects), Japan, (N = 56 subjects), and the US, (N = 61 subjects).

A total of 68 subjects in the phase 1 studies received placebo. Adverse events were judged by the investigator as possibly, probably, or definitely related to study treatment. The reported incidence of all AEs was 35.6%, (69 out of 194 subjects with at least one related AE). Of the 91 subjects reporting 196 AEs in the gadobutrol group, 111 AEs in 69 subjects were considered to be related to the injection of gadobutrol. There was one study drug related SAE, (anaphylactoid reaction). A second subject experienced a mild intensity reaction consisting of sneezing and urticaria. There were no deaths.

By system organ class, (SOC), the highest incidence of AEs in the gadobutrol group were in the central nervous system disorders, (52 subjects, 26.8%), general disorders and administration sites, (46 subjects, 23.8%), and gastrointestinal disorders, (21 subjects, 10.8%). The most frequently reported AEs in the gadobutrol group were dysguesia, (11.9%), nausea, (7.2%), parosmia, (6.7%). headache, (6.2%), feeling hot, (5.2%), and injection site coldness, (4.1%). Drug related AEs for gadobutrol were similar-dysguesia (11.9%), parosmia (6.7%), nausea (6.2%), feeling hot (5.2%) and coldness at injection site (4.1%).

88.3% of AEs in the gadobutrol group were judged to be of mild or moderate intensity and 7.7%, (15), were considered severe. Severe AEs by preferred term, (PT), were dry lip, dry mouth, nausea, asthenia, catheter site pain, chest discomfort, fatigue, pain, thirst, back pain, dysguesia, parosmia, nasal congestion, and thrombophlebitis, experienced by 2 subjects, (1.0%) in the gadobutrol group as versus 1 subject, (1.5%), in the placebo group. For the two gadobutrol subjects with thrombophlebitis, one subject was considered to have moderate intensity, the other severe. For the placebo group, the intensity was moderate. Percentage incidence is based on two subjects in the gadobutrol group and one subject in the placebo group.

Table 26 summarizes the incidence of all AEs and the incidence of drug related AEs for the S1 pool, (phase 1) studies.

Table 26: Incidence of Adverse Events S1 Pool (Phase 1), Gadobutrol Vs Placebo

Parameter	Gadobutrol 0.5 M + 1.0 M	Placebo	Total
AEs	160	40	236
Not Related	55 (43.4%)	28 (70.0%)	113 (47.9%)
Related	111 (56.6%)	12 (30.0%)	123 (52.1%)

The applicant concluded and this reviewer agreed that drug related AEs stratified by baseline characteristics, special populations, and demographics included the following:
- Two subjects, (1.0%) reported allergic reaction within 24 hours after injection of gadobutrol, of which one was classified as an anaphylactoid reaction and the other was a hypersensitivity reaction of mild intensity and short duration, (sneezing and urticaria).
- No gadobutrol related changes in renal function were observed in the phase 1 studies in 169 subjects exposed to doses between 0.04 and 1.5 mmol/kg body weight.
- No analysis was performed for hepatic impairment due to the small sample size.
- No analysis was performed for cardiovascular disorders due to the small sample size.
- Analysis of AEs based on race revealed no significant differences in incidence rates or severity. Healthy Japanese volunteers showed similar PK parameters to those in the Caucasian population.
- Age had a moderate effect on the pharmacokinetics of gadobutrol in plasma with reduced plasma clearance, (increase in systemic exposure) and in half life in the elderly >65 years.

- Gender generally had no effect on the pharmacokinetics of gadobutrol except in elderly women where a slightly higher area under the curve (AUC) and a lower clearance were observed.

Phase 2-4

The data for adverse drug reactions for the phase 2-4 studies reflects the exposure of gadobutrol in 4549 subjects in 34 studies, (4411 adults and 138 children aged 2 to 17 years), who received a dose from <0.09 to 0.51 mmol/kg bw. The majority of subjects, (2434), received the recommended dose of 0.1 (±0.01) mmol/kg bw. Overall, 58.5% of subjects were male. The ethnic distribution was 64.8% Caucasian, 27.3% Asian, 3.0% Hispanic, 1.3% Black, and 3.6% of other ethnic groups. The average age was 54.2 years with an age range of 2 to 93 years.

For the phase 2-4 studies, 480, (10.6%), of 4549 subjects experienced a total of 716 AEs. 182 subjects, (4%), reported 240 AEs which were classified as related to the study drug. A total of 21 subjects experienced SAEs, 17 (0.4% of 4549) of which were in the gadobutrol group. Only one of these, (crystallized urine in a pediatric subject), was considered by the investigator to be related to gadobutrol. Two deaths were reported, one in the gadobutrol group, not classified as drug related. Overall, the rate and severity of AEs was comparable in the studies for all three phases and did not identify a specific safety concern.

By system organ class, (SOC), the highest incidence of AEs in the gadobutrol group were in the central nervous system disorders, (92 subjects, 2.0%), gastrointestinal disorders, (56 subjects, 1.2%), and general disorders and administration sites, (24 subjects, 0.5%). The most frequently reported AEs in the gadobutrol group were headache, (1.5%), nausea, (1.2%), feeling hot, and dysguesia, (0.5% each). Comparing drug related AEs to dose, the percentages were similar for four dose groups up to 0.31 mmol/kg body weight with 3.8% incidence at the proposed 0.1 mmol/kg dose, (stratified as >0.09-0.11 mmol/kg bw). Drug related AEs at the highest dose stratification (>0.3-0.51 mmol/kg bw), were reported at a 6.4% incidence however the total number of subjects in this group was considerably lower than in the other four dose groups.

Of the total AEs reported, (716), 95.4% were mild or moderate. 83.3% of drug related AEs were of mild intensity. There was no obvious difference in the intensity of AEs with increasing gadobutrol dose. Of the drug related 240 AEs, 32 were judged to be of severe intensity and were noted for the 1.0 M concentration. There were no severe intensity AEs for the 0.5 M concentration. By dose stratification 50.0%, (16), of the severe intensity AEs were for the >0.09-0.11 mmol/kg bw dose group which is the proposed product dose.

Table 27 lists all drug related AEs ≥0.1% incidence in the S2 (phase 2-4 studies) pool

Table 27: Incidence of Drug Related AEs ≥0.1% in S2 Pool (Phase2-4 Studies)*

Adverse drug reactions	Incidence (%)
Number of subjects	4549
Headache	1.5
Nausea	1.2
Injection site reaction (various kinds)[1]	0.6
Dysgeusia	0.5
Feeling hot	0.5
Dizziness	0.4
Vomiting	0.4
Rash (includes generalized, macular, popular, pruritic rash)	0.3
Pruritis (includes generalized pruritus)	0.2
Erythema	0.2
Dyspnoea	0.2
Paresthesia	0.1

[1] Injection site reactions (various kinds) comprise the following terms: Injection site extravasation, injection site burning, injection site coldness, injection site warmth, injection site erythema or rash, injection site pain, injection site hematoma (AEs coded by MedDRA, Version 12.1)

* Source: ISS Table 30

Summary results of the various safety parameters that were assessed for the phase 2-4 studies were as follows:

- Vital signs: No relevant or consistent changes in blood pressure or heart rate were noted irrespective of several stratifications performed.
- 42 subjects, (0.9%) in the gadobutrol group reported transitions from baseline physical exam, most one day post injection, no subjects with clinically abnormal findings.
- No significant effect of gadobutrol was detected for the QRS or PQ interval. The change in mean value in heart rate from 0 minutes to 1 day post injection ranged from -2.3 to 2.5 bpm.
- Laboratory data showed no remarkable fluctuations in the mean values of the single blood and urine parameters over the course of the study. For both gadobutrol and comparator drugs, there were instances of subjects' laboratory

values ≥2ULN and ≥3ULN which were less than 3.0% and 0.5% for blood parameters, respectively.
- Baseline characteristics and demographic analysis showed no effect of gadobutrol on the subgoups that were analyzed by the applicant. No substantial changes were noted in the pediatric population from baseline to follow up.
- Out of 38 subjects with eGFR<30 mL/min, 8 subjects reported 10 AEs. Of 328 subjects with eGFR 30 to <60 mL/min, 27 subjects reported 45 AEs. Based on Study Report 245 which was a dedicated study on renal impairment and dialysability, no influence of gadobutrol was found on renal function in subjects with severe or chronic renal impairment.

Reviewer Comment: Overall, there was no difference in the incidence or type of AEs in subjects who received gadobutrol at any of the evaluated doses. The safety profile and the specific AEs were similar to other agents in this class.

7.1 Methods

7.1.1   Studies/Clinical Trials Used to Evaluate Safety

Forty three clinical studies involving dosing of 4549 subjects with gadobutrol, (either 0.5 M or 1.0 M) and 996 subjects in crossover studies and global post-marketing information provide the data for this safety review. This includes administration to 4411 adult subjects and 138 pediatric subjects.

In addition to two phase-3, one phase-2, and one pediatric study submitted in support of the proposed indication, the following studies were performed: 17 phase 3 studies (5 studies using 0.5 M gadobutrol, 12 studies using 1.0 M gadobutrol), 12 phase 2 studies, and 7 phase 1 studies. 3547, approximately 78% of subjects that were studied, were injected with the 1.0 M gadobutrol concentration and 1002, approximately 22%, received the 0.5 M concentration.

One of the phase 1 studies, a thorough QT/QT_c study (study 307362), was performed using 1.0 M gadobutrol. Two special population studies were performed, a phase 1 study in the elderly (study 308183) and a phase 3 study in renally impaired subjects (study 95062), also using 1.0 M gadobutrol. One phase 4 supportive study that was submitted was also performed with 1.0 M gadobutrol.

The 4 "covered" clinical studies supporting the efficacy and safety of gadobutrol in the US include a phase 2 dose selection study, (study 308200), 2 pivotal phase 3 studies, (study 310123 and 310124), and a phase 1 pediatric pharmacokinetic (PK) study, (study 310788) in children ages 2-17 years.

The patient populations that participated in the above noted phase 2 and phase 3 studies consisted of subjects referred for contrast-enhanced MRI of the CNS based on clinical symptoms or results from a previous imaging procedure, (the phase 3 studies) or, for the phase 2 study, subjects with known or highly suspected focal blood brain barrier disturbances and/or abnormality of the central nervous system.   Referral for the pediatric PK study was for evaluation of any organ system or for MRA evaluation.

Including the pivotal phase 3 studies and the dose selection phase 2 study, the majority of phase 2-4 studies, (20), were performed for a CNS indication. 9 body studies, 5 MRA studies (including the pediatric study), and 1 myocardial perfusion study were also performed. Approximately 54% of subjects received the 0.1 mmol/kg bw dose.

The safety data was also evaluated according to subject pooling, (S1 or S2 pool, see section 7.1.3 below). Demographic data from the S1 pool (phase 1 studies) was evaluated for body weight and region. Demographic data from the S2 pool (phase 2-4 studies) was evaluated for sex, age, weight, height, race, and gadobutrol concentration, (0.5 M or 1.0 M). Tables 26 and 27 in section 7.2.1 contain listings of the studies by phase, study design, concentration and dose of gadobutrol, and subject demographics.

Most subjects received only one dose (exposure) of the drug.

7.1.2   Categorization of Adverse Events

Medical Dictionary for Regulatory Activities (MedDRA) Version 12.1 was used for categorization (coding) of adverse events.

7.1.3   Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Analysis of safety data included the following:
- Six individual studies, also a part of the integrated analysis pool: 4 "covered" clinical studies, (phase 3 pivotal studies 310123 and 310124), phase 2 dose selection study, (study 308200), and phase 1 pediatric pharmacokinetic study, (310788); age and gender study, (study 308183): and QT/QT$_c$ study, (study 307362)
- Integrated analysis pool S1: phase 1 studies
- Integrated analysis pool S2: phase 2-4 studies

Pooling of data for purposes of analysis (S1 and S2 pools) was done on a post hoc basis. Data used to create the S1 and S2 safety pools is contained in Table 28 below.

Table 28: Integrated Analysis Pools

Integrated Analysis Pools	Study Phase	Number of Studies	Subjects Enrolled and Treated	Subject Treatments**
S1 **Phase 1**	All gadobutrol studies	9	313	313
	All placebo-controlled studies (a subset of S1)	6	262	262
	Total	**9**	**313**	**313**
S2 **Phase 2** **to Phase 4**	**Gadobutrol** Phase 2	13	1326	1326
	Phase 3	20	3174	3174
	Phase 4	1	49	49
	Total	**34**	**4549**	**4549**
S2 **Phase 2** **to Phase 4**	**Gadobutrol/Comparator** Phase 2	13	1333	1715
	Phase 3	20	4163	4629
	Phase 4	1	49	49
	Total	**34**	**5545**	**6393**

*   Total S1 and S2 (all phases) = 43 studies

** Subjects from crossover studies (308200, 309762, 310123, 310864) were analyzed by period and therefore, the number of analyzed subjects based on subject treatments is higher than the number of enrolled subjects

The majority of studies in the two integrated analyses pools are for the CNS indication. The applicant noted that other indications such as lesions in other body regions were included in the pools as the safety risks were felt to be the same.

As may be seen in Table 28, the applicant created two analysis sets within the S1 integrated pool. The first analysis was for subjects in the 9 phase 1 studies who received only gadobutrol injection (313 subjects). The second analysis set was created to compare gadobutrol with placebo in the six placebo controlled studies, (262 subjects, 194 injected with gadobutrol compared with 68 injected with placebo).

This table shows how a similar division of the phase 2-4 studies was created and used for the analyses of safety. 5545 subjects were in the S2 pool, of which 4549 were treated with gadobutrol. Due to the cross-over design, subjects from studies 308200, 309762, 310123, and 310864 were analyzed by period and counted twice when they continued in the second period with another study drug. Subjects from cross-over study 94383 were counted only once because different gadobutrol doses were administered.

Thus, for the S2 pool, the total number of subjects analyzed, (6393), was greater than the number of subjects enrolled, (5545).

The integrated safety analysis was performed for each data pool. Two tables/listings were created for the S1 pool. The first set is for subjects who received gadobutrol only. Subjects in this group were assigned to the highest dose they received in any of the treatment periods in case of cross-over studies. All findings, thus, were assigned to that dose group. For the comparison of gadobutrol to placebo, only data from the first injection were integrated, (data from single or parallel design studies and data from the first period of cross-over). Subjects with a positive control as the first injection in cross-over studies were not considered in the pool and the three studies without a placebo arm were not integrated.

Two listings (versions) of the S2 pool were also created. The first presents the results by dose group. The second presents the results by study medication, (comparator dose groups). All cross-over periods were taken into account for analysis of the S2 pool.

All variables were analyzed by descriptive statistical methods. The number of data available and missing data, mean, standard deviation, minimum, quartiles, median, and maximum were calculated for metric data. Frequency tables with absolute and relative frequencies were generated for categorical data. All analyses were performed post-hoc and the applicant considered these analyses as purely explorative.

7.2 Adequacy of Safety Assessments

All subjects who received the study drug were included in the safety evaluations. 78.6%, (246 subjects), of subjects in the phase 1 studies received the 1.0 M injection. The majority of subjects received either the 0.5 M or the 1.0 M concentration at doses lower than 0.51 mmol/kg body weight. 38.3% of subjects received either concentration at doses from ≤0.11 - >0.11-0.21 mmol/kg bw. 3547 subjects, (78.0%), in the phase 2-4 studies received 1.0 M gadobutrol. The majority, (4122), of subject treatments with gadobutrol were in the dose range of 0.09 to 0.31 mmol/kg bw with 54% of them, (2434 treratments) at the 0.09 to 0.11 mmol/kg bw dose. Of subjects that received the proposed dose of >0.09 to 0.11 mmol/kg bw, 89.4% were enrolled in the phase 3 studies.

The studies were adequately designed and conducted. The safety assessments conducted and analyzed were complete and appropriate for this diagnostic agent.

The data was stratified by various factors such as age, race, country, and gender. The data was evaluated for predictive factors such as allergies, allergies to contrast, cardiovascular disorders, renal impairment, and hepatic impairment.

Most subjects received a single exposure of study drug. 5 phase 1 studies and 3 phase 2-4 studies were performed in subjects who received more than one injection and there were 3 phase 2-4 studies for which a single IV injection with additive dosing was used.

7.2.1   Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

4411 subjects exposed were adults >18 years of age most of whom who received a single administration of study drug. 996 adult subjects who participated in the comparator studies were exposed to an additional drug. 138 pediatric subjects were exposed to study drug. 78% of subjects received the proposed 1.0 M concentration of study drug although not necessarily for the proposed indication.

Phase 1
Table 29 presents a summary of the phase 1 study design, duration of treatment, and demographics for region, sex, and age. As noted in this table, there were 9 phase 1 studies. A total of 313 subjects received gadobutrol 0.5 M or 1.0 M. 78.6% of these subjects received the 1.0 M concentration at doses lower than 0.51 mmol/kg body weight.

Table 29: Overview of Completed Phase 1 Studies and Study Design With Number of Subjects, Region, Age, Sex, Race and Gadobutrol Concentration

Report No. Study No.	Region/ Country Study Date	Study Design	Gadobutrol 0.5 M and/or 1.0 M; Dose, (mmol/kg bw) No. of Subjects	Placebo (Saline) No. of Subjects	Age (years) Range (mean) Sex Race
A40982 308183//91 798	EU 8/08-1/09	4 parallel arms; separated by baseline characteristics	1.0 M 0.1 31	0	23-72 33.8-69.4 by demography M = 16 F = 15 Caucasian = 31
9746 92001	EU 3/92-6/92	2 parallel arms with gadobutrol & placebo at 5 dose levels	0.5 M 0.04, 0.1, 0.2, 0.3, 0.4; 40	15	21-39 31.0 M = 40 F = 0

					Caucasian = 40
9748 92010	EU 6/92-8/92	2 parallel arms with gadobutrol & placebo at 3 dose levels	1.0 M 0.3, 0.4, 0.5; 24	12	21-38 29.3 M = 24 F = 0 Race not recorded
AS29 93016	Japan 12/96-3/97	4 period crossover, different gadobutrol administration schemes	0.5 M 0.05, 0.1, 0.2, 0.4 24	8	20-34 22.3 M = 24 F = 0 Race not recorded
B534 96063	EU 12/96-3/97	4 period crossover, different gadobutrol administration schemes	0.5 M & 1.0M 0.05, 0.1, 0.2 20	0	21-44 24.2-28.4 by center M = 0 F = 20 Black = 2 Caucasian = 18
B000 97113	EU 10/98-2/99	2 parallel arms with gadobutrol at 6 dose levels & placebo	1.0 M 0.3, 0.5, 0.75 36	12	22-44 28.8-36.7 by treatment group M = 27 F = 18 Asian = 17 Caucasian = 28
B291* 98098	EU 10/98-11/98	2 period crossover with different gadobutrol concentrations	1.0M 1.25; 1.5; 2.0 45	0	22-45 32.8 M = 27 F = 18 Asian = 17 Caucasian = 28
A21381 307362	US (QT study) 3/04-6/04	5 period crossover with different gadobutrol doses and a positive control	1.0 M 0.1, 0.3, 0.5 61	13	19-60 34.2 M = 35 F = 29 Asian = 4 Hispanic = 2

					Black = 35 Caucasian = 22 Other = 1
A39759 310865	Japan 6/07-10/07	2 parallel arms with gadobutrol and placebo	1.0 M 0.1, 0.2, 0.3 32	8	20-34 25 M = 40 F = 0 Asian = 40
Total			313 subjects N = 84 (0.5 M) N = 249 (1.0 M) 20 subjects rec'd both concn's	68 subjects	

* Applicant considered this as a phase 2 study in the tabular listings for efficacy

The applicant summarized complete demographics, by dose, for the phase 1 studies, both for subjects that received gadobutrol and subjects that received placebo. Using data contained in Table 29 and data presented in Table 11, page 24 of the ISS, phase 1 study demographics for subjects that received gadobutrol are summarized as follows:

- 233, (74.4%) were males and 80, (25.6%) were females with the proportion of male subjects noted to be higher than that of female subjects for all dose groups of gadobutrol..
- The mean age and standard deviation of subjects in the gadobutrol group was 32.3 ± 10.8 years with 91% of subjects in the age range of 18 to < 45 years.
- The mean weight was 72.59 ± 13.5 kg.
- Mean height was 174.32 cm ± 9.50 cm.
- About half, (55.6%) of the subjects who received gadobutrol were Caucasian.
- The trials originated in Europe, (N = 196 subjects), Japan (N = 56 subjects), and the US, (N = 61 subjects)

As noted in the table, there were 6 placebo-controlled phase 1 studies, (N = 68 subjects). Using data from the above table and from Table 12, page 25 of the ISS subject demographics for placebo were as follows:

- 63, (92.6%) were males and 5, (7.4%) were females.
- The mean age and standard deviation of subjects was 28.8 ± 6.8 years with the majority of subjects, (97.1%) in the age range of 18 to < 45 years.
- The mean weight was 75.22 ± 12.44 kg.

- The mean height was 179.50 ± 8.80 cm.
- 30, (44.1%), of subjects who received placebo were Caucasian.

The demographics were appropriate for phase 1 studies and were comparable for subjects that received gadobutrol and subjects that received placebo. In addition to noting demographics for the gadobutrol and placebo groups, the applicant tabulated demographic variables, (sex, age, body weight, height, study region, and race) using 7 gadobutrol dose ranges, (0.11, >0.11-0.21, >0.21-0.31, >0.3100.51, >0.51-1.01, >1.01-1.51, and >1.51 mmol/kg). On review of these variables by dose group, this reviewer noted no relevant differences between the dose groups with regards to demographics.

Phase 2-4
As noted in Table 30 below which summarizes study design information and demographics, including the "covered" studies, (two pivotal phase 3 studies, one phase 2 dose selection study, and one pediatric PK study) there were 20 phase 3 studies (5 studies using 0.5 M gadobutrol, 12 studies using 1.0 M gadobutrol), 13 phase 2 studies, and one phase 4 study. By subject distribution the number of subject treatments in phase 2 was 29.1%, 1326), 69.8%, (3174), in phase 3, and 1.1%, (49), in the single phase 4 study. A total of 3547 subjects received gadobutrol 1.0 M and 1002 subjects received gadobutrol 0.5 M.

Table 30: Overview of Completed Phase 2-4 Studies With Number of Subjects, Region, Study Phase, Indication, and Gadobutrol Concentration

Report No. Study No.	Region/ Country Study Date	Gadobutrol 0.5 M and/or 1.0 M Dose, (mmol/kg bw)* No. of Subjects	Study Phase Study Design Indication	Age (years) Range (mean) Sex Race
AC86 92095	EU 1/93-9/93	0.5M 0.3 63	Phase 2 Single arm gadobutrol (additive doses) CNS (brain metastases)	20-83 59.6 M = 34 F = 30 Caucasian = 64
AC98 92096	EU 2/93-10/93	0.5 M 0.1, 0.2, 0.3 103	Phase 2 Single arm gadobutrol Body lesions	19-85 52.4 M = 30 F = 73 Caucasian = 102 Other = 1
AC42 92097	EU 1/93-10/93	0.5 M 0.3 47	Phase 2 Single arm gadobutrol (additive doses)l	21-76 52.4 M = 35

			CNS (primary brain tumors)	F = 12 Caucasian = 46 Asian = 1
AS30 93017	Japan 6/96-9/93	0.5 M 0.1 18	Phase 2 Single arm gadobutrol CNS (brain and spinal cord)	21-62 49 M = 8 F = 10 Race not recorded
AS31 93018	Japan 6/93-10-93	0.5 M 0.1 38	Phase 2 Single arm gadobutrol Body (body and extremity lesions)	23-75 54 M = 24 F = 14 Race not recorded
A169 94061	EU 1/95-11/95	1.0 M 0.1, 0.2, 0.3, 0.4, 0.5 89	Phase 2 Single arm gadobutrol CNS brain perfusion (CNSBP)	18-82 58.2-68.3 by center M = 65 F = 24 Caucasian = 89
B314 94369	Japan 6/94-3/95	0.5 M 0.3 62	Phase 2 Single arm gadobutrol (additive doses) CNS (metastatic brain tumor)	25-75 58.3 M = 42 F = 20 Race not recorded
B313 94383	Japan 11/94-6/95	0.5 M &1.0 M; 0.15 13	Phase 2 2 period crossover CNSBP	39-83 59.2 M = 9 F = 4 Race not recorded
B310 95364	Japan 3/96-3/97	0.5 M 0.05 or 0.1 39	Phase 2 2 parallel arms, different dose Body (renal disease)	25-79 60.9 M = 30 F = 9 Race not recorded
B204 97035	EU 11/98-1/99	1.0 M 0.05, 0.15, or 0.25 241	Phase 2 3 parallel arms, different doses MRA	29-85 62.3-63.8, mean ages for sexes M = 184 F = 57 Caucasian = 240 Black = 1
A22498 305501	EU 3/04-5/06	1.0 M 0.01, 0.025, 0.05, or .1 x 2 (stress,rest)	Phase2 Single arm gadobutrol Myocardial perfusion defects	29-83 59.7-62.9 by treatment group M = 156

		226		F = 70 Caucasian = 221 Asian = 3 Hispanic = 1 Other = 1
A40524 308200	US*** S. America 8/05-3/07	1.0 M 0.03, 0.1, 0.3 225 227 (comparator)****	Phase 2 Two period crossover with gadoversetamide CNS + BP	18-80 46.4 M = 100 F = 129 Caucasian = 104 Black = 18 Hispanic = 12 Asian = 12 Other = 93
A179 94052	EU 10/94- 10/95	0.5 M 0.1 155 140 (comparator)	Phase 3 Two parallel arms with gadobutrol and gadodiamide CNS (brain lesions)	19-86 52.6 M = 173 F = 132 Caucasian = 301 Black = 3 Asian = 1
A168 94054	EU 9/94-8/95	1.0 M 0.3 296	Phase 3 Single arm gadobutrol (additive doses) CNS (brain lesions)	17-89 50 Male + 161 F = 135 Caucasian = 244 Asian = 1 Unknown = 51 (not permitted to record)
A021140 94055	EU 11/95- 12/98	1.0 M 0.1 182	Phase 3 Single arm gadobutrol Body (lesions)	17-80 51.3 M = 111 F = 71 Caucasian = 179 Black = 2 Asian = 1
B315 94368	Japan 5/94-3/95	0.5 M 0.1 58 56 (comparator)	Phase 2/3 Two parallel arms with gadobutrol and gadopentate dimeglumine CNS (brain tumors)	20-70 Mean not provided M = 60 F = 54 Race not recorded
B245 95062	EU 10/96-2/98	1.0 M 0.3, 0.1	Phase 3 Two parallel arms	20-76 55.1

		32	with different gadobutrol doses (renal impairment or on dialysis) Body	M = 23 F = 9 Caucasian = 31 Asian = 1
AK76 95064	EU 1/96-6/96	1.0 M 0.3 44	Phase 3 Single arm gadobutrol CNSBP	29-81 63.3-63.8 (mean by sex only) M = 31 F = 13 Caucasian = 44
B311 95359	Japan 10/95-9/96	0.5 M 0.1 86 88 (comparator)	Phase 3 Double-blind comparison of gadobutrol to gadopentate dimeglumine Body (liver or pelvic disease)	25-80 58.6-59.9 (mean by sex only) M = 85 F = 89 Race not recorded
B312 95361	Japan 10/95-9/96	0.5 M 0.1 98 97 (comparator)	Phase 3 Single arm gadobutrol comparison to gadopentate dimeglumine CNS	20-82 52.3-53.9 (mean by sex only) M = 107 F = 88 Race not recorded
B309 95362	Japan 1/96-3/97	0.5 M 0.5 133	Phase 3 Single arm gadobutrol Body	21-80 57.3 M = 93 F = 40 Race not recorded
B308 95363	Japan 1/96-3/97	0.5 M 0.3 (additive doses) 100	Phase 3 Two parallel arms with different gadobutrol doses CNS (metastatic brain tumors)	33-78 59.3 M = 67 F = 33 Race not recorded
A04519 97099	EU 1/00-1/01	1.0 M 7.5/10.0mL (bw) 179	Phase 3 Single arm gadobutrol MRA	20-90 63.3 M = 133 F = 46 Caucasian = 179
A02885 302722	EU 2/00-10/00	1.0 M 15.0/20.0 mL(bw) 203	Phase 3 Single arm gadobutrol MRA	30-90 64.4 M = 139

				F = 64
				Caucasian = 201
				Black = 1
				Hispanic = 1
A04542 304300	EU 9/00-2/01	1.0 M 7.5, 10.0,15.0 or 20.0 mL (bw) 53	Phase 3 Single arm gadobutrol MRA (body and peripheral arteries)	21-85 55.2 M = 40 F = 13 Caucasian = 53
A18088 304561	EU 5/02-5/03	1.0 M 0.1; 233 233 (comparator)	Phase 3 2 parallel arms with gadobutrol and gadopentate dimeglumine Body (renal lesions)	18-90 62.1 M = 311 F = 155 Caucasians = 465 Black = 1
A13389 304562	EU 7/01-8/02	1.0 M 0.1; 292 280 (comparator)	Phase 3 2 parallel arms with gadobutrol and gadopentate dimeglumine Body (liver lesions)	21-93 58.9 M = 326 F = 246 Caucasian = 563 Hispanic = 5 Asian = 3 Other = 1
A40215 309761	China 9/06-4/07	1.0 M; 0.1 71 75 (comparator)	Phase 3 2 parallel arms with gadobutrol and gadopentate dimeglumine CNS (lesions)	18-68 43.4 M = 71 F = 75 Asian = 146
A40727 309762	China 10/06- 10/07	1.0 M 0.2-0.3/0.4-0.6 (comparator) 78 83 (comparator)	Phase 3 2 period crossover with gadobutrol and gadopentate dimeglumine MRA	19-77 53.1 M = 54 F = 29 Asian = 83
A47567 310123	US IND EU, S.America, Japan, Australia	1.0 M; 0.1; 399 392 (comparator)	Phase 3 Two period crossover with gadobutrol and gadoteridol CNS	18-84 50.8 M = 175 F = 277 Caucasian = 235 Asian = 112 Black = 23 Hispanic = 31 Other = 1

A47570 310124	US IND China, S.Korea. S.America	1.0 M 0.1 343	Phase 3 Single arm gadobutrol CNS	18-87 47.7 M = 146 F = 197 Asian = 161 Hispanic = 87 Caucasian = 68 Black = 9 Other = 18
A41119 310864	Japan 8/07-8/08	1.0 M 0.2 161 162 comparator	Phase 2/3 Two period crossover with gadobutrol and gadoteridol CNS (metastases)	27-88 61.7 M = 90 F = 74 Asian = 164
A40794 310788	EU/Can 5/07-4/08	1.0 M; 0.1 138	PK, phase 1/3 Single arm gadobutrol (children) MRA, CNS	2-17 19.2 M = 85 F = 53 Caucasian = 133 Black = 2 Asian = 1 Other = 2
A12063 302600	EU 8/00-9/02	1.0 M 0.2 (12 or 15 mL) 49	Phase 4 Single arm gadobutrol CNSBP(acute ischemic brain event)	39-85 62.4 M = 34 F = 15 Caucasian = 49
Total all studies	N = 4549	0.5 M, N=1002; 1.0 M, N= 3547 Pediatric (2-17 yrs.), N=138	Phase 1 ,N = 9 Phase 2-4, N = 34	

*   When doses were cumulative, e.g.0.1 mmol/kg + 0.1 mmol/kg (2 injections), the total dose is noted
**   Brain perfusion
*** Performed under US IND 56410; additional listing reflects study centers
****Comparator = other study drug (parallel arm or crossover)

The majority, (4122) of the 4549 subject treatments with gadobutrol were in the dose range of 0.09 to 0.31 mmol/kg body weight while most of them (2434 treatments) were at a 0.09 to 0.11 mmol/kg body weight dose. By concentration of gadobutrol, 78.0% of subjects were treated with 1.0 M and 22.0 % with 0.5 M gadobutrol. Using data contained in Table 30 and data presented in table 22, appendix 5, ISS, demographics for subjects that received gadobutrol in the phase 2-4 studies are summarized as follows:

- 2663, (58.5%) were males and 1886, (41.5%) were females with the proportion of male subjects who received either the 0.5 M or the 1.0 M concentration proportionally higher than female subjects.
- The mean age was 54.2 ± 15.6 years with 44.1% of subjects ages 45 to <65 years.
- Mean weight was 69.5 ± 17.0 kg with most subjects 60 to <90 kg.
- Mean height was 167.4 ± 12.3 cm.
- 64.8% were Caucasian and 27.3% were Asian
- The trials were performed in the EU, (N = 2745 subjects, 60.3%), Asia, (N = 1223 subjects, 26.9%), South/Central America, (N = 301 subjects, 6.8%), US/Canada, (N = 264 subjects, 5.8%), and Australia, (N = 9 subjects, 0.2%).

The applicant analyzed similar data for 5 dose categories--≤ 0.09 mmol/kg, >0.09-0.11 mmol/kg, >0.11-0.21 mmol/kg, >0.21-0.31 mmol/kg, and >0.31-0.51 mmol/kg. Comparison with the mean demographic data demonstrated mean values of all demographic characteristics were similar in all dose groups with the following comments by this reviewer:

- The proportion of male subjects was comparable except for the highest dose group which was composed of 72.3% male subjects.
- The distribution of subjects by age was comparable except in the highest dose group where 38.3% of subjects were ages 65- <80 compared to the mean for all doses which was 28.2%.
- Height and weight distributions were comparable.
- Study regions were similar, most in the EU followed by Asia, which apart from the>0.21-0.31 mmol/kg, and >0.31-0.51 mmol/kg. doses was reflected in subjects' races, (73.0% and 95.7% Caucasian, respectively).

As noted in Table 31, mean values of the demographic data for the phase 2-4 subjects that received gadobutrol were also generally similar to similar variables for the comparator drugs and to the studies as a whole, (6393 subject treatments with study drug and 4 comparator/reference drugs).

Table 31: Demographic Comparison Phase 2-4 Studies, Gadobutrol Vs Gadopentate Dimeglumine, Gadodiamide, Gadoversetamine, and Gadoteridol

Parameter	Gadobutrol (0.5 M + 1.0 M)	Gadopentate Dimeglumine Gadodiamide Gadoversetamine Gadoteridol	Comments
Number of Subjects	4549	1844	

Percent Male Subjects	58.5%	56.8%	Gadoversetamide, 44.1%; gadoteridol,46.8%; comparability otherwise
Mean Age	54.2 years	54.3 years	Gadoversetamide, 46.4 years; gadopentate dimeglumine, 57.4 years; comparability otherwise; similar mean
Mean Weight	69.5 kg Most subjects 60-<90 kg	69-72 kg	Gadoteridol, 40% in weight range, 44.7% < 60 kg, otherwise comparable; similar mean
Race	Caucasian, 64.8% Asian, 27.3%	Variable by study region	Gadoversetamide with greater number of Blacks, (7.9%) and with Other, (40.5%)
Study Country/Region	EU,60.3% Asia, 26.9% S/Central America, 6.8% US/Canada, 5.8%	EU, 55.3% and Asia, 29.6% overall with either region in first position ex. Gadoversetamide study	Gadoversetamide, 67.8% of studies conducted in South/Central America, 5.4% with gadoteridol US/Canada studies only for gadoversetamide and gadoteridol

In summary, the demographics for phase 2-4 studies for subjects who received gadobutrol or other ("comparator") drug were comparable for age and weight, proportionately similar for percentage of males in two of the "comparator" groups, and with subject race reflecting the country/region of study origin. The distribution of subjects by age category and dose of study drug show that the majority of subjects in the ≥18 to<80 year age range received >0.09 to 0.31 mmol/kg bw dose of gadobutrol

Explorations for Dose Response

Information relevant for dosing recommendations of gadobutrol 1.0 M originates from the following studies:

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

- Study 95062 which assessed the pharmacokinetics of gadobutrol 1.0 M in renally impaired patients and demonstrated that renal impairment does not affect the pharmacokinetics of gadobutrol 1.0 M after injection of doses up to 0.3 mmol/kg.
- Study 310788 that assessed the pharmacokinetics of gadobutrol 1.0 M in pediatric patients and demonstrated that BW-adjusted dose proposed for adults is also appropriate for pediatric patients aged 2 to 17 years.

The findings from study 308200 are described below. Study 95062 in the renally impaired population is contained in section 7.2.5 which describes the metabolic, clearance, and interaction work up. The findings from study 310788 are summarized in sections 7.3 under "covered" clinical studies.

Protocol 308200 (Study Report A40524) submitted as one of the four "covered" studies to support the clinical indication, was a phase 2 study performed under US IND and constituted the main dose selection study. Dose comparison was performed using three different doses of gadobutrol 1.0 M for the determination of safety and efficacy in subjects for central nervous system (CNS) imaging.

Safety results are summarized below, with dose frequencies as presented by the applicant:

- 79 (35.1%) of subjects in the gadobutrol group reported at least one AE; 52 (22.9%) of subjects in the comparator group reported at least one AE in the same time frame.
- Incidence of subjects with AEs was similar among dose groups, (36.8%, 36.7%, 31.3% for 0.3, 0.1, and 0.03 mmol/kg respectively).
- Most commonly reported AEs for gadobutrol were headache, (8.0%), dizziness, (2.2%), and nausea and diarrhea, (both 1.8%).
- Four subjects that received gadobutrol experienced severe intensity AEs; 2 subjects that received comparator experienced severe AEs.
- 22 (9.8%) of subjects experienced drug related AEs, (5-7.4%, 12-13.3%, and 5-7.5% in the 0.3, 0.1, and 0.03 mmol/kg dose groups respectively); 5.7% of subjects receiving comparator drug experienced drug related AEs
- Headache was the most common drug related AS, reported with similar frequency among groups, (2.9%, 3.3%, and 3.0% in the 0.3, 0.1, and 0.03 mmol/kg dose groups respectively).
- There were no deaths or discontinuations from the study due to an AE; one subject in the gadobutrol and one subject in comparator group experienced an SAE, not drug related.
- Mean changes in clinical chemistry and hematology parameters were not clinically relevant; one subject in each dose group experienced a change in clinical chemistry parameters, not drug related

- Vital sign changes showed no notable differences between dose groups and were not considered to be related to study drug.
- One subject in the 0.03 mmol/kg group had EKG change of ST segment depression; one subject had an increase (≥60 msec) in QT interval according to Fridericia's method.

7.2.3   Special Animal and/or In Vitro Testing

The results of the non-clinical studies indicate that gadobutrol is an effective agent for MRI. It was generally well tolerated in non-clinical pharmacology and toxicology studies and studies conducted on safety pharmacology did not yield results suggestive of concern for the proposed single use dose in humans.

Following intravenous injection, gadobutrol was rapidly distributed, primarily in the extracellular space, and was rapidly and almost exclusively eliminated in the urine. Dose proportional pharmacokinetics were observed in rats and in Beagle dogs with no metabolites detected in these species. There was minimal transplacental transference of radioactivity to rabbit fetuses and in maternal milk to nursing neonatal rats.

Single and repeated IV administrations of gadobutrol to mice, rats, and dogs were generally well tolerated with mild clinical signs noted such as hypoactivity in rats and vomiting and transient reddening of the skin of the ear or mucosal membranes immediately after administration to dogs. There was vacuolization of renal proximal tubular cells and upper tract urothelium with a trend to complete reversibility after daily (over 4 weeks) administration to rats and dogs without any evidence of impaired renal function.

Results in pediatrics and effects on embryo-fetal development are summarized in sections 7.6.2 and 7.6.3 of this document.

Overall, the non-clinical pharmacology, toxicology, and absorption, distribution, metabolism, and excretion studies conducted with gadobutrol did not yield any results of concern for single dose use in humans.

7.2.4   Routine Clinical Testing

The routine clinical testing of subjects was adequate.

7.2.5   Metabolic, Clearance, and Interaction Workup

During clinical development, both a compartment model independent and a compartment model dependent approach, (open two compartment model), were used for the analysis of plasma and urine concentrations. They provided similar results. The results of the PK analysis indicated that the kinetics of gadobutrol were of the first order as described by a two compartment model and that they were proportional to dose. After injection, gadobutrol was distributed predominantly in the extracellular space. The renal clearance was almost identical to the total clearance and was attributed mainly to glomerular filtration since it was simlar to creatinine clearance.

The terminal half life of gadobutrol in plasma was 1.7 to 2.1 hours. After 12 hours, up to 98% was excreted renally. No dose or concentration dependent differences in various PK parameters, (clearance, apparent volume of distribution at steady state and terminal half life), were observed. Gadobutrol is not metabolized and is excreted unchanged. Gadobutrol has no effect on the zinc or iron metabolism.

There are no ethnic differences in the pharmocokinetics of gadobutrol in Caucasian and Japanese populations. The pharmacokinetics of gadobutrol is similar in the pediatric population, aged 2-17, compared to adults. Age had a moderate effect on the pharmacokinetics of gadobutrol in plasma showing reduced plasma clearance and thus an increase in systemic exposure and terminal half life. Gender had no effect on the pharmacokinetics of gadobutrol except in elderly women where a slightly higher area under the plasma concentration versus time curve, (AUC), and a lower clearance were noted.

Safety was evaluated for several special groups and situations. The first situation was that of allergies/allergic reactions. In phase 1 studies, the AEs of allergic reaction were reported in 2 of 313 (1.0%) of subjects within 24 hours after injection of gadobutrol. The first subject, a 24 year old male, (subject 410 study 310865), received gadobutrol at the ≤ 0.11 mmol/kg to 0.21 mmol.kg bw dose and experienced sneezing and urticaria characterized as mild intensity. Sneezing began and ended immediately and urticaria started at 13 minutes and lasted 37 minutes. Other AEs concurrently were rhinorrhea, (0.03 minutes after injection lasting 0 minutes), oral paresthesia (0 minutes) and vomiting, all mild except for 1 minute of moderate intensity vomiting. The AEs resolved upon withdrawal of the contrast agent. The second subject, a 27 year old male, (subject 209 study 310865) received gadobutrol.and at the ≥ 0.11 to 0.21 mmol/kg dose and experienced a moderate intensity SAE of anaphylactoid reaction which started immediately after injection and lasted 120 mnutes and then resolved This was considered a drug related SAE,.

In phase 2-4 studies, 6 subjects, (0.1%) reported allergic reactions within 24 hours after injection of gadobutrol. None of these subjects had a history of allergy to contrast media. Five subjects received doses of >0.09 to 0.11 mmol/kg body weight, one subject

received >0.21 to 0.31 mmol/kg bw dose. Of these six subjects considered to have intermediate type hypersensitivity reactions, 3 subjects reported erythema, pruritis, rash, and urticaria, two subjects reported hypersensitivity, one subject reported respiratory arrest, and one subject reported hypotension.

The allergic reactions of the five subjects in the 0.09 to 0.11 mmol/kg bw dose group were considered drug related. The allergic reaction of the 6th subject who received the higher dose was considered an SAE. The AEs were considered of mild intensity for 3 subjects, of moderate intensity for one subject, and of severe intensity for two subjects.

7.2.6   Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

As of 12-31-10, ten cases of nephrogenic systemic fibrosis, (NSF), have been reported to the IND 56,410.

7.3 Major Safety Results

Table 32 is a safety summary of the 4 "covered" clinical studies.

Table 32: Safety Summary: "Covered" Clinical Studies

Parameter	Study 310123 Gadobutrol	Study 310123 Gadoteri-dol	Study 310124 Gadobutrol	Study 308200 Gadobutrol	Study 308200 Gadover-setamide
No. Subjects (N)	399	393	343	225	227
N (both drugs)	402 (any drug)	390 (both drugs)	N/A	229 (any drug)	217 (both drugs)
Total No. AEs & Incidence # Subjects	100 25.1% 96	96 24.4% 95	94 19.5% 67	79 35.1% Incidence by dose group, highest to lowest- 36.8%, 36.7%, 31.3%	52 22.9%

Most Common AEs	Headache 13,(3.3%) Nausea 11, (2.8%)	Headache 10. (2.5%) Nausea 17, (4.3%)	Headache (3.5%) Nausea (2.3%) Fatigue (1.5%) WBC in urine (1.5%) RBC in urine (1.2%)	Headache (8.0%), Dizziness (2.2%), Nausea and diarrhea (both 1.8%)	
Drug Related AEs # Subjects	40 10.0% Similar for all dose groups	38 9.7%	14 4.1%	22 9.8% Incidence by dose group, highest to lowest, 5 (7.4%), 12 (13.3%), 5 (7.5%)	13 5.7%
Treatment Related AEs (≥1%)	Nausea 6 (1.5%) Remainder of events ≤1% Similar for all treatment groups	Nausea 10 (2.5%) Remainder of events ≤1%	Nausea 6, (1.7%) Remainder of events in one subject each	Headache 3.1% overall, similar for all 3 dose groups	Headache 1.3%
SOC AEs (All AEs) 6 most common	Gastrointestinal 28, (7.0%) Nervous system 27, (6.8%) Investigations 18, (4.5%) General disorders and administration site conditions 17, (4.3%)	Gastrointestinal 27, (6.9%) Nervous system 26, (6.6%) Investigations 14, (3.6%) General disorders and administration site conditions 18, (4.6%)	Nervous system 22. (6.4%) General disorders and administration site conditions 16, (4.7%) Investigations 16, (4.7%) Gastrointestinal 11, (3.2%)	Nervous system 35, (15.6%) Gastrointestinal disorders 16, (7.1%) General disorders and administration site conditions 13, (5.8%) Respiratory, thoracic,	Nervous system 23, (10.1%) Gastrointestinal disorders 8, (3.5%) General disorders and administration site conditions 8, (3.5%) Musculo-

	Skin and subcutaneous disorders 13, (3.3%) Infections and infestations 9, (2.3%)	Skin and subcutaneous disorders 8, (2.0%) Respiratory, thoracic, mediastinal 7, (1.8%)		mediastinal 9, (4.0%) Skin and subcutaneous tissue disorders 9, (4.0%)	skeletal and connective tissue disorders 6, (2.6%) Skin and subcutaneous tissue disorders 5, (2.2%)
Severe Intensity AEs	6(1.5%) 2 (0.5%) were related (dysguesia *Subject 140050008* & hematuria *Subject 140160008*)	3 (0.8%) 2 (0.5%) were related (vomiting & upper abdominal pain *Subject 580070003*))	2, (0.6%) Not drug-related Fatigue and sciatica	4 subjects, (1.8%); 3 with headache, one with nausea, vomiting also; 2 subjects 0.1 mmol/kg, 2, 0.3 mmol/kg bw, all possibly drug-related; headache in one did not resolve	2 subjects, (0.9%), one with headache and one with Hospitalization, both unrelated to study drug
Serious AEs	2 subjects, one SAE each, unrelated; brain metastasis *(Subject 100180001)* and aggravation of hydrocephalus, *(Subject 200030019)*	1 subject with 2 SAEs, unrelated; worsening of general condition and somnolence *(Subject 100080002)*	1 subject with a TIA, not drug-related	1 subject with brain edema, increased intracranial pressure, neurological symptoms *Subject 19010-*unrelated	1 subject with a known glial tumor, no change in symptoms, hospitalized prior to surgery *Subject 27006-*unrelated

Deaths Discontin-uations	None 3 (0.7%) *Subject 100080002*, SAE; *Subject 200030008*, injection site swelling AE, *Subject 200090015*, blurred vision (duration 139 days)	Subject above died 8 days after received both drugs (DC-ed from study) 1 (0.3%); *Subject 140240001*, lower respiratory allergic reaction, 1 hour duration	None No D/C due to AEs	None No D/C due to AEs	None No D/C due to AEs
Labora-tory Investigat-ions	*Baseline, 1, 24 hrs, 72 hr creatinine for 2nd drug* A few drug-related chemistry AEs, mean changes from baseline not clinically relevant; 1 SAE (hematuria), *Subject 140160008*, severe intensity noted 10 days after period 1, a few subjects with hematology drug-related AEs Es	*Baseline, 1, 24 hrs, 72 hr creatinine for 2nd drug* A few drug-related chemistry AEs, mean changes from baseline not clinically relevant; few subjects with hematology drug-related a few subjects with hematology drug-related AEs Es	*Baseline, 1, 24, 72 hrs* Few chemistry changes, most mild intensity, not drug-related; hematology changes not considered as drug-related AEs	*Baseline, 2 to 4, 24, 72 hours)* 3 subjects with changes in clinical chemistry were AEs. not related to study drug;	*Baseline, 2 to 4, 24 hours)*

	,				
Vital Signs and ECG Changes	Fluctuations noted in mean systolic/ diastolic blood pressure, most within 20 mm Hg for SBP and 15 mm Hg for DBP of baseline, (≥85% for both SBP and DBP); 3 subjects with hypertens'n and 1 with hypotension reported as AEs, only one hyper-tension related (*Subject 200030006*; heart rate fluctuations, ≥86.9% within 15 bpm of baseline; AEs noted 1 subject each, irregular heart rate, bradycardia, tachycardia, irregular beat and	Blood pressure fluctuations similar to gadobutrol; no AEs related to blood pressure; similar hear rate changes, one tachycardia drug related; respiration and body temperature changes similar	Blood pressure and heart rate fluctuations within 20 mm Hg from baseline for SBP and 15mm Hg DBP ≥91% and ≥83.6% heart rate within 15 bpm of baseline; 5 subjects with blood pressure changes, only one drug-related; one subject with tachycardia 27 hours post injection, not drug-related, (4 mild, 1 moderate); no respiration or body temperature changes	Blood pressure and heart rate fluctuations within 20 mm Hg from baseline for SBP and 15 mm Hg DBP ≥85.5%; 3 AEs but none of the blood pressure changes considered as AEs were assessed as drug related; ≥85.7% heart rate within 15 bpm of baseline; one subject with increased heart rate as an AE was assessed as event unrelated to study drug; one clinically significant shift in ECG from normal	

tachycardia drug related; no significant changes in respiration or body temperature			at baseline to ST segment depression and one subject had an increase (≥60 msec) in QT interval corrected according to Fridericia's method.	

Based on the above table, the following conclusions may be made concerning the safety of gadobutrol based on the two phase 3 pivotal trials and the phase 2 dose selection study:

- For the crossover study 310123, the safety profile of gadobutrol was comparable to gadoteridol.
- For study 308200, (dose selection study), there were no obvious differences in the safety profile among the 3 doses of gadolinium.

Reviewer's Comment: On review of the individual study reports, this reviewer noted the volume of gadobutrol administered ranged from 3.1 mL to 20.0 mL for study 310123 and from 4.0 to 18.0 mL for study 310124. In addition, it was noted that subject 140180007 who was randomized to the gadobutrol:gadoteridol sequence of the 310123 study did not receive the comparator drug, gadoteridol. Based on weight, (55 kg),he should have been dosed with 5.5 mL of gadobutrol. During study period 1 the subject received 6 mL and then received 11 mL ("double dose") in study period 2. Based on concerns for a potential for misadministration associated with the increased molarity of gadobutrol relative to other GBCAs and for the development of NSF in renally impaired patients, this reviewer requested a listing of all subjects' weights and doses administered for the two pivotal phase 3 studies Dosing information received from the applicant for review of possible misadministrations revealed that 7/716 subjects enrolled in studies 310123 or 310124 received "double" the recommended body weight dose. Based on the potential for dose misadministration, this reviewer recommends appropriate labeling and product marketing to address the concern that the appropriate gadobutrol dose is one half the volume of other GBCAs approved for CNS use. An information request regarding the potential for misadministration was sent to the applicant. The applicant noted in response that for the pivotal phase 3 trials, most dosing errors occurred for the first subject at each site and resolved with a reminder

newsletter to the sites. It was also noted that there were 3 reports of "overdose" in the Global Postmarketing (GPV) Reports. Review of these 3 case reports revealed that none resulted in any known sequelae.

Study 310788 Pediatric PK Study in Children Ages 2-17 years

Safety results noted good tolerance overall with no indications for a different profile than known for adult patients.

The safety analysis set consisted of 138 subjects in the following age groups: 46 subjects in age goup 1, (2 to 6 years), 44 subjects in age group 2, (7 to 11 years), and 48 subjects in age group 3, (12 to 17 years).

A total of 74 AEs were recorded for 49, (35.5%) of the 138 subjects. At least one drug related AE occurred in 8 (5.7%) of subjects. As assessed by the investigators 10 of the 74 AEs were related to the administration of gadobutrol. Related AEs were dysguesia (2 AEs), feeling hot (2 AEs), crystallized urine, headache, nausea, rash, rash pruritic, and pruritis (1 AE each). Of 74 AEs, 2 were severe intensity, back pain in subject 2012, and crystallized urine insubject 8002. The reaction in subject 8002 was also considered a serious drug reaction. For the remainder of reactions, intensity was moderate for 13 with the majority of mild intensity.

There were 3 SAEs in 2 subjects, (1.4%), as noted one subject (8002) with crystallized urine and pneumonia (not related to study drug) requiring hospitalization. The other SAE (meningitis) was reported in subject 2017 and related to the subject's underlying clinical condition. All subjects with SAEs recovered, (SAE resolved).

No deaths were reported.

There were differences in the time of onset between 64 unrelated AEs and 10 AEs that the applicant noted as drug-related AEs. The majority of unrelated AEs started within the first 3 hours to 7 days after injection of gadobutrol, (46 of 64 AEs) whereas the majority of drug-related AEs started within 3 hours after injection of gadobutrol, (7 of 10 AEs). This finding is of uncertain significance.

Laboratory parameters showed no substantial changes from baseline to follow-up in any of the parameters evaluated for any of the three age groups.There were no significant change in vital signs.

7.3.1 Deaths

There was a single death reported in the gadobutrol group of the total 4549 subjects. The narrative of this follows.

Subject 1211/Study 95365/Report B308

The subject was a 72 year old Japanese male in the terminal stages of lung cancer and entered the study with pneumonia as a complication. He received 0.5 M gadobutrol at a dose of 0.3 mmol/kg bw. After the MRI he experienced increased breathing difficulties and increased right sided pleural effusion 5 days after the injection. He was treated with oxygen and thoracentesis. 11 days after the injection he died of respiratory failure. The death was considered to be caused by deterioration of primary disease (lung cancer).

7.3.2   Nonfatal Serious Adverse Events

<u>S1 Pool, (Phase 1 Studies)</u>

Subject 209/Study 310865/Report A3975

The subject was a healthy 27 year old Japanese male volunteer with no history of allergy. The subject received 14.0 mL, (0.2 mmol/kg bw 1.0 M concentration) of gadobutrol. During the administration, he developed numbness of the tongue, then cough, bulbar hyperemia, wheezing, decreased peripheral oxygen saturation, and wheals. There were no changes in other vital signs such as blood pressure. The symptoms were diagnosed as anaphylactoid reaction. The subject was treated with pharmacotherapy therapy and oxygen inhalation and confirmed as recovered 2 hours after study drug administration.

<u>S2 Pool, (Phase 2-4 Studies)</u>

Out of 4549 subjects, 21 subjects in the S2 pool experienced serious adverse events (SAEs) of which 17 (~0.4% of subjects) were in the gadobutrol group. Seven SAEs occurred at the proposed dose, 2 occurred at lower doses and there were 3 in the highest dose group, (>0.21-0.31 mmol/kg bw). This reviewer noted that most SAEs were attributed to the subject's underlying clinical condition and reflected a CNS process.. The investigator considered only one SAE to be related to study drug, (crystalluria in a pediatric patient). This review concurs with this assessment. One, (0.4%) SAE was seen in the gadoversetamide group. Three, (0.5%) SAEs were seen in the gadoteridol group.

7.3.3   Dropouts and/or Discontinuations

Subjects who did not receive any study drug were considered as dropouts.

Of the 313 subjects in the gadobutrol group of the phase 1 studies, 311 subjects completed study medication treatment. Of the 2 subjects who discontinued treatment,

both received gadobutrol at the ≤0.11 mmol/kg bw dose One subject, (subject 20008 in study 96063) discontinued to a reason categorized as "other," (evaluations of signal intensity and imaging could not be performed due to a broken leg and hospitalization). The other subject discontinued due to a drug related AE, (described below, subject 410 in study 310865).

In the placebo-controlled studies, 67 of 68 subjects who received placebo completed the study medication and one subject, (subject 1015 in study 307362), discontinued due to technical problems.

Two out of 313 subjects from the phase 1 studies who received gadobutrol discontinued the study due to AEs, one of them due to drug related AEs, (subject 410 in study 310865). The first subject discontinued secondary to an anaphylactoid reaction. The second subject discontinued due to EKG changes that the investigator termed as probably related. The narratives for these two subjects follow in the paragraph below.

The first subject, a 24 year old Asian male, (*subject 410 study 310865*), received gadobutrol at the ≤ 0.11 mmol/kg to 0.21 mmol.kg bw dose and experienced sneezing and urticaria characterized as mild intensity. Sneezing began and ended immediately and urticaria started at 13 minutes and lasted 37 minutes. Other AEs concurrently were rhinorrhea, (0.03 minutes after injection lasting 0 minutes), oral paresthesia (0 minutes) and vomiting, all mild except for 1 minute of moderate intensity vomiting. The AEs resolved upon withdrawal of the contrast agent.

The second subject was a 45 year old Black male, (*subject 1022, study 307362*) who experienced chest pain and T-wave changes after dosing. The AE started 0.03 minutes after injection and lasted for 4 hours. The AE was of mild intensity and was considered probably related. The subject recovered and the AE resolved.

Of the 4549 subjects in the gadobutrol group, 4530 completed the study medication treatment. The reasons for the discontinuation of study medication in the 19 subjects were withdrawal of consent by 2 subjects, (subject 70003, study 92095 and subject 580030002, study 310123), protocol deviation by one subject, (subject 100002, study 302722), technical problems in 2 subjects, (subject 19003, study 308200 and subject 21004, study 308200), AEs in 6 subjects, and "other" reasons in 8 subjects. The "other" reasons for discontinuation in the 8 subjects included technical and drug administration problems (protocol deviations) and subject's clinical condition to include inability to cooperate.

In the S2 pool, (phase 2-4 studies), subject withdrawals from gadobutrol studies included six subjects who prematurely discontinued study medication treatment and seven subjects who discontinued the study due to AEs. This reviewer notes overlap of these categories, (i.e. some subjects discontinuing study drug also discontinued from the study). Of these, only one subject, (subject 2003, study 95954), discontinued study

due to drug related AEs. Table 33 lists these subjects with actions and outcomes. Table 8 contained in the efficacy review presents a general summary of subject disposition.

Table 33: Subjects who Prematurely Discontinued Study Medication or Discontinued Study Due to AEs, S2 Pool, (Phase 2-4)

Subject Study D/C Drug or Study	Gadobutrol Dose mmol/kg bw	AE (by PT)	Relation-ship to Gadobutrol	Action & Outcome
300011 305501 D/C drug	≤0.09	Dyspnea, asthenia, chills	Not related	Dose reduced Recovered
20003 94054 D/C drug	>0.09-0.11	Hypersensitivity/allergic reaction with blood pressure decreased	Related	Drug withdrawn Recovered/resolved
50019 94954 D/C drug	>0.09-0.11	Nausea	Related	Dose reduced Recovered/resolved
200030008 310123 D/C drug	>0.09-0.11	Injection site swelling	Not related	Drug withdrawn Recovered/resolved
30009 302600 D/C drug D/C study	>0.11-0.21	Cardiac failure	Not related	No change in dose Unknown
30001 302600 D/C drug D/C study	>0.21-0.31	Hypotension	Not related	Drug withdrawn Recovered/resolved
30001 305501 D/C study	≤0.09	Dyspnea, asthenia, chills	Not related	Dose reduced Recovered
20003 94054 D/C study	>0.09-0.11	Hypersensitivity/allergic reaction with blood pressure decreased	Related	Drug withdrawn Recovered/resolved
50019 94954 D/C study	>0.09-0.11	Nausea	Related	Dose reduced Recovered/resolved
19010	>0.09-0.11	Intracranial oressure	Not related	No change in dose

308200 D/c study		increased, brain edema, surgery, no comparator MRI performed		Not recovered/not resolved
100080002 310123 D/C study	>0.09-0.11	General physical health deterioration and somnolence, subject referred to hospice	Not related	No change in dose Not recovered/not resolved
200030008 310123 D/C study	>0.09-0.11	Injection site swelling	Not related	Drug withdrawn Recovered/resolved
200090015 310123 D/C study	>0.09-0.11	Vision blurred	Related	No change in dose Recovered/resolved

In the comparator groups, only 2 subjects discontinued the study drug, one subject in the gadodiamide group due to "other" reason and one subject in the gadoversetamide group due to technical problems.

Based on the above subject data for all subjects studied, the conclusion is that discontinuation due to study drug AEs is not a significant issue.

Reviewer's Comment: The ISS contains tables and narratives consistent with 9 study discontinuations, 3 of which were study drug related. Narratives for these three subjects follow.

Subject 20003/Study 94054: Subject was a 59 year old Caucasian male who was injected with >0.09-0.11 gadobutrol and had a hypersensitivity reaction consisting of decreased blood pressure, increased heart rate, vomiting, nausea, flushing, and sweating, starting immediately after injection and lasting 3 hours. The AEs were considered severe and drug related and resolved upon drug withdrawal.

Subject 50019/Study 94054: Subject was a 52 year old female Caucasian who experienced nausea immediately after injection of >0.09-0.11 gadobutrol. The nausea was mild in intensity and lasted for 40 minutes. The subject recovered after a reduction in dose.

Subject 200090015/Study 310123: Subject was a 70 year old female who discontinued the study 2:01 minutes after injection of >0.09-0.11 gadobutrol due to blurred vision. The AE was of mild intensity and lasted 139 days. The subject recovered. The AE was considered as resolved.

7.3.4   Significant Adverse Events

Table 35 below shows the most common adverse events independent of drug relationship. The majority of the reported adverse events is consistent with those observed with other gadolinium based contrast agents.

For phase 1 studies, of 194 subjects that received gadobutrol 91 experienced AEs, (46.9%) and 20 subjects out of 68 that received placebo, (29.4%) experienced AEs. For phase 2-4 studies, 480 of the 4549 subjects, (10.6%) that received gadobutrol experienced AEs. The percent of all comparator AEs was variable, ranging from 4.7% to 18.4%.

For the phase 1 studies, the most frequently reported AEs in the gadobutrol group were dysguesia, (11.9%), followed by nausea, (7.2%), parosmia, (6.7%), headache, (6.2%), feeling hot, (5.2%), and injection site coldness, (4.1%). For placebo, the most frequently reported AEs were injection site coldness, (5.9%), headache, (4.4%), and pyrexia, (4.4%). The incidence of remaining AEs was less than 4.0% in either group. There was no definite relationship noted between incidence of AEs and gadobutrol dose.

When the occurrence of all adverse events was characterized by number of subjects and reported intensity, in the gadobutrol group 88.3% of AEs were of mild or moderate intensity, 7.7% of severe intensity. For total number of AEs reported in the gadobutrol treatment group, 92.6% were of mild or moderate intensity, 4.7% of severe intensity, and 2.7% were unknown. There were no obvious dose related differences in intensity. The severe intensity AEs were reported by SOC similar to all AEs in the gadobutrol group with the addition of musculoskeletal and connective tissue disorders, respiratory, thoracic, and mediastinal disorders, and vascular disorders.

One serious adverse event was reported for the phase 1 studies. The narrative of this event is contained in section 7.3.2.

For the phase 2-4 studies, 480, (10.6%), of 4549 subjects experienced a total of 716 AEs. The most frequently reported AEs in the gadobutrol group were headache, (1.5%%).), nausea, (1.2%), feeling hot, and dysguesia, (0.5% each). By system organ class, (SOC), the highest incidence of AEs in the gadobutrol group were in the central nervous system disorders, (92 subjects, 2.0%, gastrointestinal disorders, (56 subjects, 1.2%), and general disorders and administration sites, (24 subjects, 0.5%).

Of the total AEs reported, (716), 95.4% were mild or moderate and 4.5 % were severe with 83.3% of drug related AEs also of mild intensity. There was no obvious difference in the intensity of AEs with increasing gadobutrol dose.

As noted in Table 34, the incidence of AEs in the comparator groups was variable. In the comparator groups, 104, (18.7%) of 555 subjects reported 156 AEs in the gadoteridol group, 39, (17.2%), of 227 subjects reported 51 AEs in the gadoversetamide

group, 47, (5.2%), of 912 subjects reported 65 AEs in the gadopentate dimeglumine group, and seven, (4.7%), of 150 subjects reported 9 AEs in the gadodiamide group. At the 0.1 mmol/kg dose, the incidence of AEs for gadoteridol was 21.6%, gadoversetamide was 17.2%, gadopentate dimeglumine was 4.8%, and gadodiamide was 4.7% compared to 11.1% for gadobutrol. Comparing AEs by SOC and PT, similar AEs were noted for the comparators. Intensity of AEs for the mild and moderate group was similar for gadobutrol and the four comparator drugs. There was a 2.0% of severe intensity AEs for one drug and a 3.2% incidence for another of the four comparators, and none reported for the other two drugs as compared to the 4.5% incidence for gadobutrol.

A total of 21 subjects experienced serious adverse events (SAEs), 17 (0.4% of 4549) of which were in the gadobutrol group. There was one SAE with gadoversetamide and there were 3 SAEs with gadoteridol. Discussion of non fatal SAEs is contained in section 7.3.2.

Table 34 : Adverse Events Most Commonly Reported for Phase 1 Studies and Adverse Events Reported With a Frequency of ≥0.5% in Phase 2-4 Studies in Subjects by Body System Independent of Drug Relationship

Phase Drug	Body System/ Adverse Event	Frequency N = Number of subjects(%) N = Subjects with any AEs (%) Total number of AEs
Phase 1 Gadobutrol	Nervous system disorders, (149 subjects, 3.3%) 　Dysguesia, (23, 11.9%) 　Parosmia, (13, 6.7%) 　Headache, (12, 6.2%) Gastrointestinal disorders, (114 subjects, 2.5%) 　Nausea, (14, 7.2%) General disorders and administration site conditions, (99 subjects, 2.2%) 　Feeling hot, (10, 5.2%)	194 (100%) 91 (46.0%) 196
Phase 1 Placebo	Injection site coldness, (4, 5.9%) Headache, (3, 4.4%) Pyrexia, (3, 4.4%)	68 (100%) 20 (29.4%) 40
Phase 2-4 Gadobutrol	Gastrointestinal disorders 　Nausea, (56, 1.2%) General disorders and administration site	4549 (100%) 480 (10.6%) 716

	conditions
	   Feeling hot, (24, 0.5%)
	Nervous system disorders
	   Dysguesia, (23, 0.5%)
	   Headache, (69, 1.5%)
	Laboratory investigations, (76, 1.0%)	

Phase 2-4 Comparators	<u>Gadoteridol</u>
	   Nervous system disorders, (headache and dysguesia)
	   Skin and subcutaneous tissue disorders, (ecchymosis, rash, pruritis)
	   Respiratory, thoracic, mediastinal, (oropharyngeal pain)
	   Reproductive system and breast disorders, (dysmenorrheal)
	<u>Gadoversetamide</u>
	   Nervous system disorders, (headache, dizziness, pareasthesia, dysguesia)
	   Respiratory, thoracic, mediastinal, (wheezing)
	   Skin and subcutaneous disorders, (pruritis)
	<u>Gadopentate dimeglumine</u>
	   Nervous system disorders, (headache, dysguesia, dizziness, paresthesia)
	<u>Gadodiamide</u>
	   Nervous system disorders, (dizziness, tremor)
		<u>Gadoteridol</u>-555 subjects total, 104(18.7%) with 156 AEs
		<u>Gadoversetamide</u>-227 subjects total, 39 (17.2%) with 51 AEs
		<u>Gadopentate dimeglumine</u>-912 subjects total, 47 (5.2%) with 65 AEs
		<u>Gadodiamide</u>-150 subjects total, 7 (4.7%) with 9 AEs

Adverse Drug Reactions

Adverse drug reactions**,** defined as drug-related AEs, were reported for 69 subjects receiving gadobutrol, for the phase 1 studies, (111 events representing a 56.6% incidence). The most frequently reported AEs were dysguesia, (11.9%), followed by parosmia, (6.7%), nausea, (6.2%), feeling hot, (5.2%), and injection site coldness, (4.1%) By system organ class, (SOC), AEs were greatest for the nervous system, general disorders and administration conditions, and the gastrointestinal system. For drug related AEs, there was no clear relationship for concentration. The incidence was

somewhat greater for the >0.51-1.01 mmol/kg bw group however the number of subjects in the group was small.

In the placebo group, of the 20 subjects reporting 40 AEs, 9 subjects reported drug related events. The most commonly reported drug related AE in the placebo group was injection site coldness, (5.9%).

For the phase 2-4 studies, 240 adverse drug reactions, (33.5%) were seen in 182 subjects, (4.0% of subjects). The most frequently reported drug related AEs in the gadobutrol group were similar and occurred with similar incidence to all AEs: headache, (1.5%), nausea, (1.2%), feeling hot, and dysguesia, (0.5% each) with various types of injection site conditions such as pain or erythema listed in addition, having an 0.6% incidence. By system organ class, (SOC), AEs were greatest for the gastrointestinal system, (0.8%), followed by general disorders and administration site conditions, (0.5%), and nervous system disorders, (0.5%). Comparing drug related AEs to dose, the percentages were similar for four dose groups up to 0.31 mmol/kg body weight with 3.8% incidence at the proposed 0.1 mmol/kg dose, (stratified as >0.09-0.11 mmol/kg bw). Drug related AEs at the highest dose stratification (>0.3-0.51 mmol/kg bw), were reported at a 6.4% incidence however the total number of subjects in this group was considerably lower than in the other four dose groups. For drug related AEs, there was no clear relationship for concentration with 3.9% AEs for the 0.5 M concentration and 4.0% AEs for the 1.0 M concentration.. Of the drug related 240 AEs, 32 were judged to be of severe intensity and were noted for the 1.0 M concentration. There were no severe intensity AEs for the 0.5 M concentration. By dose stratification 50.0%, (16), of these were for the >0.09-0.11 mmol/kg bw dose group which is the proposed product dose.

Drug related AEs for comparator drugs were also most common for the gastrointestinal system, (nausea), general disorders and administration site conditions, (feeling hot), and nervous system, (dysguesia).

A total of 21 subjects experienced SAEs, 17(0.4% of 4549) of which were in the gadobutrol group. Only one of these, (crystallized urine in a pediatric subject), was considered by the investigator to be related to gadobutrol.   Two deaths were reported, one in the gadobutrol group, not classified as drug related. Overall, the rate and severity of AEs was comparable in the studies for all three phases and did not identify a specific safety concern.

Table 35 lists the most common drug related AEs reported for the phase 1 studies and all drug related AEs ≥1% incidence in the phase 2-4 studies.

Table 35: Most Frequently Reported Drug Related AEs in Phase 1 Studies and Incidence of Drug Related AEs ≥1.0% in Phase 2-4 Studies

Primary System Organ Class and Preferred Term Study Phase	Number/Incidence
Phase 1 Total	Total number of subjects = 313 (100%) Total number of events = 196 (100%) Total number of subjects with any drug related event = 69 (35.6%) Number of drug related events = 111 (56.6%)

Nervous system disorders-phase 1
  Dysguesia
  Parosmia
	Number of subjects = 23 (11.9%)
	Number of subjects = 13 (6.7%)

Gastrointestinal disorders-phase 1 Nausea	Number of subjects = 12 (6.2%)

General disorders and administration site conditions
  Feeling hot
  Injection site coldness
	
	Number of subjects = 10 (5.2%)
	Number of subjects = 8 (4.1%)

Phase 2-4 Total	Total number of subjects = 4549 (100%) Total number of events = 716 (100%) Total number of subjects with any drug related event = 182 (4.0%) Number of drug related events = 240 (33.5%)
Gastrointestinal disorders Nausea	Number of subjects = 35 (0.8%)
General disorders and administration site conditions Feeling hot	 Number of subjects = 22 (0.5%)

Nervous system disorders	
Dysguesia	Number of subjects = 22 (0.5%)

7.3.5   Submission Specific Primary Safety Concerns

This reviewer concurs that the safety profile of gadobutrol is similar to other approved GBCAs. The applicant should address the potential for misadministration ("double dose") during discussions for labeling and marketing. The potential of the drug to cause NSF (risk category) also needs to be addressed.

7.4 Supportive Safety Results

7.4.1   Common Adverse Events

For phase 1 studies, of 194 subjects that received gadobutrol 91 experienced AEs, (46.9%) and 20 subjects out of 68 that received placebo, (29.4%) experienced AEs. For phase 2-4 studies, 480 of the 4549 subjects, (10.6%) that received gadobutrol experienced AEs. The percent of comparator all AEs was variable, ranging from 4.7% to 18.4%.

For the phase 1 studies, the most frequently reported AEs in the gadobutrol group were dysguesia, (11.9%), followed by nausea, (7.2%), parosmia, (6.7%), headache, (6.2%), feeling hot, (5.2%), and injection site coldness, (4.1%). For placebo, the most frequently reported AEs were injection site coldness, (5.9%), headache, (4.4%), and pyrexia, (4.4%). The incidence of remaining AEs was less than 4.0% in either group. There was no definite relationship noted between incidence of AEs and gadobutrol dose.

For the phase 2-4 studies, 480, (10.6%), of 4549 subjects experienced a total of 716 AEs. The most frequently reported AEs in the gadobutrol group were headache, (1.5%%).), nausea, (1.2%), feeling hot, and dysguesia, (0.5% each). By system organ class, (SOC), the highest incidence of AEs in the gadobutrol group were in the central nervous system disorders, (92 subjects, 2.0%, gastrointestinal disorders, (56 subjects, 1.2%), and general disorders and administration sites, (24 subjects, 0.5%).

7.4.2   Laboratory Findings

Laboratory parameters were examined at baseline, (pre-dose), and at various time points post injection, (up to 7 days) depending on the study.   Subject evaluations included included clinical chemistry, hematology, and urinalysis. Not all studies

included all laboratory measurements and the time points were variable for different studies. The following can be summarized and concluded from these studies:

Phase 1 studies: A higher incidence of ≥2x upper limit of reference range (ULN) values for a few laboratory parameters was observed in the gadobutrol group compared to placebo and ≥3xULN values in direct bilirubin (also noted for placebo) and triglycerides, most not considered clinically significant.

Phase 2-4 studies: Laboratory evaluations included blood cell counts, (with differential count), serum chemistry and special serum markers, electrolytres, clotting parameters, and urine parameters. Laboratory values were evaluated post injection from 30 minutes to 7 days. Laboratory data showed no remarkable fluctuations in the mean values of the single blood and urine parameters over the course of the study. Most individual fluctuations remained within the reference range and were not associated with other simultaneous changes in laboratory parameters. For both gadobutrol and comparator drugs, there were instances of subjects' laboratory values ≥2ULN and ≥3ULN which were less than 3.0% and 0.5% for blood parameters, respectively. Urine parameters showed more variability with total protein at 7.2% for both values however this was noted to be 6.4% for one of the comparators.   Baseline characteristics and demographic analysis showed no effect of gadobutrol on the subgoups that were analyzed. No substantial changes were noted in the pediatric population from baseline to follow up.

7.4.3 Vital Signs

For purposes of safety analysis, vital signs were pooled within the integrated safety analysis pools, (S1 and S2) with summary statistics presented for each parameter by time window and its change from the last value measured prior to the injection of contrast medium. Summary statistics were presented by various demographics such as weight categories and region. Demographic analysis was more extensive for the S2 pool. In addition, shift tables were presented. For systolic blood pressure, (SBP), an increase or decrease of more than 20 mm Hg compared to the value measured prior to injection of contrast medium was considered a relevant change. For changes in diastolic blood pressure, (DBP), changes of more than 15 mm Hg were considered relevant. With respect to pulse, an increase or a decrease of >15 beats per minute, (bpm), was considered as a relevant change to the value measured prior to injection of contrast medium. Vital signs were performed prior to injection and at various time points after injection. Respiration rate and body temperature were only measured for a few of the phase 1 and phase 2-4 studies. No vital sign safety signals were seen with the following general conclusions:

- Phase 1 studies: No relevant or consistent changes in blood pressure or heart rate were noted irrespective of several stratifications performed.

- Phase 2-4 studies: No relevant or consistent changes in blood pressure or heart rate were noted irrespective of several stratifications performed.

7.4.4   Electrocardiograms (ECGs)

The evaluation for cardiac rhythm, (regular vs irregular), was based on information collected during the ECG assessment. Only two phase 1 studies had cardiac rhythm assessments. Assessments for the phase 2-4 studies represent a pooled analysis. Electrocardiogram evaluations were performed for all studies in the S1 pool except study 96063. QT interval assessments corrected according to Fridericia, (QTcF) were performed in study 307362. Electrocardiogram evaluations were performed in 9 studies of the S2 pool: 93017, 93018, 94369, 97099, 302722, 304300, 30551, 308200, and 310788. Data of QT interval was measured in studies 97099, 302722, 304300, and 308200. Sufficient information to derive QTcF was only available in studies 30551 and 308200.
Time frame windows applied were the same as those for the physical evaluation and included pre-dose, (baseline), and various post injection times up to .3 days. The following general conclusions were made based on the subject pools:

- Phase 1 studies: The mean values at baseline and difference from mean values at baseline was noted for heart rate, QT interval, QRS interval, PQ interval, QTcF, and also atrial and ventricular extrasystoles. Clinically significant changes were pre-specified. The mean values of heart rate showed a small change post-injection of gadobutrol. The mean value change from baseline ranged from between -0.3 to 6.6 beats per minute from 0 minutes to 3 days post-injection and was comparable to placebo, (-1.7 to 5.4 beats per minute). A thorough ECG study which evaluated the effect of gadobutrol on cardiac repolarization demonstrated no effect of gadobutrol on cardiac repolarization for doses up to 0.5 mmol/kg bw, there were no subjects with a corrected QT interval (by Fredercia method, QTcF) greater than 480 msec or an increase from baseline of greater than 60 msec, and no abnormalities were detected in the ECGs. The evaluation of this study by the FDA TQT Team revealed that effects on QT prolongation were likely to be small and should not have important clinical significance, there were no events of clinical importance identified (such as seizures), ECG acquisition and interpretation was acceptable, and PR and QRS interval changes were not clinically relevant.
- Phase 2-4 studies: A few cases of rhythm disturbances (atrial, supraventricular, and ventricular extrasystoles) were observed at varying post-injection times, many of which were also seen pre- injection. There were no clinical signs or symptoms seen with these. There were no pathological changes in the PQ or QRS intervals and no ST segment elevation or depression was noted. Central ECG evaluations showed no relevant differences in the recordings immediately post-injection compared to baseline for mean heart rate, mean duration of the P-

wave, and mean QRS interval. ECG data indicated no relevant effect on repolarization attributable to gadobutrol doses up to 0.5 mmol/kg bw. No significant effect of gadobutrol was detected for the QRS or PQ interval. The change in mean value in heart rate from 0 minutes to 1 day post injection ranged from -2.3 to 2.5 bpm. The change in mean value from baseline for QRS interval and PQ interval ranged between -0.3 to 0.5 msec and 1.3 to -0.9 msec respectively from 0 minutes to 1 day post injection. No effect of gadobutrol was detected for either variable.

One subject in the gadobutrol group, Subject 1096, showed an increase in QTcF>460 msec from baseline >15 to 30 minutes after injection. The subject was a Black female with a predose QTcF value of 424 msec which increased to 461 msec, (37 msec change from baseline). Four subjects (3 gadobutrol, 1 placebo) showed increases in QTcF values 30 to 60 msec from mean of baseline to post-injection. Subject 1041, a Black male with a baseline QTcF value of 379 msec, experienced an increase to 410 msec >1 to 2 hours after injection of gadobutrol. Subject 1084, a Black male with a baseline QTcF value of 400 msec, experienced and increase to 432 msec >2 to 4 hours after injection of gadobutrol. Subject 1096 a Black female with a baseline QTcF value of 424 msec experienced and increase to 461 msec >15 to 30 minutes after injection of gadobutrol. Subject 1015 a Black male with a baseline QTcF value of 395 msec experienced and increase to 425 msec >1 to 2 hours after injection of placebo.

For the phase 2-4 studies, the number of subjects with potential risk factors, (mean values of QTcF ≤ 460 msec and increases of 30 to 60 msec after baseline) and change in mean values of QTcF from mean values at any time point after injection with gadobutrol, and the overall assessment of ECG was provided. Using a pre-specified guidance for ECG changes, a total of 57, (7.2%) of subjects in the gadobutrol group as versus 9, (4.0%), subjects in the gadoversetamide group had clinically significant changes in ECG from baseline. 25, (12.1%) were subjects at the <0.09 mmol/kg bs dose, 20, (6.2%) were subjects at >0.09 to 0.11 mmol/kg bs dose, and 12, (13.0%) were subjects at >0.11 to 0.21 mmol/kg.   ECG changes were assessed by the investigator. The applicant provided interpretation of the findings by a board-certified cardiologist. On review, most subjects had baseline findings and ECG changes were felt not to relate to gadobutrol injection. In some cases, ECG interpretation by the cardiologist differed slightly from the investigator's interpretation. On review of these cases, this reviewer concurs that the ECG changes do not appear to be related to gadobutrol.
The applicant conducted a thorough ECG study to support the effect of gadobutrol on cardiac repolarization and on cardiac rhythm. Study 307362, (Report 21381), was a single center, randomized, placebo controlled, 5-period crossover, dose comparison phase 1 study with a concurrent positive control, (moxiflxacin). The design was double blind for gadobutrol and placebo. 35 healthy male subjects and 29 healthy female subjects ages 19 to 60 years were randomized to treatment sequence and received at least one dose of study medication (61/64 subjects received gadobutrol). Subjects were

required to have an ECG without clinically significant abnormalities. The objective of the study was to evaluate the electrocardiographic effects, especially a potential influence on cardiac repolarization, of gadobutrol. Gadobutrol was administered with a power injector as a 2mL/sec bolus at 3 doses, (0.1 mmol/kg bw, 0.3 mmol/kg bw, and 0.5 mmol/kg bw). QT measurements were compared to placebo, (0.9% normal saline), as a negative control and to moxifloxacin 400 mg as a positive control. 56 subjects completed the study. Results of the ECG study indicated that there was no effect of gadobutrol on cardiac repolarization (including total time for ventricular depolarization and repolarization, [QT prolongation], and torsade de points, [TdP]), at doses up to 0.5 mmol/kg bw. None of the subjects had a QT interval corrected by the Fredericia method, (QTcF), greater than 480 msec or an increase in QTcF from baseline of greater than 60 msec. No abnormalities were detected in ECGs.

7.4.5   Special Safety Studies/Clinical Trial

Special Population safety studies included a phase 1 study for age and gender, a phase 3 study in subjects with renal impairment, and a phase 1/3 PK study in pediatric subjects ages 2-17 years.

Safety and pharmacokinetics of gadobutrol after a single i.v. bolus administration of 0.1 mmol/kg bw was studied in a group of healthy volunteers (males and females ages 18 to 45 years) and in elderly male and female subjects ≥65 years, (study 308183, report A40982). Results of previous pharmacokinetic analysis indicated that the pharmacokinetics were dose-proportional for gadobutrol injection and that they could be described by an open two-compartment model. Following injection, the compound is distributed predominantly in the extra cellular space. Renal clearance is almost identical to total clearance according to glomerular filtration rate. The terminal half-life in plasma is 1.7-2 hours. About 98% of the dose is excreted renally. There are no metabolic products or biotransformations. Gadobutrol has neglibible plasma protein binding and has no effect on zinc or iron metabolism. The purpose of this study was to evaluate the influence of age and gender on the pharmacokinetics of gadobutrol at the routinely administered clinical dose (0.1 mmol/kg body weight) in order to complete the clinical pharmacology information for the package insert of gadobutrol. Additional determination of urine zinc and other metals in 24-hour urine was performed to complete safety data with regard to the complex stability of gadobutrol.

Safety analysis for the age and gender study showed the most frequent AE overall was headache followed by puncture site disorders, (hematoma, pain). Adverse events judged by the investigator to be related to study drug were increased blood pressure, (1 subject), headache, (5 subjects), and proteinuria, (1 subject). There were no serious and no severe AEs. There were no concerns pertaining to the safety of gadobutrol based on the pattern of AEs, the clinical laboratory values, or the measured vital signs.

Determination of urine zinc, copper, and iron was performed in a 24-hour urine collection and showed no increase in these elements after gadobutrol administration relative to baseline in any age or sex group.

Following i.v.bolus injection of 0.1 mmol/kg gadobutrol, plasma concentrations of gadobutrol decreased rapidly with urinary excretion almost completed 12 hours after injection. The study found no notable differences between the groups. Studies of plasma clearance for the groups noted a moderate effect for the volunteer's age with clearance reduced by approximately 25% and 35% in elderly men and women respectively as compared with non-elderly subjects paralleled with an increase in systemic exposure, (33% and 58% respectively). Gender had no effect on total clearance but there was a slightly higher area under the plasma concentration time curve (AUC) for elderly women.

The applicant provided summary information regarding hepatic impairment based on previous pharmacokinetic studies using a single intravenous dose of gadobutrol in healthy volunteers. As per agreement with the Division prior to submission of the NDA, a specific hepatic impairment study was not performed. The clin pharm reviewer and the applicant both noted the following points:

- Pharmacokinetics of gadobutrol were linear in the dose range studied to include the proposed dose with serum concentrations and AUC increased dose-proportionally within the range.
- Gadobutrol distributed predominantly in the extracellular space.
- Renal clearance was attributed mainly to glomerular filtration, similar to creatinine clearance, with urinary elimination almost complete 12 hours after administration.
- Fecal excretion was measured in only one study in which it was 0.03-0.06% of the injected dose.
- Gadobutrol is not metabolized as demonstrated by the lack of gadolinium containing compounds in the plasma.

Based on the baseline ALT and AST laboratory values as a basis of hepatic impairment, the number of AEs was evaluated for the gadobutrol group and the comparator groups in the phase 2-4 studies. The number of AEs reported was similar. The conclusion regarding the results based on liver function values was that there was no difference in safety between subjects with or without hepatic impairment.

Study 95062 (report B245) was a dedicated study on renal impairment and dialysability. 32 patients were equally distributed in three groups of different stages of renal impairment as defined by serum creatinine clearance: (1) moderate impairment of creatinine clearance, (clearance <80 and >30 mL/min); (2) severe impairment (clearance <30 mL/min) and; (3) requiring dialysis. Patients randomly received 0.1 or 0.3 mmol/kg bw doses. Sampling times were 6 hours, 24 hours, 48 hours, and 72 hours

for all groups with additional sampling at 96 hours and 120 hours for group 3. No dose differences were found.

Four out of 21 patients in groups 1 and 2 demonstrated clinically relevant changes in creatinine clearance which for 2 cases represented a worsening of renal function. None of the changes were considered related to gadobutrol administration, but rather to the underlying diseases or to other causes. Glomerular filtration markers (creatinine, cystatin C, and β2-microglobulin) demonstrated a clinically significant increase in creatinine for one patient but no changes in the markers otherwise. There were no clinically relevant changes in urinary total protein or in microglobulin.One patient had a clinically significant change in α1-microglobulin and N-acetyl-β-D-glucosaminidase attributed to the patient's significant disease.

The conclusion by the applicant, thus, was that there was no influence of gadobutrol on renal function in patients with moderate or severe chronic renal impairment. Decreased clearance of gadobutrol was associated with increasing renal impairment. In the group of patients with severe renal impairment, the maximum elimination half-lives were 23 hours for the 0.1 mmol/kg bw dose and 44.3 hours for the 0.3 mmol.kg bw dose. In patients with mild renal impairment, regardless of dose, the recovery of gadobutrol in urine was complete within 72 hours. In patients with severe renal impairment, recovery was not complete within the study period of 120 hours. In the group of patients with chronic hemodialysis, it was demonstrated that gadobutrol can be eliminated from the body via dialysis with more than 94% of the dose eliminated after three routine dialysis cycles.

The conclusion from the study of renally impaired patients was that while elimination was prolonged, no dosage adjustments were necessary. The details of this study will be considered further by the clin pharm reviewer.

Safety analysis was performed for this study and showed 10 AEs were reported in 6 of 32, (18.8%) of subjects, which included one SAE. Only one AE was of severe intensity. None of the AEs was considered by the investigator to be drug-related. 3 subjects had AEs which continued past the study period and which were attributed to underlying diseases, (kidney malfunction, vertigo, heart failure). In all other subjects, the duration of AEs was from 3 hours to 2 days. The SAE (hemorrhage) occurred more than 3 days after gadobutrol injection and was secondary to a biopsy. The AE profile and frequency was similar for the 2 dose groups, (0.1 mmol/kg and 0.3 mmol/kg bw). AEs classified according to subject number and renal function showed overall 6 subjects with 10 events, 2 subjects and 4 events at <80 and >30 mL/min clearance, 1 subject and 2 events at <30 mL/min clearance, and 3 subjects with 4 events in the dialysis population. Clinically relevant changes in creatinine clearance were recorded in 3, (14.3%) of the 21 subjects with impaired renal function, none related to gadobutrol. Clinically relevant changes from baseline were recorded for 5, (15.6%), of the 32 subjects, none related to gadobutrol. The conclusion by the applicant was that gadobutrol in doses up to 0.3

mmol/kg bw did not affect the safety of subjects with impaired renal function or subjects on hemodialysis. Laboratory results did not show any signs of further renal damage to the subjects in this study attributable to gadobutrol.

Study 310788 in pediatric patients, ages 2-17 years, was a PK study that confirmed similar pharmacokinetics in the pediatric population as in the adult population and concluded that the 0.1mmol/kg bw dose was appropriate for this population. No safety concerns specific for the pediatric population were generated.

Reviewer's Comment: The study in renally impaired subjects was undertaken from 10/96 to 2/98 and was a small clinical trial. Because the association between GBCAs and the development of NSF was not widely known at the time, the trial was appropriate for the population and the conclusions regarding renal function at the time of and shortly after gadobutrol injection are valid.

7.4.6   Immunogenicity

By SOC, it is noted that one subject in the phase 1 studies experienced an anaphylactoid reaction which is considered an immune system disorder. The narrative for this subject follows.

Subject 209/Study 310865/Report A3975

The subject was a healthy 27 year old Japanese male volunteer with no history of allergy. The subject received 14.0 mL, (0.2 mmol/kg bw 1.0 M concentration) of gadobutrol. During the administration, he developed numbness of the tongue, then cough, bulbar hyperemia, wheezing, decreased peripheral oxygen saturation, and wheals. There were no changes in other vital signs such as blood pressure. The symptoms were diagnosed as anaphylactoid reaction. The subject was treated with pharmacotherapy therapy and oxygen inhalation and confirmed as recovered 2 hours after study drug administration.

The overall incidence for allergic reactions in the phase 2-4 studies was <0.1%. Two subjects, (also <0.1% of the total 4549), in the phase 2-4 studies experienced hypersensitivity reactions, also considered an immune system disorder. The narratives for these two subjects follow.

Subject 2003/Study 94054

The subject was a 59 year old male who was injected with gadobutrol >0.09 to 0.11 mmol/kg bw on 7 September 1994. A hypersensitivity allergic reaction consisting of decreased blood pressure, increased heart rate, vomiting, nausea, flushing, and sweating was noted immediately and lasted for 3 hours. Maximum intensity of the

reaction was reported as severe. The reaction was considered to be drug-related but was not considered serious. The drug was withdrawn.

Subject 80691/Study 304562

The subject was a 68 year old male who was injected with gadobutrol >0.09 to 0.11 mmol/kg bw on 10 June 2002. One minute after injection, the subject experienced a hypersensitivity allergic reaction which lasted for 18 hours. Maximum intensity of the reaction was reported as moderate. The reaction was considered to be drug-related but was not considered serious. The drug dose was not changed.

7.5 Other Safety Explorations

7.5.1   Dose Dependency for Adverse Events

Adverse event analysis for the S1 pool, (any adverse event) showed a higher incidence for dose groups >0.31 mmol/kg with nervous system disorders, gastrointestinal disorders, and general disorders and administration site conditions common for all dose groups.

For drug related AEs, there was no clear relationship for concentration. The incidence was somewhat greater for the >0.51-1.01 mmol/kg bw group however the number of subjects in the group was small.

AEs for dose ranges for the S2 pool were analyzed for both the 0.5 M and the 1.0 M concentration of gadobutrol. There was no apparent difference in the overall incidence of AEs between dose groups for the 1.0 M group. Drug related dose AEs were minimally more in the >0.31-0.51 dose group and were similar to comparators, (about 4%). This reviewer noted that gadoteridol did have an 8.7% incidence at the 0.1 mmol/kg bw dose but only 4.3% at the 0.2 mmol/kg bw dose.

For the 0.5 M group there was a higher incidence of AEs, (21.4%) for the >0.11-0.21 mmol.kg bw dose group compared to the other dose groups, (4.25-6.7% with 0% for two subjects only in the >0.31-0.51 mmol/kg bw group). This may have been caused by the relatively small number of subjects in this group since the incidence of AEs in 637 subjects receiving this dose at the 1.0 M concentration was only 10.8%.

Drug related dose AEs were minimally more in the >0.31-0.51 dose group and were similar to comparators, (about 4%). This reviewer noted that gadoteridol did have an 8.7% incidence at the 0.1 mmol/kg bw dose but only 4.3% at the 0.2 mmol/kg bw dose. Drug related AEs by molarity group were generally similar for dose ranges within each molarity group apart from the >0.11-0.21 dose in the 0.5 M concentration group in which

the incidence was 21.4% for the 0.5 M versus 2.8% for the 1.0 M. Drug related AEs incidence was similar for the comparator drugs.

Overall, there was no apparent dose relationship for drug related AEs in the phase 2-4 studies

7.5.2   Time Dependency for Adverse Events

For the phase 1 studies, of the 337 AEs in the gadobutrol group, 50.1% were reported within 30 minutes after the injection and most of the AEs developed within 24 hours after the injection. Twenty three, (6%), AEs of which 3, (1.5%), were drug related developed beyond 24 hours, (>24 to 72 hours) after gadobutrol injection. The percentage of AEs in the 0-30 minute time frame was increased for subjects dosed >0.21 mmol/kg-1.51 mmol/kgbw as well as the two subjects dosed at >1.51 mmol/kg.

For the phase 2-4 studies overall 4.0% of 4549 subjects reported one or more AEs during a follow up period from 24 hours to 7 days after gadobutrol administration. Of the 716 AEs, (all AEs, both drug related and non drug related), reported in the gadobutrol group, 28.0% were reported within 30 minutes after the injection and most developed within 24 hours after the injection. 70.5% of the drug related AEs occurred within the first 3 hours after injection. Fifteen, (6.3%) of the 132, (18.4%) AEs reported 24 to 72 hours after gadobutrol injection were assessed as being drug related. Similar trends were observed in the comparator group.

7.5.3   Drug-Demographic Interactions

The demographics of the trials were reflective of the demographics of the country in which the trial was performed. For phase 1 studies, the following conclusions were noted:

- Analysis of AEs based on race revealed no significant differences in incidence rates or severity.
- Healthy Japanese volunteers showed similar PK parameters to those in the Caucasian population.
- Age had a moderate effect on the pharmacokinetics of gadobutrol in plasma with reduced plasma clearance, (increase in systemic exposure) and in half life in the elderly >65 years.
- Gender generally had no effect on the pharmacokinetics of gadobutrol except in elderly women where a slightly higher area under the curve (AUC) and a lower clearance were observed.
- On evaluation of drug related AEs, incidence and severity was similar for subgroups by sex, age, and body weight.

For the phase 2-4 studies, the following conclusions were noted:

- The incidence of AEs with 1.0 M gadobutrol, (11.9%) was higher than with 0.5 M gadobutrol, (5.7%).
- When stratified by gender, 3.3% of males and 4.9% of females experienced drug related AEs.
- The incidence of all AEs and drug related AEs for subjects 18 to <45 years was slightly higher than other age groups in the same category. There was a 5.8% incidence of drug related AEs in the 138 pediatric subjects.
- Both the overall incidence of AEs and the incidence of drug related AEs was similar for each weight category in each group.
- By ethnic group, incidence of drug related AEs was greater in Blacks, (13.8%) and Hispanics, (8.1%) however there were small numbers of subjects enrolled from these ethnic groups, (58 and 135 respectively as versus 2949 Caucasians and 1242 Asians).
- The incidence of drug related AEs was noted to be greater in the US and Canada but no racial or ethnic trending was noted.

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In summary, evaluation of safety data by demographics revealed no safety signals.

7.5.4   Drug-Disease Interactions

Gadobutrol must be used with caution in patients with chronic renal impairment or acute injury. Gadolinium is thought to act as a "trigger" for nephrogenic systemic fibrosis which potentially may be caused by any gadolinium-based contrast material. The potential for contraindication of this drug in patients with chronic renal disease or acute kidney injury was discussed at the 1-21-11 FDA Advisory Committee meeting.

7.5.5   Drug-Drug Interactions

Gadobutrol is an extracellular gadolinium-based contrast agent which is rapidly distributed in the extracellular space after administration. It is not metabolized and is eliminated by the kidneys via glomerular filtration. The extrarenal elimination is negligible.

There is no potential risk for drug-drug or drug-food interactions. No relevant drug-drug or drug-food interactions have been identified in clinical trials or in post marketing experience.

No drug interaction was observed in clinical trials. As gadobutrol is not metabolized, a metabolic drug interaction with a co-administered drug is unlikely.

7.6 Additional Safety Evaluations

In phase 1 studies, the AEs of allergic reaction were reported in 2, (1.0%) of subjects within 24 hours after injection of gadobutrol, one subject at ≤0.11 mmol/kg bw dose, (subject 410, study 310865), and one subject at >0.11 to 0.21 mmol/kg bw, (subject 209, study 310865.

Subject 209/Study 310865/Report A3975 (see section 7.4.6 above)

The subject was a healthy 27 year old Japanese male volunteer with no history of allergy. The subject received 14.0 mL, (0.2 mmol/kg bw 1.0 M concentration) of gadobutrol. During the administration, he developed numbness of the tongue, then cough, bulbar hyperemia, wheezing, decreased peripheral oxygen saturation, and wheals. There were no changes in other vital signs such as blood pressure. The symptoms were diagnosed as anaphylactoid reaction. The subject was treated with pharmacotherapy therapy and oxygen inhalation and confirmed as recovered 2 hours after study drug administration.

Subject 410/Study 310865/Report A3975

The second subject, a 24 year old Asian male, received gadobutrol at the ≤ 0.11 mmol/kg to 0.21 mmol.kg bw dose and experienced sneezing and urticaria characterized as mild intensity. Sneezing began and ended immediately and urticaria started at 13 minutes and lasted 37 minutes. Other AEs concurrently were rhinorrhea, (0.03 minutes after injection lasting 0 minutes), oral paresthesia (0 minutes) and vomiting, all mild except for 1 minute of moderate intensity vomiting. The AEs resolved upon withdrawal of the contrast agent.

In the S2 integrated analysis pool, (4549 subjects), 6, (0.1%), subjects reported allergic reactions within 24 hours. 5 subjects received >0.09 to 0.11 mmol/kg bw and one subjects received >0.21 to 0.31 mmol/kg bw dose. No AEs were reported in subjects with a history of allergy to contrast media.

Of the 6 subjects identified as having "Intermediate Type Hypersensitivity Reactions", 3 subjects reported AEs in the SOC skin and subcutaneous disorders, (erythema, pruritis, rash, and urticaria), 2 subjects reported immune system disorders, (hypersensitivity), 1 subject reported symptoms in the respiratory, thoracic, and mediastinal disorders, (respiratory arrest), and one subject reported vascular disorder, (hypotension). By preferred term, (PT), each reaction occurred with a < 0.1% incidence. There were no reported reactions in the comparator groups.

The allergic reactions of 5 of the 6 subjects, (all injected with >0.09 to 0.11 mmol/kg bw), were considered drug-related. The allergic reaction of one subject injected with>0.21 to 0.31 mmol/kg bw dose was considered an SAE. The narrative of this

subject, (subject 30001/study 302600), follows Table 36. The AEs of 3 subjects were of mild intensity, 1 subject of moderate intensity, and 2 subjects severe intensity. Relevant details of the allergic reactions are contained in Table 36 below.

Table 36: Subjects With Allergic Reactions Within 24 Hours After Gadobutrol Injection; S2 Integrated Analysis Pool

Study Subject Gender/Age	Gadobutrol Dose Mmol/kg bw	Adverse Event (Preferred Term)	Onset (Relative to Injection) Duration Serious/ Maximum Intensity	Study Drug Action	Relation to Study Drug
94054 20003 Male/59	>0.09-0.11	Hypersensitivity allergic reaction with decreased blood pressure, increased heart rate, vomiting, nausea, flushing, and sweating	0:00 3 hours No/severe	Drug withdrawn	Related
302600 30001 Female/77	>0.21-0.31	Respiratory arrest Hypotension	1:21; 2 sec; Yes/severe 1:21; 5 hours; Yes/severe	Drug withdrawn	Not related
304562 80691 Male/68	>0.09-0.11	Hypersensitivity/ allergic reaction	0.01 18 hours No/moderate	Dose not changed	Related
310123 1400200009 Female/36	>0.09-0.11	Urticaria Pruritis	0:00; 1 day; No/mild 0:00; 98 minutes; No/mild	Dose not changed	Related
310123 140030006ff Female/30	>0.09-0.11	Erythema Pruritis	10:17; 1 hr; No/mild 10:17; 1 hr; No/mild	Dose not changed	Related
310788 1032 Female/14	>0.09-0.11	Rash Pruritis	0:18; 3 hrs; No/mild 0:03; 1 hr; No/mild	Not applicable	Related

Subject 30001/Study 302600/Report A12063
Subject was a female Caucasian who discontinued the study due to an AE of hypotension. The AE started 1 hr 21 minutes after injection of >0.21-0.31 mmol/kg bw gadobutrol. It lasted for 5 hours. The investigator considered it an SAE, severe in intensity, but not related to study drug. The drug was withdrawn and the subject recovered.

Of the total 4549 subjects treated with gadobutrol, 462 subjects had a history of allergies, including allergies to contrast media. 33 subjects had a history of allergies to contrast media. 81, (17.5%), of the 462 subjects developed AEs, only one of which was a hypersensitivity reaction, (subject 1032, study 310788). Seven, (21.2%) of the 33 subjects with a history of allergies to contrast media developed AEs however none of thee were allergic reactions.

7.6.1   Human Carcinogenicity

No carcinogenicity study was performed. Genotoxicity studies were negative in ICH battery.

7.6.2   Human Reproduction and Pregnancy Data

There is no available information on drug exposure in pregnant women for this drug. Gadolinium based contrast agents are known to cross the placenta and thus to result in fetal exposure. Non-clinical studies for gadobutrol showed that minimal amounts of radioactivity were transferred transplacentally to rabbit fetuses or in maternal milk to nursing neonatal rats. Lactating rats were given 0.5 mmol/kg bw Gd-153 gadobutrol with less than 0.01% of the total radioactivity transferred to the neonates via maternal milk within 24 hours.

Retardation of the embryonal development and lethality of the embryo occurred in pregnant rats receiving maternally toxic doses of gadobutrol that were 12.2 times the human equivalent dose based on body surface area and in pregnant rabbits receiving doses that were 8 times the recommended human dose, also based on body surface area. In rabbits, this occurred without evidence of maternal toxicity.

The effects of gadobutrol on reproduction and embryo-fetal development in rats, rabbits, and Cynomolgus monkeys were limited to embryotoxicity in rats at dose levels of ≥5.0 mmol/kg and in pregnant rabbits and Cynomolgus monkeys at dose levels of ≥2.5 mmol/kg. Gadobutrol was not teratogenic when given intravenously during organogenesis at doses up to 16.2 times, (rats), 32.4 times, (rabbits), and 8.1 times, (monkeys), the recommende single human dose based on body surface area. The

repeated daily dose to pregnant animals resulted in significantly higher exposure than the single dose administered to humans.

Single and repeated administrations to mice, rats, and dogs caused only mild clinical signs such as hypoactivity in rats and vomiting with transient reddening of the ear or mucosal memberanes in dogs immediately after administration. Repeated administration daily over 4 weeks did cause vacuolization of renal proximal tubular epithelial cells and urothelia of the upper urinary tract in rats and dogs. Study of embryotoxicity in rats at dose levels ≥5.0 mmol/kg and in pregnant rabbits and Cynomolgus mokeeys at dose levels of ≥2.5 mmol/kg showed that gadobutrol was not genotoxic in vitro or in vivo and there was no evidence of contact sensitization potential. Local irritation only was observed after paravenous administration of the 1.0 M formulation to rabbits.

7.6.3   Pediatrics and Assessment of Effects on Growth

A single dose study in neonatal/newborn rats was performed to support the use of gadobutrol in children below one year of age. Preliminary results of this completed study did not reveal any adverse effects at doses of 0.6 to 6.0 mmol/kg. A PK study, (study 310788) was performed in children ages 2-17 years for dose selection and image evaluation. This study is described in section 7.3 "covered" clinical studies.

7.6.4   Overdose, Drug Abuse Potential, Withdrawal and Rebound

This is not applicable as Gadobutrol is a single administration drug.

7.7 Additional Submissions / Safety Issues

<u>Safety in Subjects With Renal Failure</u>
Analyses of AEs in subjects with renal impairment were not performed for the phase 1 studies due to the small sample size.

For the phase 2-4 studies, out of 38 subjects with eGFR<30 mL/min, 8 subjects reported 10 AE, 3 subjects, each reporting one drug related AE. Of 328 subjects with eGFR 30 to <60 mL/min, 27 subjects reported 45 AEs, with 6 subjects reporting 9 drug related AEs.. Overall percentage of AEs was increased in subjects with eGFR < 30 ml/min, 7.9% versus 3.6% representing the average of all subjects having ≥30 ml/sec to include 2.3% of subjects with a missing value. There was no difference in the incidence of AEs for subjects with renal impairment compared with the incidence of AEs in the total subject population.

Nephrogenic Systemic Fibosis (NSF)
The applicant has reported 10 cases of nephrogenic systemic fibrosis, (NSF) as of 12-31-10, submitted to the US IND 56,410. The number of exposures reported as of this same date is over 6.0 million.

There are two unconfounded (single agent) cases, 200828599GPV and 200923701GPV, described below, both of which are considered as "not excluded" by the applicant:

- **200923701GPV**

  – 60 y.o. M, chronic renal insufficiency since 2003
  – 90 kg
  – 2008 Jun: 17.5 ml Gadovist (MRA)
  – 2008 Jun: skin rash, musculoskeletal pain, thickened skin on legs
  – 2008 Jun: skin biopsy → acute NSF
  – 2009 Mar: skin biopsy → chronic NSF
  – Bayer: "Not excluded"
  – Cowper Score 3,4: consistent with NSF

- **200828599GPV**

  – 68 y.o. M, terminal renal failure, hemodialysis since 2001
  – 61 kg
  – 2005 Apr: 30 ml Gadovist (MRA)
  – 2006 Jun: 10 ml Gadovist
  – 2006 Summer: contractures and fibrotic changes of extremities
  – 2007 Aug: skin biopsy + NSF
  – Bayer: "Not excluded"
  – Cowper Score 4, 2: consistent with NSF

8 Postmarket Experience

The source of review for postmarketing adverse events were the safety updates contained in the NDA submission, (2-26-98 birthdate to January, 2009), the 16th annual PSUR, the 120 day safety update submitted to the NDA, and additional global pharmacovigilance (GPV) data through September, 2010.

The number of exposures to gadobutrol reported **is** approximately 6.0 million.

The applicant reported 1175 Adeverse Event (AE) case reports, 317 of which were Serious Adverwse Events (SAEs) and 3 of which were reports of "overdose." 15 deaths have been reported since 1998, 8 of which were secondary to

anaphylactic/anaphylactoid reaction. There are various reasons for the other 7deaths, for example advanced cardiac disease, GI bleed, and metastatic disease, none of which appear to be related to gadobutrol. The incidence of anaphylactic/anaphylactoid reaction is < 1/1000.

On review of the case reports from birthdate of the product through 9-2010, this reviewer agrees with categorization of 8 deaths as secondary to anaphylaxis/anaphylactoid reaction based on inclusion of two recently reported case reports of fatal pulmonary edema, one of these patients reported as having pulmonary embolism.

The applicant is currently participating in a study to assess the magnitude of potential risk with the administration of gadobutrol in patients with moderate to severe renal impairment or the development of nephrogenic systemic fibrosis, (NSF). This study, referred to as the GRIP-Study is entitled "Prospective non-randomized (pharmacoepidemiologic) cohort study (open-label, multicenter) to assess the magnitude of potential risk with the administration of Gadovist in patients with moderate to severe renal impairment for the development of nephrogenic systemic fibrosis (NSF) based on diagnostically specific clinical and histopathologic information.

Cases reporting NSF have not been received so far for this study.

The conclusion of this reviewer is that the overall postmarketing safety profile is acceptable.

9 Appendices

9.1 Literature Review/References

No additional literature review or references were used for this NDA review.

9.2 Labeling Recommendations

Labeling review has begun. No major labeling issues are anticipated.

9.3 Advisory Committee Meeting

An Advisory Committee meeting took place on 1-21-2011.

The committee voted 16-0 that clinical and postmarketing data support gadobutrol approval.

The committee concurred 15-1 to the labeling of gadobutrol without an NSF contraindication in the at risk population.

The committee discussed plans to address the dosing/volume issues.

TABLES

CLINICAL REVIEW

Application Type	Safety Evaluation Regarding Nephrogenic Systemic Fibrosis (NSF) Risk
Application Numbers	Magnevist--------- NDA 019596, 021037; Prohance--------- NDA 020131, 021489; Omniscan -------- NDA 020123, 022066; Optimark --------- NDA 020937, 020975, 020976; Multihance-------- NDA 021357, 021358; Eovist-------------- NDA 022090; Ablavar------------ NDA 021711; Gadovist----------- NDA 201277 (pending), IND 056410; Dotarem----------- IND (b) (4)
Reviewer Name(s)	Lucie Yang, DMIP / ODE IV / CDER
Review Completion	July 25, 2010

Trade---Name	Established Name	
	Magnevist---------	Gadopentetate dimeglumine;
	Prohance----------	Gadoteridol;
	Omniscan---------	Gadodiamide;
	Optimark----------	Gadoversetamide;
	Multihance--------	Gadobenate dimeglumine;
	Eovist--------------	Gadoxetate disodium;
	Ablavar------------	Gadofosveset trisodium;
	Gadovist-----------	Gadobutrol;
	Dotarem-----------	Gadoterate

Sponsors		
	Bayer----------------	Magnevist, Eovist, Gadovist
	Bracco--------------	Prohance, Multihance;
	Covidien-----------	Optimark;
	GE Healthcare---	Omniscan;
	Guerbet------------	Dotarem
	Lantheus-----------	Ablavar

Diagnostic Class	Gadolinium Based Contrast Agents (GBCAs) for Magnetic Resonance Imaging (MRI)

Table of Contents

Table of Tables

Table of Figures

1 EXECUTIVE SUMMARY

In the four years since the association between Gadolinium-Based Contrast Agents (GBCAs) and Nephrogenic Systemic Fibrosis (NSF) was made, there have been many scientific advances in this field. When the Boxed Warning about NSF was added in 2007 to the prescribing information of all GBCAs approved in the United States, there was not enough information to justify differential risk-based labeling.

This review focuses on whether the prescribing information for GBCAs adequately represents the current science regarding differential risk of NSF among the approved GBCAs. In the course of completing this review, additional issues related to GBCAs and NSF came to the attention of the reviewer.

The reviewer concludes that (a) the prescribing information for GBCAs does not reflect the current science regarding differential NSF risk and (b) Gadovist should be categorized as a GBCA conferring higher NSF risk if/when it is approved in the U.S.

Highlights of the science-based recommendations regarding GBCAs and NSF risk are listed below. The full recommendations start on page 40, and the recommendations are justified on pages 40-50.

- In the Boxed Warning for Omniscan, Optimark, and Magnevist, contraindicate their use in individuals with acute kidney injury (AKI) or severe chronic renal disease (Glomerular Filtration Rate [GFR] < 30 mL/min/1.73m^2).

- Clearly specify in the prescribing information for the three GBCAs listed above and in communications to the public that the contraindication only applies to the at-risk individuals described above (the ~900,000 yearly with AKI and the ~700,000 (0.4%) with severe chronic renal disease in the United States (U.S.)).

- Retain the Boxed Warning about NSF for Multihance, Eovist, Ablavar, and Prohance without adding a contraindication for use in the at-risk population.

- In the prescribing information, recommend screening for acute and severe chronic renal disease, restrict the maximum recommended dose to 0.1 mmol/kg for all GBCAs, and recommend the recording of the GBCA name and dose when administered.

- In the prescribing information for Multihance, correct misleading information regarding relaxivity.

- Contraindicate Gadovist, but not Dotarem, if/when approved in the U.S.

- Determination of NSF risk associated with GBCAs should involve careful consideration of drug-specific effects.

- Collect prospective data on human NSF cases.

2 Introduction and Regulatory Background

2.1 Intent and Scope of This Review

The purpose of this document is (a) to examine whether the current prescribing information for Gadolinium-Based Contrast Agents (GBCAs) adequately reflects the current science regarding the risks of NSF and issues related to NSF risk; (b) to assess potential NSF risks associated with GBCAs not yet approved in the United States; and (c) to recommend steps to reduce the risk of NSF.

Reviewer examined the following information:

- FDA review of GBCAs for regulatory action regarding NSF finalized May 30, 2007;
- Office of Surveillance and Epidemiology (OSE) Review finalized November 6, 2009;
- Addendum to OSE Review finalized June 24, 2010;
- Background material (FDA and sponsors) and transcript for the December 8, 2009 FDA Advisory Committee Meeting [1];
- 2010 American College of Radiology Manual on Contrast Media Chapter on Nephrogenic Systemic Fibrosis [2];
- FDA Drug Safety Oversight Board Minutes from June 17, 2010;
- Submissions from companies marketing GBCAs in response to FDA's Information Request dated June 1, 2009 (August 25, 2009 for Eovist and Ablavar);
- Gadovist MedWatch reports
- Slides from the October 5, 2009 European Medicines Agency Review of GBCAs
- GBCA literature

2.2 Gadolinium Based Contrast Agents (GBCA)

2.2.1 Approved GBCAs, Their Indications, and Recommended Doses

There are currently 7 U.S. FDA-approved GBCAs for magnetic resonance imaging (MRI) (Table 1). Before Eovist and Ablavar were approved in 2008, all approved GBCAs

were indicated for brain and spine MRI. Magnevist and Omniscan were also indicated for abdominal MRI. The chest and pelvic cavities were additional Omniscan indications. Liver MRI was an additional indication for Optimark.

Eovist, approved in 2008, was the first MRI contrast agent approved solely for liver MRI. Ablavar, also approved in 2008, was the first contrast agent approved for magnetic resonance angiography (MRA) in the U.S.

The recommended dose of GBCAs approved prior to 2008 is up to 0.1 mmol/kg administered intravenously (IV) except for Omniscan and Prohance which is indicated for up to 0.3 mmol/kg IV for central nervous system imaging in adults (a second injection of 0.2 mmol/kg within 20 – 30 minutes after the first injection). The two recently-approved agents have much lower recommended doses: 0.025 mmol/kg for Eovist and 0.03 mmol/kg for Ablavar.

2.2.2   Off-Label Use of GBCAs

There has been significant off-label use of GBCAs both in terms of indication and dose. For example, Omniscan has been used as a contrast agent for invasive catheter angiography [3;4]; such intra-arterial administration of contrast is typically performed using an iodinated contrast agent. Omniscan has also been used for venography and computed tomography (CT) at high doses of up to 200 mL (1.4 mmol/kg for a 70 kg individual) [3]. This is much higher than even the highest recommended Omniscan dose which is up to 0.3 mmol/kg (only for the central nervous system).

In addition, breast MRI [5;6] and cardiac MRI [7;8] are performed using GBCAs. No GBCA is currently approved for these indications.

At two U.S. university tertiary care centers, Multihance is currently being dosed at half the recommended dose (0.5 mmol/kg) for gadolinium contrasted MRI studies in adult patients, pediatric patient < 1 y.o., and pediatric patients at risk of developing NSF [9].

Magnetic resonance angiography (MRA, renal, pelvic, lower extremity) is an off-label indication for all GBCAs except for Ablavar. MRA has been routinely performed with administration of double or triple the recommended dose for MRI [10;11], even for Multihance [12, sponsored by Bracco].

2.2.3   Marketed GBCAs That Have Not Attained Approval in the United States

Gadovist (Gadobutrol, sponsored by Bayer) and Dotarem (Gadoteridol, sponsored by Guerbet) are macrocyclic GBCAs that do not have marketing approval in the United States but are marketed in other countries (Figure 1). Current knowledge regarding the risk of NSF associated with these agents is also reviewed in this document.

2.2.4   Highlights of Differences Among GBCAs

2.2.4.1   Physicochemical properties

The most widely accepted theory for NSF development is based on differences in the physicochemical properties of GBCAs [13]. For this reason, a brief overview of GBCA chemistry follows.

Because "free" (unbound) gadolinium ion (Gd^{3+}) is toxic, the gadolinium ion is bound to a ligand to form a chelate in all approved GBCAs [14, sponsored by Guerbet]. The structure of the chelated gadolinium can be linear (open-chain) or macrocyclic, and these molecules can be further described by charge: nonionic or ionic (Figure 1). The nine coordination sites of the gadolinium represent the number of bonds between atoms (nitrogen [N] or oxygen [O]) in the ligand (or a water molecule) and the metal ion [15]. Both the number and the nature of the bonds (carboxyl, methyl amide, or other) determine the stability of the chelate.

In a _macrocyclic_ chelate (Prohance, Gadovist, Dotarem), the ligand is a preformed ring that fits around the gadolinium ion. Macrocyclic GBCAs are thought to have greater difficulty releasing free Gd^{3+} than linear chelates due to the tight packing and rigidity [16, sponsored by Guerbet]. _Linear nonionic_ chelates (Omniscan, Optimark) are thought to form free Gd^{3+} more readily than the other classes of GBCAs because the groups forming bonds to the gadolinium ion are less basic (and therefore bound more weakly) and have increased flexibility and conformational mobility [14, sponsored by Guerbet]. Among the _linear ionic_ chelates, those that have a bulky aromatic group (Multihance, Eovist, Ablavar) may have less flexibility and therefore greater kinetic stability than those that do not (Magnevist) [14, sponsored by Guerbet;17, see article for potential conflicts of interest].

Different amounts of free ligand are present in the formulations of different GBCAs (Table 2). It is theorized that excess ligand is added to reduce the amount of free Gd^{3+} formed. Linear nonionic GBCAs are formulated with the greatest amount of excess ligand--Optimark with the most, followed by Omniscan.

The amount of free gadolinium ion present likely depends on the structure and charge of the chelate, as well as the amount of excess ligand (Table 2). Some of these characteristics determine the thermodynamic and kinetic stability of the GBCAs (see below). These _in vitro_ measurements may help assess the likelihood of free gadolinium ion formation _in vivo_.

The thermodynamic stability constant describes the strength of association between the Gd^{3+} and the ligand at equilibrium. When measured at physiologic pH, it is called conditional stability. A higher value implies greater stability and lower amounts of free gadolinium ion. The ionic GBCAs have a higher conditional stability constant than the nonionic GBCAs (Table 2). Factors that influence thermodynamic stability include 1)

how basic the ligand is, 2) the number of 5-membered rings (N-Gd-N and N-Gd-O) formed between the gadolinium and atoms of the ligand (8 for macrocyclic chelates, 6 for linear chelates), and 3) for macrocyclic chelates, the cavity size of the ligand ring, and the preorganization, rigidity, and conformation of the ligand [16, sponsored by Guerbet].

The conditional stability values in Table 2 were mostly adapted from [18]. Importantly, these values were not obtained in a single experiment. It would be very useful to know the conditional stability of all GBCAs measured under identical conditions.

The kinetic stability constant describes the rate of dissociation of the gadolinium-ligand complex, which could be influenced by displacement of the gadolinium ion by endogenous metals such as zinc, calcium, iron, or copper (transmetallation). One measure of kinetic stability is the half-life of dissociation ($t_{1/2}$) of the gadolinium-chelate complex. Although these *in vitro* kinetic stability measurements are performed under acidic conditions (due to faster dissociation at low pH), it is accepted as a reliable predictor of *in vivo* stability [19, sponsored by Bristol-Myers Squibb]. A longer $t_{1/2}$ implies slower formation of free gadolinium ion. Of the approved GBCAs for which $t_{1/2}$ is available, Prohance (a macrocyclic GBCA) has the highest kinetic stability (Table 2). Dissociation half-lives are significantly longer for macrocyclic (hours) than for linear chelates (seconds to minutes) when measured using the same assay [14 and references therein, sponsored by Guerbet;20, sponsored by Guerbet].

In vitro kinetic stability of GBCAs has also been assessed in human serum under physiologic conditions ($37^{o}C$, pH 7.4) and under conditions simulating those in patients with end-stage renal disease ($37^{o}C$, pH 7.4, +10 mmol/L phosphate), many of whom have elevated phosphate levels [21, sponsored by Bayer-Schering]. In serum, the initial free gadolinium ion release rates of linear nonionic GBCAs (Omniscan and Optimark) were higher than those of linear ionic GBCAs (Magnevist, Multihance, Eovist, Vasovist), which were higher than those of the macrocyclic GBCAs (Prohance, Gadovist, and Dotarem) (Table 3). These differences were magnified by the addition of 10 mmol phosphate (PO_4). Similar trends were seen in the total amount of Gd^{3+} released after 15 days, including differences between the classes of GBCAs and the magnification of these differences after addition of phosphate.

To put conditional stability and kinetic stability in the context of one another, conditional stability describes the ratio of concentrations of the metal, ligand, and metal-ligand complex at equilibrium. Kinetic stability describes the rate of dissociation of the metal-ligand complex and therefore the time required to achieve equilibrium. The ability of different individuals to eliminate GBCAs varies: for most GBCAs, this depends on renal function status. In some individuals, renal function may be so minimal that equilibrium is achieved or nearly achieved even for GBCAs with great kinetic stability (see sections 2.3 and 3.2.2.2).

In vivo study results appear consistent with predictions based on the physicochemical properties of GBCAs. Studies in rodents demonstrate greater amounts of gadolinium

retained in the skin and other tissues after exposure to linear GBCAs than to macrocyclic ones [22, sponsored by Bayer-Schering;23, sponsored by Bracco;24, sponsored by Bayer-Schering]. Addition of excess ligand reduced skin retention of linear nonionic formulations and lowered the number of animals with increased skin cellularity and fibrosis, suggesting a role for free gadolinium ion in the pathogenesis of NSF [25, sponsored by Bayer-Schering].

Human studies are also consistent with *in vitro* measurements suggesting that a macrocyclic GBCA is less likely to release free gadolinium ion than a linear nonionic chelate [26;27]. Omniscan administration results in two to four times more gadolinium in the bone 3 to 8 days after injection than Prohance administration at the same dose (0.1 mmol/kg) in different patients.

The main criticism of previous human studies detecting gadolinium in tissue is that the available methods do not differentiate between free gadolinium ion and chelated gadolinium. A 2010 publication provides the first direct evidence for release of gadolinium ions from the chelate in human tissue [28].

2.2.4.2   Elimination

All GBCAs are excreted through the urinary system. With the exception of three approved GBCAs, hepatic excretion is negligible (Table 2). According to their respective Prescribing Information, excretion through bile is 50% for Eovist, 0.6-4% for Multihance, and ~5% for Ablavar.

2.2.4.3   Relaxivity

GBCAs also differ in relaxivity [29] (Table 2). Some agents have higher relaxivity due to transient binding to albumin. Among the approved agents, Vasovist has the highest relaxivity (19.0 at 1.5 Tesla). The linear nonionic GBCAs (Omniscan, Optimark), the macrocyclic GBCAs (Prohance, Gadovist, Dotarem), and Magnevist have the lowest relaxivities, in the 3.5 to 5 range. Multihance and Eovist have slightly higher relaxivities (6.7 and 6.9, respectively), but still ~3 times lower than the relaxivity of Vasovist. For agents with higher relaxivity, a smaller dose may achieve a given "enhancement" level [30, see article for potential conflict of interest]. As noted above, the recommended dose for Eovist (0.025 mmol/kg) and Vasovist (0.03 mmol/kg) are much lower than for all the other approved agents (typically 0.1 mmol/kg).

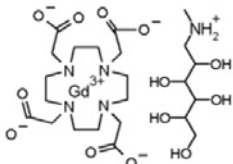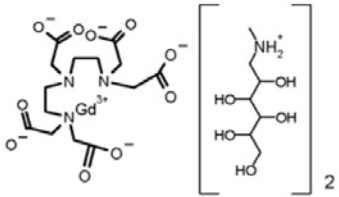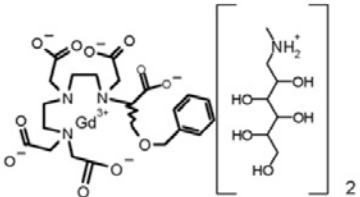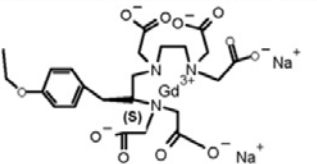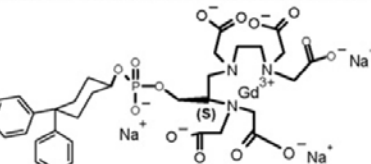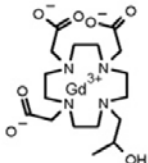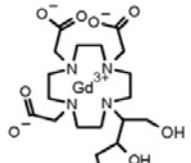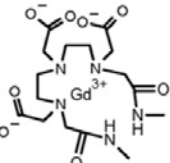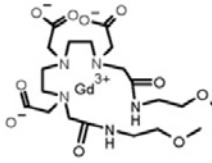Due to the reported relaxivity difference, Multihance is being used at half the recommended dose (0.05 mmol/kg) at some institutions [9;31]. Of note, FDA has not approved the efficacy of the half-dose of Multihance. In fact, the current Prescribing

Table 1. GBCAs (ordered by date of 1st U.S. approval), their indications, doses, and intended populations.

Trade Name (Marketer)	NDA#	Approval Year	Established Name	Dosing Regimen (mmol/kg)		Indication
				Adults	Pediatric	
Magnevist (Bayer)	19596, 21037	1988, 2000	Gadopentetate dimeglumine	0.1	≥2 y.o.: 0.1	MRI-- brain, spine; body (noncardiac)
Prohance (Bracco)	20131, 21489	1992, 2003	Gadoteridol	0.1; for CNS, 0.2 may be given 30 min later	CNS: 0.1; extracranial / extraspinal: N/A	MRI-- brain, spine
Omniscan (GE Healthcare)	20123, 22066	1993, 2007	Gadodiamide	0.1 except kidney (0.05) & CNS (0.2 may be given 20 min later)	≥2 y.o.: 0.1 except kidney (0.05)	MRI-- brain, spine; thoracic (noncardiac), abdominal, pelvic cavities; retroperitoneal space
Optimark (Covidien)	20937, 20975, 20976	1999, 1999, 1999	Gado-versetamide	0.1	N/A	MRI-- brain, spine; liver
Multihance (Bracco)	21357, 21358	2004, 2004	Gadobenate dimeglumine	0.1	>2 y.o.: 0.1	MRI-- brain, spine
Eovist (Bayer)	22090	2008	Gadoxetate disodium	0.025	N/A	MRI-- liver
Ablavar (Lantheus)	21711	2008	Gadofosveset trisodium	0.03	N/A	MRA-- aortoiliac

CNS: Central Nervous System; MRA: Magnetic Resonance Angiography; N/A: not applicable

Figure 1. Chemical structures of GBCAs marketed worldwide.

Note:

Primovist =
Eovist in U.S.

Vasovist =
Ablavar in U.S.

Figure adapted from [32, sponsored by Guerbet]. Open-chain means linear. Primovist is marketed as Eovist in the U.S., Vasovist is now marketed as Ablavar. Dotarem (marketed by Guerbet) and Gadovist (marketed by Bayer) are not approved in the U.S.

Table 2. Worldwide marketed GBCAs grouped by structure and charge.

Trade Name	Established Name	Structure	Charge	Excess Ligand (mmol/L)	Conditional Stability (pH 7.4, log K_{cond})	Kinetic Stability[^] ($t_{1/2}$; hours)	Excretion[^^]	Relaxivity[^^^]
Omniscan	Gadodiamide	Linear	Nonionic	25	14.9	0.01	Renal	4.6
Optimark	Gado-versetamide	Linear	Nonionic	50	15.0	NA	Renal	5.2
Magnevist	Gadopentetate dimeglumine	Linear	Ionic	1	17.7-18.4	0.16	Renal	4.3
Multihance	Gadobenate dimeglumine	Linear	Ionic	0	18.4	NA	Renal (>96%); Biliary (0.6-4%)	6.7
Eovist	Gadoxetate disodium	Linear	Ionic	**	18.7*	NA	Renal (50%); Biliary (50%)	6.9
Ablavar	Gadofosveset trisodium	Linear	Ionic	**	18.9*	NA	Renal (95.3%); Biliary (4.7%)	19.0
Prohance	Gadoteridol	Macrocyclic	Nonionic	0.5	16.9-17.2	1.6	Renal	4.4
Gadovist	Gadobutrol	Macrocyclic	Nonionic	1	14.7-15.5[†]	7.0	Renal	5.2
Dotarem	Gadoterate	Macrocyclic	Ionic	0	18.8-19.3	23.0	Renal	3.6-4.2[††]

Table adapted from [18] unless otherwise noted. For certain conditional stability, [18] states that the data or data range are from several sources. NA: not available. * adapted from Eovist Briefing Document for December 8, 2009 Advisory Committee [1]. ** 1.0 mg/mL for Eovist, 0.27 mg/mL for Ablavar, both adapted from Eovist Briefing Document for December 8, 2009 Advisory Committee [1]. [†] 15.5 from [21, sponsored by Bayer-Schering]. [^] 37°C, pH 1, adapted from [18]; according to [21, sponsored by Bayer-Schering], at pH 5.3, 25°C, the $t_{1/2}$ of Gadovist (65 yrs) was longer than that of Prohance (36 yrs). See also [15;33;34, sponsored by Guerbet;35, sponsored by Bayer-Schering]. [^^] Adapted from the respective Prescribing Information. [^^^] T1-relaxivity in plasma [L/(mmol*s)], 37°C, 1.5 Tesla, values adapted from [29, see article for potential conflict of interest]. [††] 4.2 in [18].

Table 3. Initial Gd^{3+} release rate and the amount of Gd^{3+} released.

	Initial Gd^{3+} release rate (%/day)		Release of Gd^{3+} after 1 day (% of total Gd^{3+})		Release of Gd^{3+} after 15 days (% of total Gd^{3+})	
	Serum	+PO$_4$	Serum	+PO$_4$	Serum	+PO$_4$
Omniscan	0.16 (0.15-0.17)	61 (26-87)	0.14 (0.12-0.15)	21 (19-21)	20 (17-20)	37 (35-40)
Optimark	0.44 (0.40-0.51)	42 (37-132)	0.61 (0.58-0.65)	19 (17-20)	21 (19-22)	37 (36-40)
Magnevist	0.16 (0.12-0.36)	5.4*	0.34 (0.26-0.43)	1.8 (0.5-3.1)	1.9 (1.2-2.0)	2.2 (0.9-3.5)
Multihance	0.18 (0.13-0.38)	5.2*	0.35 (0.27-0.47)	1.9 (0.7-3.1)	1.9 (1.3-2.1)	2.2 (1.0-3.4)
Eovist	0.07 (0.05-0.08)	0.9 (0.7-1.8)	<0.1	0.56 (0.52-0.62)	1.1 (0.8-1.2)	1.5 (1.4-1.5)
Vasovist	0.12 (0.11-0.18)	1.4 (1.0-3.2)	0.26 (0.18-0.31)	0.63 (0.56-0.66)	1.8 (1.4-1.9)	1.8 (1.7-1.9)
Prohance	<0.007	<0.007	<0.1	<0.1	<0.1	<0.1
Gadovist	<0.007	<0.007	<0.1	<0.1	<0.1	<0.1
Dotarem	<0.007	<0.007	<0.1	<0.1	<0.1	<0.1

Adapted from [36], a study sponsored by Bayer-Shering Pharma.
Serum: under physiologic conditions (serum, pH 7.4, 37°C);
+PO$_4$: under conditions that simulate those in patients with severe renal impairment (serum + 10 mmol/L PO$_4$, pH 7.4, 37°C).

Figure 2. Table in current prescribing information for Multihance.

TABLE 2: RELAXIVITY ($mM^{-1}s^{-1}$) OF GADOLINIUM CHELATES		
	Human plasma	
	r_1	r_2
Gadobenate	9.7[1]	12.5[1]
Gadopentetate	4.9[1]	6.3[1]
Gadodiamide	5.4[2]	--
Gadoteridol	5.4[2]	--

r_1 and r_2 relaxivities indicate the efficiency in shortening T1 and T2 relaxation times, respectively.
[1] In heparinized human plasma, at 39°C.
[2] In citrated human plasma, at 37°C.
-- Not available

Adapted from [31].

Figure 3. Relaxivities of select GBCAs in plasma at 37°C at various magnetic field strengths.
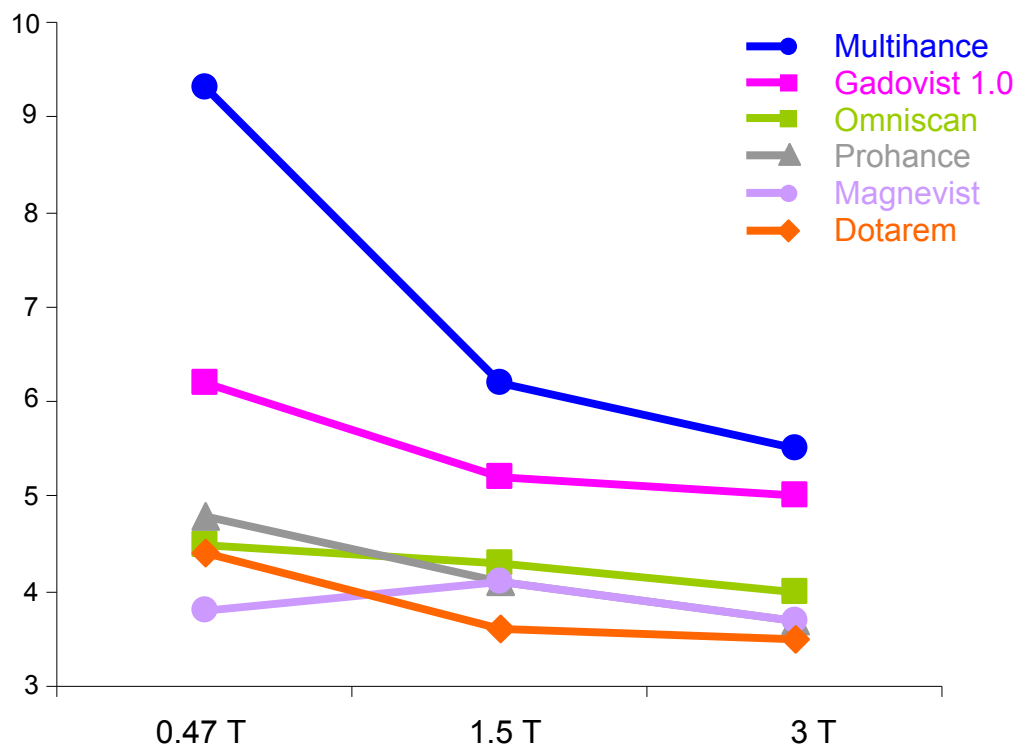
Adapted from [37].

Information states "the 0.05 mmol/kg dose of MultiHance provided inconsistent visualization results between readers."

The relaxivity of Multihance is listed in a table in the Prescribing Information as approximately twice that of other tested GBCAs [31] (see also Figure 2). However, it is not stated that these relaxivities were measured at 0.47 Tesla [38, sponsored in part by Schering] and that relaxivities depend on the field strength of the magnet. The clinically relevant magnet strengths are 1.5 Tesla and 3 Tesla. At 1.5 Tesla, the relaxivity of Multihance is only about 1.5 fold higher than the other GBCAs currently listed in the Multihance prescribing information [39, see also Table 2]. At 3 Tesla, the difference in relaxivity among GBCAs further diminishes [37] (see also Figure 3).

2.3   What is NSF and Who is at Risk

The association between GBCAs and NSF was made by Grobner in 2006 [40].

Nephrogenic systemic fibrosis is characterized by pain, dermopathy, and joint contractures [41]. NSF presents with skin thickening and hardening. As a result, the condition was initially called Nephrogenic Fibrosing Dermopathy. However, when it was discovered that the widespread fibrosis and collagen deposition extend beyond the skin to affect muscles, heart, lungs, diaphragm, esophagus, kidneys, and testes, the name was revised to Nephrogenic Systemic Fibrosis. NSF usually presents within months following GBCA administration, though the range is from days to years following exposure. NSF can be a severely debilitating condition which may progress to joint stiffness and contractures, cachexia, difficulty breathing, difficulty swallowing, and in some cases, death.

One of the difficulties in determining NSF incidence in the three years following Grobner's discovery is that there was no generally accepted diagnostic criteria for NSF. One effort to change this was spearheaded by Shawn Cowper (a Dermatology and Pathology Professor who maintains an NSF registry at Yale University) who, together with a multidisciplinary team of clinicians and dermatopathologists, completed a clinicopathological definition of NSF [42] in 2009. This definition uses a combination of clinical and histological features [43;44, see also section 6.2], but the manuscript is still undergoing peer review and the definition is not widely accepted yet.

Individuals with acute kidney injury or severe chronic renal impairment (GFR < 30 mL/min/1.73m^2) who are administered GBCA are at highest risk for NSF [41]. Of note, only a small minority of patients with severe chronic kidney disease who are administered a GBCA develop NSF [45;46]. Other risk factors include high or multiple GBCA dose and proinflammatory conditions [41;47]. In patients with severe renal compromise, the elimination half-life of extracellular fluid GBCAs (all but Ablavar) may exceed 30 hours, significantly longer than the half-life in healthy volunteers (~1.5 hours) [11;16, sponsored by Guerbet].

The percent of GBCA recovered in the urine is lower in subjects with greater renal impairment [48]. For example, in subjects with normal renal function, GBCA recovery in urine is complete by 7 days after administration and >90% is recovered in urine within 12 hours. In 4 patients with a creatinine clearance < 30 mL/min who were administered 0.3 mmol/kg Gadovist, the mean percent recovery in urine by 5 days after dosing was ~85% [49, sponsored in part by Schering]. The mean recovery dropped to ~75% after 5 days for humans with a creatinine clearance < 10mL/min.

For those with chronic renal dysfunction, all NSF patients had a GFR < 30 mL/min/1.73m^2 except for a few who had a GFR between 30 and 60 mL/min/1.73m^2 [2]. NSF has no predilection based sex or race [50].

The at-risk population includes patients with acute renal failure and patients with severe chronic renal failure (GFR < 30 mL/min/1.73 m^2 [Stage 4 or 5]). Based on an estimate of 288 per 100,000 U.S. population in 2002 with acute renal failure [51] and an estimated current U.S. population of nearly 310 million [52], the yearly incidence of acute kidney injury is ~893,000. The prevalence of Stage 4 or 5 chronic renal disease is 0.4% (700,000) of the U.S. population [53]. Of note, it has been estimated that only 45% of patients with GFR between 30 and 60 mL/min/1.73m^2 are aware of their poor kidney function status [54].

To date, there is no effective treatment for NSF [50].

2.4 2006-2007 FDA Advisories and Regulatory Actions Pertaining to NSF

In 2006 and 2007, the U.S. FDA issued two Public Health Advisories to increase awareness of NSF and recommended actions to reduce the risk of NSF. FDA also requested that manufacturers of all GBCAs add the following Boxed Warning to the Prescribing Information stating the population considered to be at highest risk for NSF and actions to mitigate the risk.

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS

Gadolinium-based contrast agents increase the risk for nephrogenic systemic fibrosis (NSF) in patients with:

- **acute or chronic severe renal insufficiency (glomerular filtration rate < 30 mL/min/1.73m2), or**
- **acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period.**

In these patients, avoid use of gadolinium-based contrast agents unless the diagnostic information is essential and not available with non-contrast enhanced magnetic resonance imaging (MRI). NSF may result in fatal or debilitating systemic fibrosis affecting the skin, muscle and internal organs. Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests. When administering a gadolinium-based contrast agent, do not exceed the recommended dose and allow a sufficient period of time for elimination of the agent from the body prior to any readministration [*see Warnings and Precautions (x)*].

Furthermore, FDA requested additional text in the Warnings or Warnings and Precautions sections of the Prescribing Information for all GBCAs:

> Gadolinium-based contrast agents increase the risk for nephrogenic systemic fibrosis (NSF) in patients with acute or chronic severe renal insufficiency (glomerular filtration rate <30 mL/min/1.73 m2) and in patients with acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period. In these patients, avoid use of gadolinium-based contrast agents unless the diagnostic information is essential and not available with non-contrast MRI. For patients receiving hemodialysis, physicians may consider the prompt initiation of hemodialysis following the administration of a gadolinium-based contrast agent in order to enhance the contrast agent's elimination. The usefulness of hemodialysis in the prevention of NSF is unknown.
>
> Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of a gadolinium-based contrast agent and the degree of renal function impairment at the time of exposure.
>
> Post-marketing reports have identified the development of NSF following single and multiple administrations of gadolinium-based contrast agents. These reports have not always identified a specific agent. Where a specific agent was identified, the most commonly reported agent was gadodiamide (Omniscan™), followed by gadopentetate dimeglumine (Magnevist®) and gadoversetamide (OptiMARK®). NSF has also developed following sequential adminstrations of gadodiamide with gadobenate dimeglumine (MultiHance®) or gadoteridol (ProHance®). The number of post-marketing reports is subject to change over time and may not reflect the true proportion of cases associated with any specific gadolinium-based contrast agent.
>
> The extent of risk for NSF following exposure to any specific gadolinium-based contrast agent is unknown and may vary among the agents. Published reports are limited and predominantly estimate NSF risks with gadodiamide. In one retrospective study of 370 patients wit severe renal insufficiency who received gadodiamide, the estimated risk for development of NSF was 4% (J Am Soc Nephrol 2006; 17:2359). The risk, if any, for the development of NSF among patients with mild to moderate renal insufficiency or normal renal function is unknown.
>
> Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests. When administering a gadolinium-based contrast agent, do not exceed the recommended dose and allow a sufficient period of time for elimination of the agent prior to any readministration [*see Dosage and Administration (x) and Clinical Pharmacology (y)*].

Notably, the 2007 changes to the Prescribing Information requested by the U.S. FDA did not stratify NSF risk among GBCAs.

FDA also requested that companies marketing GBCAs commit to conducting a prospective observational study to quantify NSF incidence in individuals with moderate renal impairment and in individuals with severe renal impairment. These became PostMarketing Requirements (PMR).

2.5 2007 European Medicines Agency (EMEA) Advisories and Regulatory Actions Pertaining to NSF

In contrast to the regulatory actions of the U.S. FDA, the European Medicines Agency (EMEA) differentiated among GBCAs regarding NSF risk in 2007. The Direct Healthcare

Professional Communication (DHPC) issued by the EMEA in February 2007 stated that Omniscan should not be used in patients with severe renal dysfunction (GFR < 30 mL/min/1.73 m^2) or in individuals awaiting liver transplantation. A June 2007 DHPC added a similar contraindication for Magnevist and advised careful consideration before using Omniscan or Magnevist in patients with moderate renal impairment (30 mL/min/1.73m^2 < GFR < 60 mL/min/1.73m^2) or in children up to 1 year old. The DHPC also advised careful consideration for using other GBCAs in patients with severe renal dysfunction.

Of note, Optimark was not approved by EMEA until July 23, 2007, which was after the DHPC were issued [55]. Upon marketing in 2007, the Prescribing Information for Optimark included a contraindication similar to those for Omniscan and Magnevist: patients with severe renal impairment (GFR < 30 mL/min/1.73m^2) and individuals who have had or are undergoing liver transplantation [56].

The 2007 European Society of Uroradiology guidelines similarly contraindicate Omniscan, Magnevist, and Optimark for imaging patients with GFR < 30 mL/min [57].

2.6   2007 American College of Radiology (ACR) Recommendations Regarding NSF

In 2007, the ACR convened a panel of experts and published a Guidance Document for Safe Magnetic Resonance Practices [58]. This document recommended against the use of Omniscan for patients with any renal insufficiency. For other GBCAs, a risk-benefit consideration was recommended prior to administration. Below are quotes from this document.

> "Patients with any level of renal disease should not receive Omniscan for their contrast-enhanced MR examinations."

> "For patients with stage 3, 4, or 5 kidney disease or those with acute kidney injury (AKI), it is recommended that one consider refraining from administering any GBMCAs unless a risk-benefit assessment for that particular patient indicates that the benefit of doing so clearly outweighs the potential risk(s)."
> GBMCA: gadolinium-based MR contrast agent

2.7 Public Health Effects of 2006-2007 Regulatory Actions and Professional Society Recommendations Regarding NSF

2.7.1 Impact of Regulatory Actions and Professional Society Recommendations on NSF Incidence

As a result of the 2006-2007 regulatory actions and professional society recommendations, there was a significant decline in the number of new NSF cases. According to the FDA Briefing document for the December 8, 2009 Advisory Committee, "Very few of the reports received by the FDA since January 1, 2008 describe cases in which administration of a GBCA was on or after 2006, when FDA [issued] its first public advisory on the issue of NSF with GBCAs."

This decline in the number of new NSF cases since 2007 is corroborated by information from the pharmacovigilance databases of companies marketing GBCAs (Table 4, [1]). This decrease in NSF cases may in part be due to clinicians ordering computed tomography (CT) exams instead of MRI exams in high risk patients despite the risk for contrast induced nephropathy from iodinated contrast agents [59].

Notably, GE Healthcare reports 0 NSF cases plausibly associated with Omniscan with onset date after September 2007 [60] (Table 4); the 2008 and 2009 numbers are a significant drop from > 80 NSF cases per year with onset dates in 2006 and 2007. A similar trend is seen for Optimark and Magnevist, though the number of cases did not reduce to 0 or 1 until 2009.

The number of cases <u>reported</u> were steady or increased between 2007 and 2009 for Omniscan, Optimark, and Magnevist (Table 5), but the <u>onset dates</u> of these cases were mostly prior to 2007 (Table 4).

Of note, different companies use different definitions of "event date." GE Healthcare does not explicitly define what is meant by "date of onset." For Bayer, event date is defined as the onset date of signs and symptoms suggestive of NSF (or the diagnosis date by skin biopsy or clinically, when onset date is unclear or not provided). For Covidien, event date represents the diagnosis date with or without biopsy.

In addition, a significant number of cases do not have known onset dates. For example, according to GE Healthcare, 284 NSF cases associated with Omniscan do not have a known onset year.

The dramatic reduction in the number of NSF cases over the last 3 years is in part due to adoption of more restrictive policies for GBCA use and, at some institutions, switching between GBCAs.

Table 4. Worldwide cases <u>with known onset date</u> in company pharmacovigilance databases, by <u>event dates</u>.*

Contrast agent	# Cases with known onset date**	2000 Jan-Jun	2000 Jul-Dec	2001 Jan-Jun	2001 Jul-Dec	2002 Jan-Jun	2002 Jul-Dec	2003 Jan-Jun	2003 Jul-Dec	2004 Jan-Jun	2004 Jul-Dec	2005 Jan-Jun	2005 Jul-Dec	2006 Jan-Jun	2006 Jul-Dec	2007 Jan-Jun	2007 Jul-Dec	2008 Jan-Jun	2008 Jul-Dec	2009 Jan-Jun
Omniscan^	337	9	5	5	5	9	14	24	23	20	29	41	47	40	47	17	2	-	-	-
Optimark	53	-	-	-	1	-	-	2	-	-	2	1	3	9	8	14	9	2	1	1
Magnevist	208	-	-	-	-	5	6	10	7	13	9	10	24	25	28	36	17	9	9	0
Multihance	7	-	-	-	-	-	1	-	-	-	-	2		1		-	1	2	-	-
Eovist	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Vasovist	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Prohance	11	1	-	-	-	-	-	-	-	-	-	-	2	1	4	-	2	1	-	-

* Single-agent and multi-agent cases.
**Of the 281 "reportable" cases shown in Table 10, section 6.1 for Magnevist.
^ Numbers for Jul-Dec include the cases in which the month is unknown for that year. The number in 2000 Jan-Jun also includes the 3 cases with onset dates between 1996 and 1999.

Table 5. Worldwide cases in company pharmacovigilance databases, by <u>reporting dates</u>.

Contrast agent	2006 Jan-Jun	2006 Jul-Dec	2007 Jan-Jun	2007 Jul-Dec	2008 Jan-Jun	2008 Jul-Dec	2009 Jan-Jun
Omniscan	24	48	119	94	141	79	102
Optimark	-	2	6	10	11	28	13
Magnevist	-	13	72	25	59	70	42
Multihance	-	1	1	2	-	4	2
Eovist	-	-	-	-	-	-	-
Vasovist	-	-	-	-	-	-	-
Prohance	-	-	3	-	6	6	-

22

One institution administering Omniscan and Magnevist implemented policies regarding screening for renal dysfunction prior to GBCA use and conservative use of GBCAs in patients with severe renal dysfunction [4]. As a result, the NSF incidence dropped from 36.5 cases per 100,000 GBCA procedures between 2004 and 2006 to 4 cases per 100,000 GBCA procedures between 2007 and 2008. There were no new cases in 2008 at this institution.

Two other institutions (a) implemented screening and restrictive GBCA use policies and (b) switched from Omniscan to Multihance (adults and pediatric patients at risk of NSF) and Magnevist (all other pediatric patients) [9]. In high-risk patients, Multihance is administered at half the recommended dose (0.5 mmol/kg). As a result, there have been no new NSF cases at these two institutions (not even in the 549 patients at high risk for NSF who were administered a GBCA).

Another institution also instituted strict screening and GBCA use policies, and changed from Omniscan to Multihance [61]. The NSF incidence at this institution also decreased from 6 NSF cases in 91 at-risk individuals before the changes to 0 NSF cases in 81 at-risk individuals afterwards.

At the U.S. Veterans Affairs health care system, the 2007 regulatory actions and professional society recommendations resulted in increased laboratory screening of renal function (serum creatinine) and decreased use of GBCAs in patients with GFR < 30 mL/min/1.73m^2 [62, see article for potential conflict of interest]. The effect of these changes on NSF incidence at Veterans Affairs centers is not stated.

2.7.2 Impact of Regulatory Actions and Professional Society Recommendations on Prospective Observational Studies

As mentioned in section 2.4, FDA also required companies marketing GBCAs to conduct prospective observational studies to quantify NSF incidence resulting from use of their products. For each marketed product, 400 subjects with GFR < 30 mL/min/1.73 m^2 and 600 subjects with GFR between 30 and 60 mL/min/1.73 m^2 (total of 1000 subjects) were to be enrolled in the study.

By Fall 2009, the studies for Omniscan, Optimark, and Magnevist had not enrolled even 30 subjects. In contrast, the studies for Multihance, Eovist, and Prohance had all enrolled at least 30 subjects (Table 6). The companies marketing Omniscan and Optimark report that enrollment into the studies is largely hindered by hospitals not using those products in patients with renal impairment (see section 6.1), among other reasons. The company marketing Magnevist relaxed the exclusion criteria in the protocol to exclude only patients with exposure to any GBCA *except Magnevist* because they had difficulty enrolling when the protocol excluded subjects with a history of any GBCA exposure.

Table 6. Summary of progress on Post Marketing Requirements as of Fall 2009.

Contrast agent	Date protocol finalized	Date 1st patient enrolled	# Patients enrolled to date	# NSF cases to date	Sites
Omniscan	NR	NR	1	NR	1 enrolling
OptiMARK	Apr 2008	-	0	-	1 enrolling
Magnevist	Feb 2008	Nov 2008	26	0	12 activated
MultiHance	Sept 2007	Jan 2008	174	0	13 enrolling
Eovist	Oct 2008	May 2008	34	0	19 activated
Vasovist	-	-	-	-	-
ProHance	Sept 2007	Feb 2008	50	0	5 enrolling

NR: not reported

In November 2009, the company marketing Optimark voluntarily contraindicated Optimark in patients with GFR < 30 mL/min/1.73m^2 and in certain patients with acute renal insufficiency [63, see also section 4.2].

2.8 Class Labeling

According to FDA [64], class labeling applies to drugs that are "closely related in chemical structure, pharmacology, therapeutic activity, and adverse reactions." However, drugs in a class are not interchangeable [64;65]. This is because a drug's effect is a combination of the class effect and the drug-specific effect. In fact, drugs within a class may have such different adverse effects that certain drugs are withdrawn from the market whereas others within the same class are allowed to continue marketing. Classes for which this has occurred include nonsteroidal anti-inflammatory drugs (NSAIDs), beta-blockers, statins, and calcium channel blockers (CCB).

For example, the COX-2 selective NSAIDs refecoxib (Vioxx) and valdecoxib (Bextra) were withdrawn due to concern for increased risk of cardiovascular events, but celecoxib (Celebrex) and a number of nonselective NSAIDs continue to be marketed [66]. The first two beta-blockers pronethalol and practolol were withdrawn due to safety reasons [64]. The statin cerivastatin (Baycol) was withdrawn after 31 deaths from rhabdomyolysis were reported [67]. Finally, the antihypertensive mibefradil (Posicor), a CCB, was withdrawn after it was discovered that the drug inhibits cytochrome P450 2D6 and 3A4 which are necessary for preventing dangerously high plasma levels of drugs metabolized by these cytochromes [68]. Many other statins and CCBs remain on the market.

Of note, assuming that drugs within a class are interchangeable and allowing cost to drive drug selection within a class can be dangerous. In New Zealand, when the government replaced simvastatin with fluvastatin as the statin approved for

reimbursement, the lipid concentrations increased in 115 of 126 patients (94%) after the switch [69]. Furthermore, the number of arterial thrombotic events increased from 9 in the 6 months before the switch to 27 in the 6 months after the switch (p<0.05).

2.9   Regulatory Basis for Contraindication

A contraindication is warranted in clinical situations with a known hazard and "the risk from use clearly outweighs any possible therapeutic benefit." [70]

2.10 Precedence for Regulatory Action Based on Spontaneous Reports

In general, the criteria for implementing a regulatory action are less stringent for safety issues than for efficacy issues [71, see article for potential conflict of interest]. Randomized controlled trials are not usually necessary to support a regulatory action-- even withdrawal of a drug--if there is a safety threat.

Auriche and Loupi [72, see article for potential conflict of interest] speculated in 1993 that drugs may be withdrawn more "on the basis of high suspicion than of certainty." Affirming this conjecture, there were 22 drug withdrawals between 1978 and 2003 for which spontaneous reports served as the primary support for withdrawal [73, sponsored by GlaxoSmithKline;74]. For example, cerivastatin was withdrawn after 31 deaths from rhabdomyolysis were reported [67]. Spontaneous reports played a similarly critical role in the withdrawals of tenafloxacin, terfenadine, and troglitazone [73, sponsored by GlaxoSmithKline].

When there is sufficient information about adverse events to raise concern about safety but insufficient information to support withdrawal, a Boxed Warning [70] can be added to the prescribing information. As with withdrawals, spontaneous reports can also provide the critical evidence supporting addition of a Boxed Warning. Based on 12 reports of torsades de pointes and one pharmacokinetic study, a Boxed Warning was added to the prescribing information for cisapride to contraindicate its use with certain drugs two years after its approval [75]. Adding pharmacokinetic and electrophysiological studies as well as clinical studies to the evidence from postmarketing reports and case reports eventually led to the withdrawal of cisapride 7 years after its approval.

2.11 Precedence for Postmarketing Dose Reduction

For new molecular entities approved between 1980 and 1999, there was a $\geq$33% dose modification for 21% of the drugs when initial prescribing information was compared to

the most recently approved version up to 2002 [76]. Approximately 80% of the dose changes were reductions due to safety concerns.

Nearly 25% of the dose changes (33% of all dose decreases) related to renal or hepatic impairment and CYP3A4-mediated drug interactions [76]. Examples of dose decreases in patients with renal or hepatic impairment include cidofovir, troglitazone, tolcapone, and trovafloxacin [77].

2.12 Precedence for Unintended Consequences Resulting from Regulatory Actions and/or Professional Society Recommendations

In an editorial about the addition of a Boxed Warning to the prescribing information for Droperidol in 2001, the author speculates that Boxed Warnings could result in a reduction of the drug's use for the "safe, indicated purpose" and replacement of the drug with other more costly drugs with less desirable safety profiles [78].

A real-life example of one unintended consequence occurred when the Boxed Warning was added to the labels of antidepressants indicating a risk of suicide in the pediatric population: the use of antidepressants declined in adults as well as in children even though the warning targeted children and there was no convincing evidence for an association of suicidality with antidepressants in adults [79]. Similarly, the Boxed Warning placed on the labels of atypical antipsychotics warned about increased mortality in elderly individuals with dementia but had the unintended consequence of reducing use in nonelderly patients without dementia [80, see article for potential conflict of interest]. Although it is not known whether these Boxed Warnings resulted in the use of other drugs with more frequent, more severe, or different adverse events, there has been a call to increase the specificity of FDA regulatory actions [80, see article for potential conflict of interest].

Of direct relevance to the issue at hand, in summer of 2007, the University of Wisconsin Department of Radiology switched from Omniscan to Multihance for all MRI protocols requiring the use of a GBCA [81]. One of the reasons for this switch was that Multihance had not been associated with any NSF cases at that time. However, the switch to Multihance resulted in an increase in the number of anaphylactoid reactions among other adverse events. Some reactions required pharmacologic intervention and admission to the Emergency Department. In a period of two months, there were 14 reactions (6 minor, 8 serious) to Multihance among 1759 patients exposed (0.8%). As a result, the institution switched back to Omniscan as the primary GBCA for outpatient facilities, and on evening and weekends in the inpatient facility and clinics. This memo is no longer accessible online, so it is included as an appendix in section 6.4.

3 Scientific Advances Regarding the Possibility of Differential NSF Risk Among GBCAs and Limitations of the Data

3.1 Scientific Knowledge Up to 2007

By 2007, GBCAs had been proposed to be the trigger for NSF [40] and a temporal association between GBCA exposure and NSF onset had been shown [10;82;83]. It was known that free gadolinium is toxic [84], but it was unclear whether the gadolinium ion, the ligand, the gadolinium chelate, or a combination of these was the causative factor [10;83;85]. The mechanism by which GBCA administration led to NSF was largely unknown. Possible risk factors in addition to severe renal impairment and GBCA exposure were noted [10;86].

Up to 2007, NSF cases in the U.S. were associated predominantly with Omniscan, with a ratio of ~8:1 over Magnevist which was the next most commonly reported GBCA [10]. However, because Magnevist and Omniscan dominated the U.S. contrast market at the time, it was not known whether the other agents on the market were less likely to cause NSF or whether the lack of cases associated with agents other than Magnevist and Omniscan was due to their relatively infrequent use [10]. Also by 2007, an association between total cumulative GBCA dose and NSF risk as well as disease severity had been suggested by several studies [87-90]. A dose response relationship had also been observed [91].

It was recognized that Omniscan had the lowest thermodynamic stability among the approved GBCAs. In 2007, it was proposed that the differences in stability among GBCAs was an important factor in the pathogenesis of NSF and clinically relevant in patients with renal impairment [92;93]. However, the uncertainty regarding the relationship between GBCA stability and NSF led Perazella to warn that all GBCAs should be used with caution [94].

The differential behavior among GBCAs in cell culture regarding cellular uptake followed predictions based on physicochemical properties of GBCAs [95, sponsored by Bracco]. Furthermore, phosphate addition increased gadolinium uptake from gadodiamide (active ingredient in Omniscan) but not from gadoteridol (active ingredient in Prohance) incubation, supporting the theory of transmetallation which others had proposed to be involved in gadolinium dissociation from ligand [40;96]. Although it was unclear how well *in vitro* measurements of stability would predict dissociation propensity of GBCAs in humans [10], there was already animal data from the 1990s showing differential retention in rodent tissue in an order predicted by the physicochemical properties of GBCAs: the least retention of macrocylic chelates, greater retention of linear ionic chelates, and the greatest retention of linear nonionic chelates [97, partially sponsored by Bracco;98, sponsored by Bracco].

Gadolinium had been detected in the tissue of NSF patients [99-101]. In hip transplant patients, higher gadolinium levels were detected in bone after administration of the linear nonionic GBCA Omniscan than after injection of the macrocyclic GBCA Prohance [26;27]. However, the form in which the gadolinium was present (free, insoluble precipitate, chelated, or other) in human tissue was debatable.

3.2 Scientific Developments Since 2007

3.2.1 Increasing Support for "Free" Gadolinium Hypothesis

Between January 2008 and July 2010, there has been a deluge of publications on NSF. Although there are over 340 articles available on PubMed between these dates, the exact pathogenesis of NSF remains largely unknown. However, over the last 2.5 years, data has been generated to support the most widely accepted hypothesis for NSF development [32, sponsored by Guerbet;102-105] which builds on proposals from 2007 based on physicochemical properties [15;93;106]. This hypothesis is as follows.

> Individuals with renal insufficiency have impaired elimination of GBCAs, resulting in prolonged exposure to GBCAs. In the at-risk group, dechelation of less stable GBCAs leads to the release of free gadolinium ion, which forms insoluble precipitates with phosphate or hydroxide groups and initiates a fibrotic response.

To date, nearly all NSF patients had acute or chronic severe renal dysfunction and many were exposed to GBCAs predicted to be less stable based on thermodynamic, conditional, and/or kinetic stability. Where a specific GBCA was identified, the most commonly reported GBCA was Omniscan, followed by Magnevist and Optimark (Table 7). One might predict based on Table 2 that GBCAs in the same subclass (e.g. linear nonionic) would confer a similar risk of NSF. However, careful examination of Table 7 together with Table 2 suggests this is not necessarily true, particularly for linear ionic and perhaps also for macrocyclic GBCAs (see also sections 3.2.2.3 and 3.2.2.2, respectively).

Although the number of NSF cases with onset dates after the 2007 advisories and recommendations decreased dramatically for all GBCAs, it is notable that there were very few new or historical cases reported for Multihance or Prohance compared to those reported for Omniscan, Optimark, and Magnevist (Table 4, Table 5), even when accounting for market share which increased for Multihance over this period [1]. In fact, there is only one single-agent* Multihance case to date [107]. For Prohance, there is only one biopsy-confirmed single-agent case (from Switzerland) [108;109, sponsored by Bracco]. It is noted that ascertainment bias is possible due to initial reports focusing on

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* Reports listing a single GBCA regardless of the number of times administered. Reports listing more than one GBCA or unspecified GBCA(s) were not considered single-agent cases.

Omniscan [47]. In addition, it may not be possible to control for disproportionate use of GBCAs among the at-risk population of acute kidney injury or severe chronic kidney failure patients [102].

To compare NSF risk across GBCAs, it would be more relevant to compare the number of NSF cases associated with each GBCA relative to the number of individuals administered the GBCA who are at risk for NSF (i.e. those with acute or severe chronic renal impairment) rather than to all individuals who were administered GBCA(s) as in Table 7. To date, there is no study comparing NSF risk associated with all marketed GBCAs in the at-risk population. There are reports of a decrease in NSF cases in the at-risk population following a switch from Omniscan to Multihance or another linear ionic GBCA [110;111]. However, it is important to keep in mind that at these institutions, screening and/or dose restriction policies were implemented at the same time as the

Table 7. U.S. and worldwide single-agent cases and drug utilization for GBCAs approved in the U.S.

GBCA	2007 AERS database (2007 FDA clinical reviews on NSF)		2009 AERS database (FDA Briefing Document for Advisory Committee)*		2009 Sponsors' Briefing Documents for Advisory Committee*	
	# Single-agent [††] cases in U.S.	~ Market share	# Single-agent cases in U.S.	# Administrations in U.S. (x10^6)[†]	# Single-agent cases worldwide	# Administrations worldwide (x10^6)[†]
Omniscan	74	30%	382	>25	505	> 49
Optimark	7	<10%	35	> 2.5	35	> 3.5
Magnevist	39	50%	195	>50	179	>105
Multihance	0	< 5%	1	> 2.5	2^^	> 7.5
Eovist	NA	NA	NR	< 0.05	0	< 0.4
Ablavar	NA	NA	NR	0	0	< 0.1
Prohance	0^	< 5%	0^	> 7	2**	> 15

* For Advisory Committee December 8, 2009 [1].
NA: not applicable as these were approved in 2008. NR: not reported.
^ One foreign single-agent case. ^^ 2 in literature but not confirmed according to sponsor.
** 1 foreign confirmed by biopsy, 1 domestic not confirmed by biopsy.
[†] From Advisory Committee Briefing Document for Eovist based on estimates provided by Arlington Medical Resources [112]
[††] Reports listing a single GBCA regardless of the number of times administered.

switch to Multihance [111;113]. In addition, GE Healthcare reports no new single-agent cases plausibly associated with Omniscan after September 2007 [114]. Therefore, the reduction in NSF cases cannot be solely attributed to the change in GBCA.

Additional studies since 2007 confirmed that gadolinium can be present in skin biopsies of NSF patients [see numerous references in 11]. In these studies, it was still not known whether the gadolinium is free gadolinium ion, an insoluble inorganic deposit such as a carbonate or phosphate salt, still a part of the chelate, or bound to a calcium-binding protein. However, in a 2010 publication, George et al [28] used synchotron x-ray fluorescence microscopy and extended absorption fine structure spectroscopy to clarify the chemical composition of the insoluble skin deposits of gadolinium with calcium, phosphorus (P), and sodium. The Gd-P distances of 3.11 Å and 3.72 Å, and the Gd-Gd distances of 4.05 Å were consistent with a gadolinium phosphate ($GdPO_4$) structure. The gadolinium in skin from one NSF patient is predominantly coordinated by phosphate and not by the GBCA ligand, thus providing the first direct evidence for release of the gadolinium ion in human tissue. This very important result supports the prevailing hypothesis, but it does not exclude the possibility that chelated gadolinium may also be involved in the pathogenesis of NSF.

Recent studies in rodents administered high doses of GBCAs support the prevailing hypothesis. The amount of gadolinium deposited in rodent tissues after administration of different GBCAs was according to the prediction based on physicochemical properties [24, sponsored by Bayer-Schering], with the most gadolinium deposited after Omniscan administration and the least gadolinium deposited after administration of Multihance or two macrocyclic GBCAs not approved in the U.S. (Prohance was not tested). A similar result was obtained in a rodent model for renal impairment [115, sponsored by Bayer-Schering]. In addition, formulations of the linear nonionic GBCAs gadodiamide and gadoversetamide with the most excess ligand resulted in the least amount of gadolinium deposited in rodent skin [25, sponsored by Bayer-Schering], further highlighting the biological significance of the intrinsic stability of GBCAs.

As described above in section 2.2.3 and Table 3, recent *in vitro* studies of GBCA stability in serum [21, sponsored by Bayer-Schering] also reflect the predictions of the physicochemical properties of GBCAs under less physiologic conditions. Another *in vitro* study that supports the hypothesis that dechelated gadolinium causes NSF showed that the concentration of GBCA required to stimulate proliferation of human dermal fibroblasts was lowest for Omniscan, higher for Magnevist, even higher for Multihance, and finally Prohance which required the highest concentration [116]. In addition, gadolinium chloride stimulates proliferation of human dermal fibroblasts *in vitro* but not in the presence of the chelating agent DTPA, suggesting that free gadolinium stimulates fibroblast proliferation. Although the *in vitro* studies support the leading hypothesis, the degree to which thermodynamic and kinetic stabilities of GBCAs predicts the amount of free gadolinium *in vivo* remains controversial [16, sponsored by Guerbet].

3.2.2 Challenges to the Prevailing Hypothesis

3.2.2.1 Alternative Hypothesis

An alternative hypothesis invoking chelated, rather than free, gadolinium as the trigger for NSF has been proposed [117, sponsored by GE Healthcare]. This alternative hypothesis is based on studies showing that chelated gadolinium such as Omniscan and Magnevist can stimulate macrophages, monocytes, and fibroblasts to produce growth factors and cytokines that can initiate a fibrotic response [118-121;122, partially supported by GE Healthcare]. In one study, intracellular signaling pathways were activated by GBCAs within minutes of exposure [118].

Of note, these two hypotheses are not mutually exclusive. Until there is a better understanding of the pathogenesis of NSF, whether free gadolinium, chelated gadolinium, or both are causative will not be known.

3.2.2.2 NSF Cases Attributed to Macrocyclic GBCAs

The "free" gadolinium hypothesis would predict that there would be none or very few NSF cases associated with macrocyclic GBCAs. An apparent inconsistency with the prevailing hypothesis is the report of several potential NSF cases following exposure to the macrocyclic nonionic GBCA, gadobutrol (Gadovist) [123;124]. This GBCA is not yet approved in the U.S., but it has been marketed in Europe since 1998. There has only been _____ (b) (4) administrations of Gadovist worldwide since marketing [112;125]. By comparison, for Prohance which is the only other macrocyclic (also nonionic) GBCA marketed in the United States, there has only been 1 associated single-agent NSF case after over _____ (b) (4) administrations worldwide (Table 7).

For Gadovist, among the three published cases and five other cases submitted to Medwatch, there may be three single-agent cases (see section 6.3 for a brief description and discussion of all eight MedWatch reports to date for Gadovist). Even though it is not known how many of the 4 million administrations of Gadovist were to individuals with acute or severe chronic renal compromise, confirmation of more than 1 single-agent NSF case attributable to Gadovist appears inconsistent with the prevailing hypothesis given its small market share.

However, one possible explanation for the potentially higher number of NSF cases associated with Gadovist than with other macrocyclic GBCAs could be the low conditional stability constant (thermodynamic stability constant at pH 7.4) of Gadovist. According to [18], the conditional stability (log K_{cond}) of the macrocyclic

nonionic GBCA Gadovist is 14.7[†], *which is in the same low range as those for the linear nonionic GBCAs Omniscan (14.9) and Optimark (15.0)* (Table 2). Among the nonionic GBCAs, the macrocyclic GBCA Prohance has the highest log K_{cond} (16.9-17.2) [18]. The <u>nonionic</u> GBCAs appear to have a lower log K_{cond} than the <u>ionic</u> GBCAs [126].

The linear ionic GBCAs (Magnevist, Multihance, Eovist, Ablavar) all have higher log K_{cond}, ranging from 17.7 to 18.9 [18]. Dotarem, which has a log K_{cond} of 18.8-19.3, has the highest among the ionic GBCAs and among all GBCAs currently marketed worldwide [18].

Although the range of conditional stabilities across the GBCAs appears quite narrow (14.5-19.5), it is important to keep in mind that these numbers represent log K_{cond}. Therefore, the K_{cond}[‡] for Gadovist is actually $10^{14.7}$ M^{-1}, and the K_{cond} for Dotarem is $10^{19.3}$ M^{-1}, making the difference in the equilibrium constants at pH 7.4 (K_{cond}) for these two GBCAs quite large.

The low thermodynamic stability of Gadovist at physiologic pH suggests that at equilibrium, the concentration of the free gadolinium ion and ligand relative to that of the chelate is similar to that for Omniscan and Optimark. The high kinetic stability of Gadovist [18;127, sponsored by Guerbet;128] simply suggests that achieving equilibrium may take longer for Gadovist than for Omniscan and Optimark.
The prolonged GBCA exposure time in those with severely impaired renal function may likely be long enough for equilibrium to be achieved and significant dissociation to occur for Gadovist. As mentioned in section 2.3, in patients with a creatinine clearance <10 mL/min, the mean recovery of Gadovist in urine is only ~75% after 5 days [49, partially supported by Schering].

Although *in vitro* measurements of Gadovist dissociation in human serum at 37°C showed no release of gadolinium ion after 15 days [21, sponsored by Bayer-Schering;similar result by 129], the reported lower limit of quantitation of the assay (0.1%, 1mmol/L GBCA) may be higher than that necessary to trigger a fibrotic reaction *in vivo*. In addition, formation of insoluble precipitates upon GBCA dechelation *in vivo*, for which there is evidence [130, see article for potential conflict of interest;131-133], would tend to drive the equilibrium toward dissociation of Gd^{3+} from the ligand that is in the Gadovist formulation.

The amount of excess ligand in the Gadovist formulation is similar to that in Magnevist, 1 mmol/L [18]. Despite being a macrocyclic GBCA, the amount of excess ligand in the Gadovist formulation is greater than for the other macrocyclic GBCAs Prohance (0.5 mmol/L) and Dotarem (0 mmol/L). Excess ligand is usually added to complex with free Gd^{3+} since free Gd^{3+} is toxic. According to a Bayer

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† reported as 15.5 in [21, sponsored by Bayer-Schering]
‡ K_{cond} is K_{therm} at pH 7.4. K_{therm} = ([M][L])/[ML] where [ ] is concentration, M is Gd^{3+} (the Metal), L is Ligand, and ML is the chelate

publication [35, sponsored by Bayer-Schering], the excess ligand was added to Gadovist for a reason unrelated to stability: to trap metal traces from glass vials during heat sterilization.

Of note, not all macrocyclic gadolinium complexes are more inert or stable than their linear counterparts. See [134] and references therein.

Like Gadovist and Prohance, Dotarem is a macrocyclic GBCA. However, Dotarem is ionic rather than nonionic like Gadovist and Prohance. As noted above, the ionic GBCAs all have higher conditional stabilities than the nonionic GBCAs. In fact, Dotarem has the highest conditional stability and the highest kinetic stability of all globally marketed GBCAs (Table 2). As might be predicted by the high thermodynamic and kinetic stability of Dotarem, as of Fall 2009, there has been at most one confirmed single-agent NSF case in ⬛⬛⬛⬛ (b) (4) administrations associated with Dotarem [125]. Dotarem is not formulated with any excess ligand.

3.2.2.3   Apparent Disparity in Case Numbers Among Linear Ionic GBCAs

Magnevist and Multihance are both linear ionic GBCAs. The "free" gadolinium hypothesis would predict that linear ionic GBCAs would behave similarly in terms of NSF risk. However, the ~180-190 single-agent cases for Magnevist appear in excess compared to the one single-agent case for Multihance, even when taking into account market share (Table 7).

A plausible explanation for this observation is that linear ionic GBCAs can be subdivided into those with bulky substituents (Multihance, Eovist, Ablavar) and those without (Magnevist). It has been proposed that GBCAs with at least one large phenyl group have greater kinetic stability due to the steric effect that may impede the ligand from peeling off the gadolinium ion [14]. In fact, a difference in kinetic stability between Magnevist and Multihance has been demonstrated *in vitro* [129] although a Bayer study reports that in serum at 37°C, Magnevist and Multihance have similar kinetic stability [21].

Of note, there is a range of conditional stabilities reported for Magnevist (Table 2), with the highest conditional stability within that range (18.4) reported in an article sponsored by the company marketing Magnevist, Bayer [21]. Incidentally, 18.4 is also the conditional stability reported for Multihance, and it would behoove Bayer to make Magnevist appear as similar as possible to Multihance and to distinguish their agent from the offending class members (Omniscan and Optimark). The lowest value in the range of conditional stabilities reported for Magnevist is 17.7 [129;Fig. 3 in 135, sponsored by Bristol-Myers Squibb], which is lower than that for Multihance but still higher than those reported for the linear nonionic agents Omniscan (14.9) and Optimark (15.0).

3.2.3   High GBCA Dose as a Risk Factor

Since 2007, there is increasing evidence for risk factors in addition to GBCA exposure and acute or severe chronic renal dysfunction [41;47]. Additional risk factors include high GBCA dose for a single MRI exam and high total cumulative GBCA dose [136]. It was also noted that a high single GBCA dose posed a greater NSF risk than multiple standard GBCA doses [46].

According to Prince et al [47], most (~90%) MRI exams with contrast are performed using a standard GBCA dose. However, as noted above in section 2.2.2, certain MRI exams are commonly performed with double or triple dose [48;137, sponsored by Bracco;138]. As a result, screening for those with renal compromise is particularly important [59]. Another precaution that has been suggested is to take particular care in performing contrasted MRI exams in those who may have impaired clearance of GBCAs [47] in order to prevent the need for repeat exams due to nondiagnostic results after the first GBCA injection [46].

3.2.4   Changes in MRI Practice Patterns Prevent NSF

Although it was possible that increased awareness about NSF among health care professionals in 2007 would result in greater recognition and reporting of new NSF cases, in reality, there has been a dramatic reduction of new NSF cases for all GBCAs over the last 2.5 years. Several institutions have demonstrated that adoption of policies to screen for those with acute or severe chronic renal insufficiency and/or policies to reduce GBCA dose can prevent NSF [111;113;137, sponsored by Bracco;139].

3.2.5   New NSF Manifestations

Also new since 2007 are reports of human cardiac and vascular manifestations of NSF as well as systemic deposition of gadolinium with the highest quantity in the kidney, heart, and blood vessels in addition to skin [140;141]. Additionally, it was recently reported that NSF can present as progressive myopathy with minimal skin involvement [142]. Airway compromise due to NSF is also a newly recognized manifestation of NSF [143].

3.3   Limitations of the Data

There are numerous limitations regarding the data that is reviewed. A few of the key limitations will be discussed.

Although the spontaneous adverse event reporting system can identify safety signals, the limitations of spontaneous reporting are well known [144, sponsored by GlaxoSmithKline;145, sponsored by Pfizer;146-148]. These include the inability to provide incidence data (incomplete numerator, no estimate of patients exposed), underreporting, multiple reports of the same case, and variable quality of the reports. Regarding NSF, it is noted that some NSF cases were reported in clusters and are therefore not independent [1]. In addition, the denominator of interest is not all individuals exposed to GBCAs. It is those with acute kidney injury or severe chronic renal disease exposed to a GBCA, and this information is not easily attainable.

In addition to the inadequacies of spontaneous reporting, the data related to GBCA use and NSF risk have limitations specific to the exposure and the outcome of interest.

Regarding exposure, the name of the contrast agent and the dose administered are not routinely recorded. When it is recorded, the GBCA may be incorrectly recorded as Gd-DTPA (Magnevist) even if some other GBCA was actually used because it was (a) the first GBCA approved and (b) the most common GBCA used for many years [149]. Furthermore, individuals may receive one GBCA at one institution and then receive a different GBCA at another institution. In these cases it is difficult to attribute the NSF diagnosis to a specific GBCA, especially if the different GBCAs were administered within a short period of time. Additionally, there is often no longitudinal record of the name or date of GBCA administration when individuals undergo MRI exams at institutions that use different GBCAs. Thus, cumulative dosing information may often be incomplete. Furthermore, without records of the agent and dose administered, it is not possible to determine whether some agent(s) were disproportionately administered at higher doses than other GBCAs.

Regarding the outcome, there is still no widely accepted definition for NSF. Even though Shawn Cowper and colleagues have drafted a clinicopathological definition of NSF, it is still not published so its acceptance is limited [150]. As a result, not only is the NSF diagnosis for many cases debated, but defining a time of onset is difficult. Based on the criteria for NSF put forth by Cowper et al, many of the historical cases do not have documented clinical or histological information to determine whether or not the patient actually had NSF. In addition, the follow-up time after GBCA administration is variable in studies, and some studies may not have allowed enough time after GBCA administration for NSF to develop.

Regarding the physicochemical and animal studies, many of the publications were sponsored in full or in part by companies marketing the GBCAs. Thus, the information presented in the articles must be considered with the knowledge that there might be conflict of interest. Even if there were no biases, *in vitro* studies and animal models of NSF may not be predictive or representative of the human condition.

As already pointed out in section 2.2.4, the conditional stability values for all the different GBCAs were not measured in a single experiment. Similarly, there is no one single experiment that estimated the kinetic stability for all GBCAs. Thus, the values,

when reported, may not be directly comparable given that the measurements were not performed under identical conditions.

These and other limitations were taken into consideration by this reviewer.

4 Response of Business, Professional Society, and Regulatory Agencies to Scientific Advances After 2007

4.1 2009 (November) FDA Office of Surveillance and Epidemiology (OSE) Recommendations – and the June 2010 addendum

The 2009 FDA OSE review (and 2010 addendum) concluded that there is differential NSF risk among the five GBCAs reviewed, with the highest risk associated with Omniscan, Magnevist and Optimark and the lowest risk associated with Prohance and Multihance [151;152]. OSE recommends contraindication of the three agents with the highest NSF risk in patients with severe renal dysfunction. An additional recommendation is to continue the Boxed Warning and text in the Warnings and Precautions sections of the prescribing information for all GBCAs regarding the risk of NSF in patients with severe renal dysfunction due to the possibility of death from NSF.

4.2 2009 (November) EMEA Actions

On November 20, 2009, the European Medicines Agency (EMEA) Committee for Medicinal Products for Human Use (CHMP) assessed the risk of NSF for GBCAs marketed in Europe [153]. CHMP recommended that GBCAs be categorized into three groups based on risk of NSF (Table 8), and that the prescribing information for the high risk group be different from that for the medium and low risk groups (Table 9).

Other CHMP recommendations regarding the prescribing information were as follows:

- Elderly: Warning that the elderly are at particular risk.
- Hemodialysis: No evidence to support initiation of hemodialysis in patients not already undergoing hemodialysis.
- NSF cases for each agent: Include information in prescribing information.

CHMP also required companies marketing GBCAs to conduct studies to determine the period of time gadolinium is retained in human bone.

Table 8. EMEA classification of GBCAs based on risk of causing NSF

High Risk GBCA	Medium Risk GBCA	Low Risk GBCA
Omniscan (gadodiamide)	MultiHance (gadobenic acid)	ProHance (gadoteridol)
OptiMARK (gadoversetamide)	Primovist* (gadoxetic acid)	Gadovist (gadobutrol)
Magnevist, Magnetica, Gado-MRT-ratiopharm (gadopentetic acid)	Vasovist (gadofosveset)	Dotarem (gadoteric acid)

* Primovist is marketed as Eovist in the U.S.

Table 9. EMEA recommendation regarding changes to the prescribing information of GBCAs

	High Risk GBCA	Medium and Low Risk GBCA
Contraindicated in these patients	Severe kidney problems; Around time of liver transplantation; Newborns < 4 wks of age	—
Warning about use in these patients	—	Severe kidney problems; Receiving liver transplant
Minimum recommended dose in these patients (> 7 days between GBCA administrations in all patients)	Moderate kidney problems; Infants < 1 year of age	Severe kidney problems; Around time of liver transplantation; Neonates & infants up to 1 yr of age
Breastfeeding	Discontinue for >24 hrs	Decision made by doctor and mother about suspending breastfeeding for >24 hrs
Screening	Screen all patients using laboratory tests prior to administering High Risk GBCA	Recommend screening all patients for kidney problems using laboratory tests prior to administering Medium or Low Risk GBCA

4.3 2009 (November) Covidien Contraindicates Optimark for Certain Populations

On November 6, 2009, Covidien voluntarily contraindicated Optimark, a linear nonionic GBCA, for use in the population at risk for NSF [154;155]. Covidien's rationale included the following:

- Desire to support changes in clinical practice that have reduced NSF incidence;
- Slow enrollment into Optimark's registry study;
- Lack of adequate animal or in vitro models for NSF;
- Pharmacovigilance and post-marketing data suggesting possible relationship between GBCAs and NSF in at-risk patients;
- The expectation that contraindication will help reinforce the progress in reducing NSF cases.

The contraindication applied to patients with acute or chronic severe renal insufficiency (GFR < 30 mL/min/1.73 m^2), or with acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period.

4.4 2009 (December) FDA Advisory Committee Recommendations

An Advisory Committee meeting was held on December 8, 2010 to discuss the data with respect to differential risk of NSF among GBCAs and to formulate recommendations to minimize NSF risk [156]. There were no voting questions. The following is a summary of the key discussion points:

1. The 2007 labeling changes were effective in reducing NSF incidence. The success may in part be due to the medical community adopting practices ahead of the label.

2. The population at risk for NSF is limited to those with severe renal disease (GFR < 30 mL/min/1.73 m^2). This should be clearly specified in the label.

3. At least two of the agents appear to be different from the other agents in terms of NSF risk. A majority suggested that there should be a contraindication for at least Omniscan and Optimark in patients with severe renal disease. Some members suggested that Magnevist should also be contraindicated, but this was not a majority opinion.

4. There is no clear evidence that any agent is safe in patients with severe renal disease. Some committee members encouraged investigations to demonstrate the safety of certain agents in this patient population, if this is in fact true for any agent.

5. Significant renal disease cannot be defined using only creatinine or an estimated GFR. The label needs to clearly specify that assessment of acute kidney injury is different from that of chronic kidney disease. Namely, creatinine is not a good index of renal function in patients with acute kidney injury.

6. FDA should use its influence as a regulatory body to devise methods for capturing information on cumulative dosing of GBCAs, and perhaps other imaging agents too.

7. The label should emphasize that the lowest possible dose should be used. Re-examine re-dosing issues for agents whose prescribing information allows a second dose within 20-30 minutes of the first dose.

8. Label and practice changes could spur new innovation and technological developments. While there may be unintended consequences, the focus should be on the positive consequences of these changes.

4.5 2010 (June) ACR Recommendations Regarding NSF

The 2007 ACR Recommendations Regarding GBCAs and NSF were recently updated in June 2010 [2]. The ACR now recommends avoidance of Omniscan, Optimark, and Magnevist in the following patients:

- End-stage renal disease on chronic dialysis
- GFR < 30 mL/min/1.73m^2 not on chronic dialysis
- Acute kidney injury

For patients with GFR between 30 and 44 mL/min/1.73m^2, the ACR recommends the consideration of precautions similar to those for patients with GFR < 30 mL/min/1.73m^2.

The ACR also recommends use of the lowest possible dose when GBCAs are necessary in the patient populations listed above.

4.6 2010 (June) FDA Drug Safety Oversight Board (DSOB) Recommendations

On June 17, 2010, the FDA DSOB discussed the Division's proposed changes to the labels of GBCAs marketed in the U.S [157]. The key Board recommendations are summarized below.

1. Regarding statements about acute renal injury in the label:
    - Specify that renal function changes "over hours to days"

- State that creatinine is a poor indicator of renal function in these patients
- Specify causes of acute kidney injury

2. Regarding the Division's proposal for physicians to follow-up at 6 and 12 months for NSF symptoms:
   - Include information in the label on why it is necessary for physicians to perform follow-up (public health surveillance, estimate risk with newer agents, prevent GBCA administration to patients with NSF)

3. Other recommendations about the label:
   - Add information about age-related decline in renal function
   - State that physicians are to screen for renal impairment and a laboratory test may be required

4. Consider alternative approaches to the registry such as:
   - Recruit radiologists to perform 6 and 12 month follow-up for NSF symptoms
   - Recruit 50-100 partners to perform prospective case control study to evaluate NSF risk associated with commonly used agents
   - Public-private partnership with American College of Radiology, National Institute of Diabetes and Digestive and Kidney Diseases

5 Reviewer's Conclusions and Recommendations

5.1 Conclusions and Recommendations Regarding Differential NSF Risk Among GBCAs and Issues Related to NSF Risk

As stated above in section 2.1, the purpose of this document is (a) to examine whether the current prescribing information for Gadolinium-Based Contrast Agents (GBCAs) adequately reflects the current science regarding NSF risk and issues related to NSF risk; (b) to assess potential NSF risks associated with GBCAs not yet approved in the United States; and (c) to recommend steps to reduce NSF risk.

The reviewer concludes that the prescribing information for GBCAs does not reflect the current science regarding differential NSF risk. Recommendations 1-7, 9, and 10 below offer potential remedies as well as methods to minimize NSF risk. Of the two GBCAs marketed in other countries but not the U.S., the reviewer recommends that Gadovist be categorized as a GBCA that confers higher NSF risk (recommendation 8 below).

Section 5.1.1 lists the reviewer's recommendations. Section 5.1.2 justifies these recommendations.

5.1.1   Reviewer's Recommendations

The following are science-based recommendations regarding GBCAs and NSF risk:

1.   Add contraindication to Boxed Warnings of Omniscan, Optimark, and Magnevist for individuals with acute kidney injury and individuals with severe chronic renal disease (GFR < 30 mL/min/1.73m^2).

2.   Clearly specify in the prescribing information and in communications to health care professionals and the public that the contraindication only applies to at-risk individuals. This population only includes the ~900,000 individuals with acute kidney injury each year and the 700,000 (0.4%) individuals in the United States with chronic renal disease and GFR < 30 mL/min/1.73m^2.

3.   Retain the Boxed Warning about NSF for Multihance, Eovist, Ablavar, and Prohance without adding a contraindication for use in the at-risk population.

4.   In the prescribing information, recommend that patients be screened for acute kidney injury prior to GBCA administration. For patients with chronically reduced renal function (diabetes, hypertension, age > 60 years), estimate GFR through laboratory testing.

5.   In the prescribing information, restrict the maximum recommended dose to 0.1 mmol/kg for all GBCAs.

6.   In the prescribing information, recommend that the name of the GBCA and the dose be recorded for each administration in the medical record for each recipient.

7.   In the prescribing information for Multihance, correct misleading information regarding relaxivity.

8.   Contraindicate Gadovist, but not Dotarem, if/when approved in the United States.

9.   For determination of NSF risk associated with GBCAs approved in the future, carefully consider the drug-specific effects rather than rely on a prediction of its associated NSF risk based on the risk of others in the same chemical subclass (e.g. linear ionic or macrocyclic).

10.   Collect prospective data on human NSF cases.

5.1.2   Justification for Recommendations

The rationale for each of the above recommendations is as follows:

1. <u>Contraindicate Omniscan, Optimark, and Magnevist for individuals with acute kidney injury and individuals with chronic renal insufficiency having GFR < 30 mL/min/1.73m^2.</u>

   General comments:

   One of the missions of FDA is to protect the public's health by assuring the safety and efficacy of human drugs. FDA is also responsible for public communication of accurate, science-based information about medicines to improve health [158].

   To fulfill these responsibilities, FDA may contraindicate certain drugs when the risk of use clearly outweighs the benefits. In order to protect the public's health, this reviewer believes that it is preferable to err on the side of safety, particularly when there are alternatives.

   NSF is a condition with poor prognosis and no established treatment. Importantly, this adverse event is preventable. Upon identification of two important risk factors for NSF in 2006 (GBCA exposure and severe renal compromise), the medical community implemented recommendations in the 2006-2007 FDA advisories and professional society guidelines. By screening for renal insufficiency, reducing GBCA dose, and avoiding certain GBCAs in the at-risk population (as evidenced by [a] certain companies being unable to enroll at-risk subjects into the prospective observational studies and [b] publications documenting a switch in GBCA), the number of new NSF cases reported decreased significantly after 2007.

   Since this adverse event appears to be iatrogenic and preventable, the focus should be on prevention. NSF can be very debilitating and there is no established treatment, so preventing each and every NSF case should be the goal. One method of preventing NSF is for individuals in the at-risk population to avoid the drug(s) that may be more likely to cause NSF.

   If patients actually administered these GBCAs to themselves, a reasonable method would be to restrict the distribution of agents with the strongest association with NSF to only those individuals without acute kidney injury or severe chronic renal dysfunction. Since patients do not administer GBCAs to themselves, an alternative is contraindication of GBCAs that confer a higher NSF risk in the at-risk population which, in effect, restricts administration of these GBCAs to only those who are not at risk.

   Do the risks clearly outweigh the benefits (criteria for contraindication) for Omniscan, Optimark, and Magnevist? On an individual patient level, the reviewer believes the answer is yes given (a) the systemic nature of NSF; (b) the significant disability and increased risk of death if affected by NSF; and (c) the

most commonly reported agent (when a specific agent was identified in an NSF case) was one of these three GBCAs.

Does the risk of NSF warrant the removal of any GBCA from the market? The reviewer does not believe so because GBCAs are effective MRI contrast agents, NSF is preventable, and the at-risk individuals represent a small sector of the entire U.S. population.

Three agents confer higher NSF risk:

Some may argue that all marketed GBCAs are equally likely to cause NSF. In 2007, there was not enough evidence to differentiate the NSF risk of some GBCAs from that of the others. As described above, scientific developments over the last three years demonstrate the converging lines of evidence for certain GBCAs being associated with a higher risk of NSF than other GBCAs.

There are limitations to spontaneous reports, *in vitro* studies, and animal studies. However, it is striking that all three avenues of investigation mostly support the hypothesis that free gadolinium may trigger the fibrosis leading to NSF (section 3.2.1). In terms of spontaneous reports, there is consistency between U.S. reports and those from other countries: the low number of reports for new or historical single-agent NSF cases associated with Multihance and Prohance relative to reports for Omniscan, Optimark, and Magnevist even when accounting for market share and even after there was increased awareness of NSF in 2006. The majority of the *in vitro* and animal studies published over the last 3 years confer chemical and biological plausibility to differential likelihood of free gadolinium formation among GBCAs.

The recent clarification of the chemical structure of human gadolinium deposits further bolsters support for the "free" gadolinium hypothesis. Many who favored the chelated gadolinium hypothesis had questioned whether human gadolinium deposits were chelated gadolinium or gadolinium complexed with anions such as phosphate. The irrefutable demonstration that human gadolinium deposits are gadolinium phosphate rather than chelated gadolinium negates any doubt that *in vivo* dissociation of the chelated gadolinium occurs.

The multiple imperfect lines of evidence in 2010 collectively convince this reviewer that contraindication of Omniscan, Optimark, and Magnevist is necessary to protect the at-risk population. Some may argue that prospective, randomized, controlled trials comparing the GBCAs in terms of NSF risk are necessary prior to contraindicating any GBCA in the at-risk population. However, this reviewer believes that erring on the side of safety is necessary to protect the public at this time. Randomized trials comparing NSF risk across marketed GBCAs in vulnerable patients may never be completed, especially given that several companies report the inability to enroll subjects into prospective studies

because imaging centers are no longer using their product(s) in the at-risk population. The absence of stronger human data supporting differential NSF risk among GBCAs does not necessarily mean that differential NSF risk does not exist.

Magnevist confers higher NSF risk:

Some may argue that Magnevist should not be contraindicated. The reviewer disagrees. First, Magnevist is the GBCA with the second most number of cases reported when an agent was identified. Even when taking its very large market share into account, the number of NSF cases associated with Magnevist is still more than that associated with certain other GBCAs such as Multihance and Prohance.

Second, the physicochemical properties appear to support an intermediate NSF risk for Magnevist, with a conditional stability reported as low as 17.7 and a kinetic stability of 0.16 (Table 2) which lies between those of the linear nonionic agents and the macrocyclic agents. It is curious that in studies sponsored by Bayer, the conditional stability and the kinetic stability of Magnevist are nearly identical to those for Multihance, another linear ionic GBCA [for example, 21]. However, this is not necessarily the case in other reports in which the conditional and kinetic stabilities are lower for Magnevist than for Multihance [18;129;135, sponsored by Bristol-Myers Squibb].

Third, the amount of Magnevist retained in skin and bone in an animal model is also consistent with an intermediate risk for Magnevist between the (a) linear nonionic GBCAs and (b) Multihance and the tested macrocyclic GBCAs. Additionally, there is a significant difference in the amount of retained gadolinium in the skin and bone five days after repeated high dose Magnevist injections versus Multihance injections [159, sponsored by Bayer-Schering].

Because (a) there are many more than one NSF case associated with Magnevist and this is significantly more than for Prohance and Multihance even when taking into account market share; (b) certain reports of the physicochemical properties of Magnevist separate it from other linear ionic agents; and (c) there are animal studies that support a difference between Magnevist and the other linear ionic agent Multihance in terms of the amount of retained gadolinium, Magnevist should also be contraindicated in the at-risk population.

With no prospective comparative study in sight, the reviewer recommends contraindicating Omniscan, Optimark, and Magnevist in the at-risk population to protect the public's health in the short- and long-term. None of the supporting data is without limitation. However, for the individual patient who suffers when afflicted by NSF, even one NSF case is one too many. In addition, there appears to be a sharp demarcation in the number of reported NSF cases between (a)

Omniscan, Optimark, Magnevist and (b) the other marketed GBCAs, even when accounting for market share. Therefore, it is the reviewer's opinion that the converging lines of evidence are compelling enough to contraindicate these three agents at this time.

Why contraindicate now when there has already been a dramatic reduction in the number of new NSF cases?

It is the reviewer's opinion that the totality of evidence today provides sufficient support for differential NSF risk among GBCAs. One of the responsibilities of FDA is to disseminate safety information in order to promote the proper use of drugs [146;158]. Therefore, the concern for public safety justifies differential risk-based labeling for GBCAs and outweighs the potential loss of marketing advantage by certain companies. As illustrated in section 2.8, allowing cost to influence drug selection within a class can be dangerous. If FDA does not communicate safety information that it believes to be true, the current GBCA labeling could be interpreted that all GBCAs confer the same NSF risk. In this case, cost could drive drug selection and result in NSF cases that could be prevented.

In 2007, the underlying mechanistic basis for NSF was largely unknown. Although the exact pathogenesis of NSF is still not known in 2010, there is now a larger body of evidence suggesting that the likelihood of GBCA dissociation varies among agents (section 3.2.1) and supporting the hypothesis that dechelation of GBCAs plays a role in NSF development.

In 2008, approximately 35 million MRIs were performed in the U.S., and ~28% of these used a contrast agent [112;160]. However, under certain circumstances, GBCA use can result in dire manifestations of NSF, some of which have only recently been discovered (section 3.2.5). In order to maximize the utility of GBCAs which are in widespread use, minimizing NSF risk is absolutely essential. One method of preventing NSF cases is to not use the agents which may confer a higher NSF risk in the vulnerable population.

As mentioned above, prospective studies investigating NSF risk for certain GBCAs in the at-risk population have not been able to enroll, suggesting that there has already been a worldwide shift in use in the vulnerable population. The contraindication of these three agents in the at-risk population would formalize what the medical community is already doing to a certain extent and reinforce the behaviors that have resulted in the reduction of new NSF cases. The contraindication will also ensure that practitioners who have not adopted certain policies for preventing NSF will follow suit.

2. <u>Clearly specify in the prescribing information and in communications to health care professionals and the public that the contraindication only applies to the at-risk individuals. This population only includes the ~900,000 individuals with acute kidney injury each year and the 700,000 (0.4%) individuals in the United States with chronic renal disease and GFR < 30 mL/min/1.73m^2.</u>

It is imperative that health care professionals and potential recipients of GBCAs know that the contraindication does not apply to the vast majority of the U.S. population. As described in section 2.12, contraindication of a drug in a specific population may affect use of the drug in the non-target population—a population in which the drug is still safe and indicated for. Even when a drug is not contraindicated in a specific population and the medical community acts in anticipation of a contraindication, there can be an unfavorable change in the type, frequency, and severity of adverse events in the population that is not the expected target of the contraindication.

The vast majority of the nearly 10 million MRIs with contrast performed each year in the U.S. would be on individuals who are not at risk for NSF. Because of the potential negative public health effects of the contraindication if the public is not aware of who the target population includes, the communications regarding the contraindication of Omniscan, Optimark, and Magnevist for the population at risk for NSF should clearly specify the limited population that this contraindication applies to.

The communications should emphasize that no GBCA is "safer" than another GBCA for the population that is not the target of the contraindication, which comprises the majority of individuals administered GBCAs.

3. <u>Retain the Boxed Warning about NSF for Multihance, Eovist, Ablavar, and Prohance without adding a contraindication for use in the at-risk population.</u>

The lower risk of NSF exemplified by certain GBCAs does not equal no risk. As described in section 6.3, given multiple repeated exposures, even the macrocyclic Prohance can be associated with NSF. In fact, two of the cases reported for Gadovist (section 6.3) suggest that administration of only macrocyclic GBCAs (in one case, just two doses) can result in NSF. These examples illustrate that no GBCA is completely free of NSF risk. Given that (a) macrocyclic GBCAs are considered by some to confer the lowest risk of NSF, (b) NSF has a poor prognosis, and (c) NSF can be prevented by judicious use of GBCAs, the prescribing information of every GBCA should continue to include a boxed warning about the risk of NSF associated with the use of all GBCAs and indicate who is at risk for NSF.

4.   In the prescribing information, recommend that patients be screened for acute kidney injury prior to GBCA administration. For patients with chronically reduced renal function (diabetes, hypertension, age > 60 years), estimate GFR through laboratory testing.

As described in section 2.7.1, institutions that implemented policies to screen for patients with renal dysfunction prior to GBCA administration reported drastic reductions in NSF incidence after the change. In addition to the contraindication of higher risk GBCAs, screening for renal function compromise is an additional measure to minimize NSF risk that should be formalized.

5.   In the prescribing information, restrict the maximum recommended dose to 0.1 mmol/kg for all GBCAs.

As described in section 3.2.3, both a high single dose of GBCA and a high total cumulative GBCA dose are additional risk factors for NSF. Additionally, certain MRI exams typically use doses that are higher than the recommended dose (see also section 2.2.2). In order to minimize the risk of NSF, the dose for a single MRI exam should be minimized. Such dose restriction should also help to minimize the cumulative GBCA dose.

The current prescribing information for Omniscan and Prohance allow a second injection of 0.2 mmol/kg, for a total of 0.3 mmol/kg for a single MRI exam. The option to repeat the dose for a single MRI exam should be eliminated. Dose reduction of drugs to protect public health is not unprecedented (section 2.11).

6.   In the prescribing information, recommend that the name of the GBCA and the dose be recorded for each administration in the medical record for each recipient.

One of the primary reasons the current human data on GBCAs and NSF risk is not overwhelmingly convincingly is that the name of the GBCA and administered dose were not routinely recorded. This information is necessary to more solidly identify agents associated with a higher risk of NSF. Recording this information should enable more rapid identification of GBCAs conferring a higher NSF risk in the future so that actions can be taken sooner to prevent as many NSF cases as possible.

7.   In the prescribing information for Multihance, correct misleading information regarding relaxivity.

As described in section 2.2.4, the current prescribing information for Multihance includes a table illustrating that the relaxivity of Multihance is nearly two fold higher than that of other tested GBCAs (Omniscan, Magnevist, Prohance).

However, the values listed in the table were measured at 0.47 Tesla rather than at 1.5 or 3 Tesla which are the field strengths of MRI scanners in clinical use today.

The field strength at which the relaxivity values were obtained is not stated in the table in the Multihance prescribing information. Stating the field strength is important because relaxivity depends on the field strength. At 1.5 Tesla, the relaxivity of Multihance is only about 1.5 fold greater than that of other GBCAs listed in the current table. At 3 Tesla, the relaxivity difference between Multihance and the other GBCAs diminishes further (Figure 3).

The issue of relaxivity is relevant to the discussion of NSF because (a) GBCA dose minimization is encouraged to minimize the risk of NSF and (b) a smaller dose of a GBCA with higher relaxivity may result in a similar contrast-to-noise ratio to that from a larger dose of a GBCA with lower relaxivity. However, the half-dose of Multihance that is being used in the medical community has not been approved for efficacy, and the relaxivity values listed in the table may be misleading clinicians about the efficacy of the half-dose in patients imaged using the 1.5 T or 3 T MRI scanner.

Thus, the reviewer recommends that TABLE 2 in the current prescribing information for Multihance be updated by replacing relaxivity values measured at 0.47 T with values measured at 1.5 T and 3 T, with clear denotation of the field strength at which the relaxivity values were measured.

8. Contraindicate Gadovist, but not Dotarem, if/when approved in the United States.

As discussed in section 3.2.2.2 and 6.3, there have already been several reports of NSF cases associated with Gadovist. Yet, Gadovist has only been administered to at most 4 million patients. Although some of the cases are somewhat limited by the absence of information, the low conditional stability of Gadovist may account for the higher-than-expected number of associated NSF cases given that Gadovist is a macrocyclic GBCA. According to some, Gadovist has the lowest conditional stability of all the globally marketed GBCAs [18]. Even in a Bayer publication, the conditional stability of the macrocyclic GBCA Gadovist is reported to be lower than that for all of the linear ionic GBCAs [21]. Given that both physicochemical and human NSF incidence data appear to suggest that Gadovist may confer a higher risk of NSF than some other GBCAs, the reviewer recommends that Gadovist be contraindicated in the at-risk population.

At this time, the human, physicochemical, and animal data on Dotarem suggest that this GBCA confers a lower risk of NSF relative to other GBCAs. Re-evaluation at the time of approval may be warranted.

9. <u>For determination of NSF risk associated with GBCAs approved in the future, carefully consider the drug-specific effects rather than rely on a prediction of the associated NSF risk based on the risk of others in the same chemical subclass (e.g. linear ionic).</u>

By chemical structure, Gadovist is classified as a macrocyclic GBCA--a subclass of GBCAs that are believed by most to have the lowest NSF risk. However, the recent reports of NSF cases associated with Gadovist cast doubt on the blanket statement that all macrocyclic GBCAs are of equally low risk for NSF (section 3.2.2.2). Differences in the ionicity (nonionic vs ionic), the cavity size of the ring, the rigidity, and the conformation of the ligand may be responsible for the large difference between the conditional stabilities of different members of this subclass (as low as 14.7 for Gadovist, as high as 19.3 for Dotarem; see section 2.2.4) which, in turn, might explain the observed differential NSF risk even within the macrocyclic GBCAs.

Similarly, by chemical structure, Magnevist is classified as a linear ionic GBCA. Another GBCA in this subclass, Multihance, has only been associated with at most one single-agent NSF case. This is lower than the expected number of cases based on those reported for Magnevist, even when adjusting for the difference in the number of administrations. It has been postulated that Magnevist, being the only linear ionic GBCA without a bulky phenyl substituent, may have a lower kinetic stability than the others in the subclass (section 3.2.2.3). In addition, Magnevist may have a conditional stability that is intermediate between those of the linear nonionic GBCAs and the other linear ionic GBCAs (section 3.2.2.3).

For Gadovist and Magnevist, the correlation between NSF incidence and physicochemical properties suggest there may be unique properties about these GBCAs that distinguish them from other members of their respective subclasses. Thus, even though there may be an expectation that all members of a subclass have the same level of NSF risk based on general chemical structure, the drug-specific properties of each GBCA must be considered when making the determination of whether the GBCA confers a lower or a higher risk of NSF.

10. <u>Collect prospective data on human NSF cases.</u>

One of the recommendations of the Drug Safety Oversight Board was that follow-up of at-risk patients who receive GBCA is necessary for three purposes: (1) to conduct public health surveillance for new NSF cases; (2) to estimate the NSF risk with more recently approved agents; and (3) to prevent GBCA administration to patients who may already be afflicted with NSF. The reviewer agrees that these are necessary in order to protect the public's health.

Once the contraindication of Omniscan, Optimark, and Magnevist is implemented in the vulnerable population, the use of these three agents in the at-risk population will be so minimal that the information collected on vulnerable individuals administered GBCAs will not be useful to assess differential NSF risk across all of the marketed GBCAs.

5.2   Collecting Additional Human NSF Data

Section 5.1.2 describes the rationale for collection of prospective data on human NSF cases. Some of the difficulties of performing this task are described in section 3.3. This section will briefly outline a few possibilities for how to begin to accomplish this task.

An important step is to obtain an International Classification of Diseases code (ICD-9 or ICD-10) for NSF. ICD codes are used to classify diseases for many purposes including billing. An ICD code for NSF may allow research using claims databases. More importantly, an ICD code for NSF would enable the possibility of active surveillance using the FDA Sentinel system [161;162].

The establishment of a set of widely accepted criteria for NSF diagnosis is necessary for collecting meaningful human data. Without this, the heterogeneity in NSF diagnoses may undermine any attempts to calculate an accurate incidence rate.

Collecting exposure and outcome data may be facilitated by the Electronic Health Record (EHR) that is becoming more widespread in the United States due to (a) incentive payments through 2014 for meeting certain "meaningful use" criteria and (b) penalties beginning in 2015 if certain criteria are not met by the health institutions [163;164]. The core set of meaningful use criteria include the recording of vital signs and implementing drug-drug and drug-allergy interaction checks. The menu set of criteria include submitting electronic syndromic surveillance data to public health agencies. The final regulation for the first two years (2011 and 2012) of the 4-year incentive program were recently released in July 2010 [164], but those for the last two years are still under discussion. If it would be possible to get the recording of contrast agent name and dose as one of the core meaningful use criteria for the future (or even as a menu set criteria), then collecting information about human NSF cases would become much easier. Of note, the American College of Radiology is actively engaged in the meaningful use rulemaking process [165;166].

In the interim, tracking use of contrast agents and NSF cases may be facilitated by health systems that already have EHR in place such as Kaiser Permanente or the Veterans Administration (VA). As of March 2010, all 431 Kaiser medical facilities were equipped with the HealthConnect EHR [167;168]. With their emphasis on secure data sharing, integrated electronic disease registries, and patient-centered view of chronic conditions, it may be worth investigating whether they the Kaiser system might be able to capture information on contrast agent administration and NSF diagnosis--and share

this information with FDA. Kaiser is also working with the VA system to securely share patient information. The VA has been using an EHR called VistA for several decades [169], so the VA may also be able to capture GBCA and NSF case information.

There is precedence for FDA and Kaiser collaborating to investigate safety signals using a managed care database. For Vioxx, FDA and Kaiser worked together to conduct a retrospective review of a large database to evaluate cardiovascular safety signals [170]. FDA has also collaborated with institutions such as Harvard Pilgrim Health Plan, Vanderbilt University, and UnitedHealth Group to conduct pharmacoepidemiology studies aimed at identifying postmarketing safety signals [171]. Thus, cooperative agreements are also possible avenues for obtaining prospective NSF case information.

As alternative to public-private partnerships, companies marketing GBCAs could be asked to establish and maintain NSF registries. One example of a such a registry is the Bosentan Patient Registry in Australia [172]. Bosentan is a treatment for pulmonary arterial hypertension. A database was established that collected and stored information about the patients taking Bosentan over a period of three years. Assessments of cardiac function were performed and recorded every 6 months. Although enrollment into this registry was voluntary, some basic principles may be applicable to GBCAs and NSF.

In the U.S. and in Europe, controlled distribution programs have helped to determine the true Bosentan post-marketing rate of hepatic injury because the actual number of events and the number of exposed patients are known [173]. In the U.S., the Bosentan distributor called each patient monthly prior to dispatching the next month's supply to determine whether the patient had a liver function test (and a pregnancy test if appropriate since Bosentan is a potential teratogen). In addition to a controlled distribution program, the Europeans developed a prospective, internet-based postmarketing surveillance database for Bosentan pharmacovigilance purposes. As a result, the European regulatory authorities could review the Bosentan adverse event data for safety signals on a weekly basis.

For GBCAs, the relevant population to track NSF is only a subset of all recipients of GBCAs. In addition, there is no monthly dispatch of the drug to serve as an incentive for an individual to obtain follow-up for NSF. Despite these key differences between the GBCA and Bosentan situations, certain aspects of the Bosentan surveillance programs could be adapted for GBCAs to obtain a more accurate numerator and denominator for calculating NSF incidence rates.

5.3 Communications Recommendations

Section 5.1.2 describes the rationale for clearly communicating to health professionals and the public that the contraindication applies only to a small, defined at-risk population. This section offers a target distribution list for this communication.

Target distribution list should include:
Radiologists
MRI technologists
Drug purchasers for hospitals and imaging centers
Nephrologists
Dermatologists
Healthcare providers on the individual customer lists of each of the sponsors
Appropriate medical societies

6 Appendices

6.1 Sponsors' Responses to the 2009 FDA Information Request Regarding NSF

In June 2009 through August 2009, FDA requested information from all the pharmaceutical companies marketing gadolinium-based contrast agents (GBCAs) in the United States. The questions were posed to help the FDA better assess the level of NSF risk associated with each product and each company's efforts to minimize the risk of NSF. Each question is listed below, followed by a brief summary of the responses from the companies.

> **FDA Request 1a. Provide summaries and analyses of the most recent cumulative findings from the prospective observational study you established under an FDA Postmarketing Commitment (PMC) described in 2007.**

All protocols have been finalized except that for Vasovist (marketed by Lantheus) which was approved for marketing in December 2008 (Table 6). Lantheus is in the final stages of finalizing their Phase 4 protocol, after several interactions with the FDA. To confirm the NSF diagnosis, all protocols plan to use the diagnosis criteria developed by Shawn Cowper and colleagues which incorporates clinical and histopathological information.

Of the GBCAs with finalized protocols, the studies for Omniscan, Optimark, and Magnevist have enrolled fewer than 30 subjects whereas the studies for Multihance, Eovist, and Prohance have enrolled more than 30 subjects. The studies are to enroll moderate and severe renal failure patients.

Studies enrolling one patient (Omniscan) or zero patients (Optimark) to date are hindered by hospitals not using these products in patients with renal impairment, among other reasons. As a result, the protocol for Omniscan has been amended to only enroll patients with moderate renal failure. Covidien is planning to submit a Changes Being Effected in 0 days (CBE0) labeling supplement to contraindicate Optimark for patients with GFR <30 mL/min/1.73m^2. Bayer had difficulty enrolling patients into the Magnevist study which excluded subjects with a history of *any* GBCA exposure within 12 months of enrollment. Bayer subsequently amended the study to exclude patients with exposure to any GBCA *except Magnevist* for 12 months prior to enrollment.

With 174 patients enrolled to date, the study with Multihance has enrolled the most subjects. To date, there are no cases of NSF in the PMC studies with any GBCA. In addition to the Phase 4 study, Bracco is conducting an additional study to evaluate the NSF incidence rate in patients with Stages 4 or 5 chronic renal failure who have not had exposure to GBCAs within the past *ten* years to obtain a background rate of NSF.

FDA Request 1b. Provide summaries and analyses of postmarketing reports of NSF from your pharmacovigilance database.

A total of 1161 NSF cases have been considered "reportable" to global regulatory authorities by pharmaceutical companies marketing GBCAs in the US (Table 10). Omniscan has the most with 611 cases, followed by Magnevist with 455 cases and Optimark with 70 cases. There have been zero cases reported for Eovist and Vasovist.

Of note, the definition of a "reportable" case differs by company. Bayer has the most conservative definition, reporting to regulatory authorities all cases reported to them as NSF/NFD or possible / suspected NSF/NFD. According to Bayer, the 455 cases reported for Magnevist includes 174 cases with no known Magnevist exposure. For all the other companies, their product must be named as a suspect drug in the report before the case is reported to regulatory authorities. Of the 281 cases (455 minus 174) with known Magnevist exposure, 86% (242) were US cases. Of the 611 Omniscan cases, 70% (425) were US cases. Of the 70 Optimark cases, 69 were from the US.

Both Magnevist and Omniscan have had cases reported as being in patients with moderate renal failure (30 mL/min/1.73 m^2 < GFR < 60 mL/min/1.73 m^2). However, the two potential Magnevist cases in patients with GFR > 30 mL/min/1.73m^2 either had a GFR recorded on an unspecified date prior to GBCA administration or a fluctuating GFR when the GBCA was administered due to active rejection of a transplanted kidney. The one potential Omniscan case in a moderate renal failure patient had a GFR of 27.9 mL/min/1.73m^2 when calculated using the extended MDRD formula instead of 33 mL/min/1.73m^2 using the standard Modification of Diet in Renal Disease (MDRD) calculation.

For Omniscan, 9.1% (26) of the cases were in acute kidney injury (AKI) patients. Similar AKI information is not presented for the other GBCAs.

It is important that there has been only one NSF case associated with Prohance where the only GBCA the subject was expossed to was Prohance (single-agent case). In this subject, 32mL was administered to the subject 6 times over 2 years (total 72 mL) before NSF developed (Table 10). This single-agent Prohance case indicates that exposure to only a macrocyclic GBCA, when at high cumulative doses, may also lead to NSF.

Single-agent case in this document is defined as exposure to only one GBCA prior to NSF diagnosis. Exposure to multiple doses of the same GBCA prior to NSF diagnosis can be counted as a single-agent case.

Of note, one of the 15 cases reported for Prohance was after Prohance x1 dose and Dotarem x1 dose. Another case was after Prohance x1 dose and Gadovist x1 dose. Both of these cases were after administration of only macrocyclic GBCAs, suggesting that exposure to only nonlinear GBCAs can also be associated with NSF.

Of the 10 cases for Multihance and 15 cases for Prohance reported to regulatory authorities since their US approvals in 2004 and 1992, respectively, none of the Multihance cases were single-agent cases and only one of the Prohance cases was a single-agent case (described above). GE Healthcare did not report the number of single-agent cases for Omniscan (US approval in 1993). Among the GBCAs with the number of single-agent cases reported, Magnevist (US approval in 1988) has the highest at 159, followed by Optimark (US approval in 1999) with 28. Eovist and Vasovist also have no single-agent cases since their US approvals in 2008.

Table 10. Worldwide "Reportable" NSF cases and single-agent cases.

Contrast agent	# NSF reports	# Single-agent cases
Omniscan	611	NR
OptiMARK	70	28
Magnevist	455 (281*)	159
MultiHance	10	0
Eovist	0	0
Vasovist	0	0
ProHance	15	1

NR: not reported; * cases with known Magnevist exposure

As stated in Table 1, the prescribing information for GBCAs recommends a dose of 0.1 mmol/kg for each GBCA except for Prohance and Omniscan which allow up to 0.3 mmol/kg with a second administration. For Omniscan and Magnevist, the number of

cases for which the GBCA dose is known was submitted. Of the 611 reportable Omniscan cases, 249 had known Omniscan doses. Of the 82 reportable Magnevist cases for which Bayer deemed possibly associated with Magnevist based on criteria proposed by Broome et al (AJR 2007; 188:586), 47 cases had known Magnevist doses.

Of the 249 Omniscan NSF cases with known doses, 21 cases were after a cumulative Omniscan dose of <20 mL or < 0.1 mmol/kg. Of the 47 Magnevist NSF cases with known doses, two developed after a cumulative Magnevist dose of <20 mL or < 0.1 mmol/kg. That these cases exist indicates that NSF can develop after lifetime exposure to only a near-standard dose (whether a dose is truly standard depends on weight for cases reported as mL administered) of certain GBCAs.

For Optimark, Covidien reports that 53 of the 70 cases had multiple exposures to GBCAs (not necessarily Optimark). It can therefore be implied that 17 of the 70 cases reported for Optimark had a single exposure to Optimark. The dose of Optimark in these 17 cases is not specified, but it is stated in response to FDA request 1c that seven Optimark cases had used doses in excess of the labeled dose. However, it is not stated how many of these seven excess-dose cases were in patients with single versus multiple exposure(s) to GBCAs. Thus, it is not possible to estimate the number of NSF cases developing after a cumulative exposure of <20 mL or < 0.1 mmol/kg of Optimark.

With regard to the main question at hand, which is whether there is differential risk among the GBCAs and whether there should be differential labeling, the information provided in the responses to the IR is limited due to the inhomogeneity in the definitions of the number of reportable cases, an undetermined number of duplicate reports despite company attempts to cross-match potential duplicates, the lack of dosing information for the majority of cases, the lack of information about the specific GBCA(s) used, the lack of information about the timing of GBCA administration relative to renal function testing and NSF diagnosis dates, the lack of consistent criteria for NSF diagnosis until 2009, and the lack of consistent criteria for assigning cases to be associated with particular GBCAs.

FDA Request 1c. Provide summaries and analyses of drug utilization data for your GBCA.

Companies other than Bayer reported estimates of the number of vials or units sold since their international birth date (Table 11). Bayer provided estimates of the number of procedures for which their products were used. For Magnevist, the estimated total number of procedures worldwide for which Magnevist has been used since approval was _____ (b) (4) by May 2009. For Eovist, this estimate was _____ (b) (4). In the Eovist submission, Bayer also reports the number of administrations for all the GBCAs from their International Birth Dates up to July 2009, as estimated by _____ (b) (4) _____ (Table 3).

Magnevist was the first GBCA to be approved internationally, and it has been administered more times than any other GBCA by at least 2 fold. By dividing the numbers in Table 10 by the estimated number of administrations for each GBCA from the third column in Table 11, there appears to be a trend toward a higher reporting rate for the linear nonionic GBCAs (Omniscan and Optimark) than for the other GBCAs (Table 12). Of note, direct comparison of the numbers in Table 12 is limited by the variable definitions of "reportable" cases among the companies (see FDA request 1b) and the uncertainty in the estimates of the total number of administrations.

Of note, a more meaningful denominator for calculating NSF incidence would be the number of administrations to individuals with a GFR < 30 mL/min/1.73m^2 or AKI rather than the total number of administrations. This is because with the exception of a few questionable cases, only those with severe renal failure or AKI are at risk for developing NSF (see response to FDA Request 1b).

Table 11. Worldwide drug utilization estimates since International Birth Date.

Contrast agent	# Vials or units sold (10^6)	# Administrations (10^6) (AMR)	International Birth Year
Omniscan		(b) (4)	1993
Optimark			1999
Magnevist			1988
Multihance			1997
Eovist			2005
Vasovist			2006
Prohance			1992

* Bayer provides the e   (b) (4) , estimated for July 2009

Table 12. Reporting rates per million administrations.

Contrast agent	# NSF reports per million administrations	# Single-agent NSF cases per million
Omniscan		(b) (4)
Optimark		
Magnevist		
Multihance		
Eovist		
Vasovist		
Prohance		

*Not calculable because the estimate for the number of single drug cases was not submitted.

Magnetic resonance angiography (MRA) is one of the procedures for which a higher dose is often administered, so GE Healthcare and Bayer provided estimates for the number of MRA procedures using Omniscan and Magnevist. Worldwide yearly MRA use is not provided for Omniscan, but estimates of the yearly number of MRA procedures performed in the US was reported for both. The number of MRAs performed in the US has increased since the mid-1990s for both Omniscan and Magnevist, from   (b) (4)   in 1993 for Omniscan to a peak of   (b) (4)   in 2006, and from (b) (4) in 1995 for Magnevist to a peak of   (b) (4)   in 2006.

GE Healthcare also provided the yearly estimated dose used in MRA procedures to demonstrate that there has been a steady increase from   (b) (4) /MRA in 1993 to a peak of   (b) (4) MRA in 2005. This estimated dose per procedure information was not provided by other companies, so conclusions regarding differential dosing among GBCAs cannot be drawn using the information submitted.

Regarding repetitive dosing, GE Healthcare claims that it is more likely that Omniscan was used repetitively in patients compared to the majority of other GBCAs because Omniscan, like Prohance, is approved in the US for cumulative dosing up to 0.3mmol/kg (0.6 mL/kg) for the central nervous system indication whereas the other GBCAs are only approved for up to 0.1mmol/kg (0.2 mL/kg). For a 70 kg human, 0.3mmol/kg would translate into 42 mL whereas for a 50 kg human, 0.3mmol/kg would translate into 30 mL.

Of note, Prohance is also approved for up to 0.3 mmol/kg and Prohance has significantly fewer NSF cases reported and only 1 single-agent case.

FDA Request 1d. Provide summaries and analyses of published literature and provide a summary of NSF reports implicating your GBCA.

For Magnevist and Omniscan, 29 and 71 publications reporting NSF cases, respectively, make reference to these specific GBCAs. In the Magnevist references, 45 of the 54 NSF cases were deemed by Bayer as following a single-agent exposure to Magnevist. Covidien reports five adverse events involving Optimark in the literature. Bracco published the only single-agent case for Prohance. Bracco stated that one publication reports two single-agent cases for Multihance. Bracco believes there has not been even one single-agent case associated with Multihance and plans to ask for a correction by preparing a letter to the editor. According to the FDA OSE review finalized on November 6, 2009, there is one single-agent report of NSF for Multihance in the FDA Adverse Event Reporting System.

FDA Request 1e. Provide summaries and analyses of outcome data on patients with a confirmed diagnosis of NSF following administration of your GBCA.

Of the GBCAs associated with numerous NSF cases, the outcomes of some cases were not known. Of the deaths, NSF contributed to some deaths but not others. Of patients who have not died, some improved, but most were not resolved or worsened. Some NSF patients tried various treatments whereas others did not try any. None of the treatments resulted in consistent improvement of NSF. Thus, there is no effective treatment for NSF.

FDA Request 1f. Provide summaries and analyses of reports of NSF in your phamacovigilance database summarized by six month increments for both event date and reporting date.

Following the 2006 FDA and European advisories, the increasing awareness of NSF was paralleled by the increasing number of reported cases (Table 5). Of note, the 72 Magnevist cases in the first half of 2007 included a cluster of 21 cases from Massachusetts. Legal cases contributed to the cases reported in 2007 and represent the majority of cases reported in 2008, which were largely historical (Table 4 and Table 5 in section 2.6 above).

Many of the "reportable cases" tabulated in Table 10 have unknown event dates. In fact, the event dates for 274 of the 611 Omniscan cases, for 17 of the 70 Optimark cases, for 71 of the 281 Magnevist cases, for 3 of the 10 Multihance cases, and for 2 of the 15 Prohance cases are unknown.

Of note, different companies have different definitions for "event date." For Bayer, event date is defined as the onset date of signs and symptoms suggestive of NSF (or the diagnosis date by skin biopsy or clinically when onset date is unclear or not provided). For Covidien, event date represents the diagnosis date with or without biopsy.

For Omniscan, the number of cases with event dates in each half year increased from ~6 in 2000 to ~40 in 2006 (see Table 4 in section 2.7.1 above), and GE Healthcare reports that this increase paralleled the increase in the number of MRA procedures performed with Omniscan. There was a sharp decline in the number of cases with event dates in 2007 for Omniscan, with no cases that GE Healthcare is aware of with an event date after September 2007. For Optimark, the most recent exposure date for a case was April 2008, which followed the next most recent exposure date of June 2007. For Magnevist, there have been no cases with symptom onset in 2009. The decline in the number of cases with event dates in recent years has been attributed by companies to the boxed warning, increased awareness of NSF, and screening for renal impairment.

FDA Request 1g. Provide summaries and analyses of your global experience as well as the subset experience within the United States.

In the cumulative dosing information that GE Healthcare provided for NSF cases reportable for Omniscan, 69% of the non-US cases and 81% of the US cases with known dose information were administered a cumulative Omniscan dose of $\leq$60mL or $\leq$0.3 mmol/kg (Table 7). It is not known how many of the cases in the 20-60 mL category were truly less than the labeled limit of 0.3 mmol/kg (shaded in gray in Table 13, the labeled limit would translate into $\leq$42 mL for a 70 kg human since 0.1 mmol/kg is 0.2 mL/kg for Omniscan). Nor is it known how many of the <20mL cases (shaded in gray in Table 13) were within the labeled limit of 0.3 mmol/kg, though the patient would need to be <33.3 kg to exceed the 0.3 mmol/kg dosing limit for Omniscan.

Despite the dosing uncertainty in the cases reported as mL administered, it is certain that 10% of the reportable Omniscan cases had a cumulative dose within the labeled limit of 0.3mmol/kg. However, it is likely that many more of the reportable Omniscan cases inside and outside the US were within the labeled dose limit, but exactly how many cannot be determined without information about the weight of the patients.

For both Omniscan and Magnevist, the proportion of NSF cases in the US (over the total number of cases worldwide) far exceeds the use of these GBCAs in the US compared to worldwide use. As noted in response to FDA Request 1b, 70% (425 of 611) of the reportable Omniscan cases and 86% (242 of 281) of the Magnevist cases with known Magnevist exposure are US cases. However, for both of these GBCAs, the total use to date in the US amounts to 50% or less than the total use worldwide (46% for Omniscan, 50% for Magnevist). For Optimark, 69 of the 70 reportable NSF cases are US cases. The relative use of Optimark within the US and outside the US was not submitted.

Of the two GBCAs with the most reportable NSF cases, there have been more reportable NSF cases for Omniscan than for Magnevist in the US despite fewer procedures being performed with Omniscan than with Magnevist. In the US, there have been 425 reportable cases for Omniscan versus 242 reportable cases for Magnevist. However, there have been approximately ⬜ (b) (4) procedures performed using Omniscan in the US between 1995 and 2008, which is significantly fewer than the nearly ⬜ (b) (4) procedures performed using Magnevist in the US during the same time period.

For the three GBCAs with the highest number of reportable NSF cases, the number of cases with event dates within each half year rose from the year 2000 to the year 2006 or 2007, and these increases paralleled the rise in the use of these particular GBCAs. For Omniscan, there was a steady increase in the number of cases with event dates every half year from ~5 in the year 2000 to ~40 in 2005 and 2006. Although the yearly number of worldwide procedures using Omniscan was not submitted, GE Healthcare does report that the number of procedures using Omniscan in the US peaked at (b) (4)

(b) (4) in 2006. For Magnevist, the number of cases with event dates each half year peaked at 36 in the first half of 2007. This increase paralleled the increase in the yearly number of worldwide procedures which peaked at 9.3 million in 2007. For Optimark, the number of cases with event dates in each half year peaked at 14 in the first half of 2007.

Table 13. Cumulative dose in NSF cases reportable for Omniscan.

Cumulative dose	Non-US (% non-US cases with known dose info)	US (% US cases with known dose info)	All (% total cases with known dose info)
Standard dose (<=0.1 mmol/kg)	1 (0.7%)	1 (0.8%)	2 (0.8%)
Possibly within labeled dose limit (<20 mL)	10 (7.7%)	9 (7.5%)	19 (7.6%)
High, but within labeled dose limit (0.1-0.3 mmol/kg)	7 (5.4%)	16 (13.4%)	23 (9.2%)
High, some within labeled dose limit (20-60 mL)	72 (55.4%)	71 (59.7%)	143 (57.4%)
Highest dose (>60 mL or >0.3 mmol/kg)	40 (30.8%)	22 (18.5%)	62 (24.9%)
# Cases with cumulative dose information	130	119	249
# Cases without cumulative dose information	56	306	362
Total # cases	186	425	611

Similar to the trend seen with Omniscan and Magnevist, the number of Optimark units distributed worldwide steadily increased since 2000, reaching (b) (4) in 2007. The use of Optimark continued to increase to (b) (4) units distributed in 2008.

It is notable that (b) (4) patients worldwide (b) (4) in US) and (b) (4) patients worldwide ((b) (4) in US) have been exposed to Prohance and Multihance, respectively. Also, 58% of the number of Prohance units sold and 38% of the number of Multihance units sold are in the US. Yet, neither Prohance nor Multihance are associated with any single-agent cases in the US, and only 15 and 10 multi-agent cases worldwide have been reported involving Prohance and Multihance, respectively. As described in response to FDA Request 1b, there is only one single-agent case associated with Prohance and this occurred in Switzerland.

FDA Request 2. With respect to the risks, pathophysiologic basis, or both for NSF, provide an overview of toxicology data from humans and animals based upon your product's development program and from the published reports of experiences with your GBCA.

Company-sponsored studies and those without apparent conflicts of interest were discussed. The studies supported either the prevailing theory for NSF pathogenesis which is that "free" Gd^{3+} triggers NSF, or an alternate theory proposing that chelated Gd^{3+} rather than "free" Gd^{3+} triggers NSF.

A few studies sponsored by Bayer were mentioned by nearly all submissions. These studies tested all the marketed GBCAs for (1) their ability to produce skin lesions in rats, (2) differential retention of Gd^{3+} in rat tissues after repetitive GBCA administration over one month, and (3) the ability of excess chelate to reduce the severity of skin lesions and decrease tissue retention of Gd^{3+}. The key findings from the Bayer-sponsored studies were that (1) Omniscan, unchelated gadodiamide (the drug substance of Omniscan), and unchelated gadoversetamide (the drug substance of Optimark) could produce skin lesions that shared some macroscopic and microscopic characteristics with human NSF, that (2) repetitive administration of linear nonionic GBCAs resulted in the highest concentration of Gd^{3+} in the skin and bone in naive and 5/6 nephrectomized rats, and that (3) excess chelate reduced the severity of skin lesions and the amount of Gd^{3+} retained in the skin for gadodiamide and gadoversetamide.

A primary concern that GE Healthcare has regarding these studies is that injecting GBCAs into the rat may not be a valid model for human NSF since the rat skin lesions seen in the Bayer-sponsored study are similar to those published 16 years ago in a study evaluating the preclinical safety of Omniscan. GE's independent pathology peer review of the original slides from the Bayer-sponsored study concluded that the skin lesions are consistent with skin trauma, a finding reinforced by a GE Healthcare-sponsored study reporting that gadodiamide or Omniscan-induced skin lesions in naive and nephrectomized rats coincided with pruritus onset. Regarding high accumulation of Omniscan in rat tissue, GE Healthcare counters that the techniques used to detect Gd^{3+} in tissue cannot differentiate between "free" Gd^{3+} and chelated Gd^{3+}, so it is possible that chelated gadolinium rather than "free" Gd^{3+} could be retained in tissue.

In response to the Bayer-sponsored study showing that (1) in human serum, the release rate of Gd^{3+} from linear non-ionic GBCAs was significantly higher than from linear ionic GBCAs in a manner accelerated by elevated serum phosphate levels and that (2) the amount of Gd^{3+} released after two weeks was significantly greater for linear nonionic GBCAs than for other GBCAs, GE Healthcare counters that the chelating column used in the Bayer-sponsored study could capture chelated as well as "free" Gd^{3+}. A similar argument is used by GE Healthcare to counter two studies sponsored by Bracco which used different analytical methods to show that human bone retention of Gd^{3+} was greater for Omniscan than for Prohance.

Bayer and GE Healthcare have both sponsored studies to investigate the mechanism of NSF. A Bayer-sponsored study showed that gadodiamide (the active ingredient in Omniscan) could stimulate the release of cytokines, including osteopontin which could be a chemoattractant for dendritic cells, macrophages, and T-lymphocytes, which in turn activate inflammatory pathways. GE Healthcare extended the findings of this study to show that Omniscan and Magnevist could both stimulate expression of multiple cytokines and growth factors, with Magnevist inducing the strongest up-regulation.

FDA Request 3. Describe your plans for any further studies and labeling changes based on the results of your analyses.

In addition to the Phase 4 studies, Bracco is conducting a study to assess the background rate of NSF. This Bracco study aims to determine the incidence of NSF in patients with Stages 4 to 5 chronic kidney disease without exposure to GBCAs in the past ten years.

Covidien is performing a retrospective database review in conjunction with Duke Cardiovascular Magnetic Resonance Center to compare morbidity and mortality in patients with and without NSF and to determine if a certain GFR level is a risk factor for NSF associated with Optimark. Covidien is also conducting a study in rats to investigate the effects of various phosphorus levels on gadolinium deposition following repeated doses of GBCAs to determine whether specific physiological / pathological conditions affect the deposition of gadolinium, calcium, and phosphorus in skin after GBCA administration.

No other companies are planning to conduct any clinical or nonclinical studies at the time of their submissions, but all companies were recently asked by the European Medicines and Healthcare products Regulatory Agency to perform clinical studies evaluating long-term retention of gadolinium in human tissues.

Regarding labeling, Covidien submitted a Changes Being Effected in 0 days (CBE0) labeling supplement in November 2009 to contraindicate Optimark for patients with a GFR < 30 mL/min/1.73m^2. No other companies are planning labeling changes.

FDA Request 4. Multiple GBCAs are currently marketed. Comment upon the factors involved in any differential risks for NSF among these products. Specifically comment upon the factors that you regard as important in distinguishing the risks for NSF with your product in comparison to other products.

Chemical stability differences, pharmacokinetics, nonclinical studies, and clinical studies were put forth by the companies to distinguish the risk for NSF with their product(s). The

majority of these topics are summarized above or covered in the FDA Briefing Document for the December 8, 2009 Advisory Committee meeting. A few points that are not covered elsewhere are summarized below.

The majority of GBCAs have a serum elimination half-life in the 1-2 h range in healthy humans. Vasovist has an extended mean elimination half-life of 18.5 h, ~10 times longer than for all other GBCAs, because it is designed to bind to albumin for retention in circulation. However, the labeled dose for Vasovist is 0.03 mmol/kg, which is 3-10 times lower than for all other GBCAs except for Eovist (0.025 mmol/kg). Vasovist can also be eliminated via bile (<9%), a property shared by Eovist but to a much greater extent (50% biliary elimination).

Both Vasovist and Eovist also have a narrow indication spectrum: MRA for Vasovist, liver lesion detection and characterization for Eovist. Serum elimination half-life for Eovist increases to a lesser extent than for some other GBCAs tested (Magnevist and Multihance) in end-stage renal failure patients.

Regarding dose, even though Multihance is approved for 0.1 mmol/kg, Bracco claims that its increased relaxivity could translate into the same or increased contrast enhancement at lower doses.

GE Healthcare lists a number of potential causes for the difference in the numbers of reported cases associated with individual GBCAs, including the possibility that Omniscan was used more extensively in patients with renal failure. GE Healthcare supports this assertion by pointing out the lack of a relationship between Omniscan sales and NSF incidence rate as well as the nonrandom geographic distribution of Omniscan cases which could also be due to differences in dose or frequency of administration).

Other causes listed by GE Healthcare include the possibility of higher Omniscan doses being administered because its labeled dose limit is higher than for most other GBCAs; earlier and more widespread availability of Omniscan (and Magnevist) than other GBCAs; potential reporting bias because GE Healthcare was the first manufacturer to identify the association of their GBCA with NSF; differential diagnostic criteria and reporting among companies; and differential contraindication of certain GBCAs in patients with renal insufficiency.

6.2 Clinicopathological Definition of NSF

The schematic below is adapted from [42].

6.3 Brief Description and Discussion of All Eight MedWatch Reports for Gadovist

►Three potential single-agent Gadovist cases.

- Case 201011655GPV is notable for a history of renal failure on dialysis, 10mL Gadovist exposure for MRA, and histological findings "typical" for NSF 1.5 years after Gadovist exposure. However, the specifics of the biopsy results, clinical exam, Gadovist concentration (0.5 M or 1.0 M), GFR on the day of Gadovist exposure, and any prior GBCA exposure are not reported.

- Case 200923701GPV [123] is notable for a history of chronic renal failure with a GFR of 34mL/min/1.73m^2 one month and 5 days prior to exposure to 17.5 mL Gadovist. Clinical exam findings and skin biopsy performed 9 months after Gadovist exposure were consistent with NSF. Renal function status on the day of Gadovist administration and Gadovist concentration are not reported.

- Case 200828599GPV [124] is notable for a history of terminal renal failure on dialysis with serum creatinine ~7.6 mg/dL (status on days of Gadovist exposure not reported), 2 Gadovist exposures, 30mL in April 2005 and 10mL in June 2007. About 16 months after first Gadovist administration, patient developed contractures and fibrotic changes on arms and legs, clinically consistent with NSF. Biopsy findings were reported as compatible with NSF though this is debated [174]. Gadovist concentration not reported.

►A fourth case has been reported as an NSF case associated with Gadovist, but has several features that may not be consistent with NSF:

Case 200931796GPV [123] is notable for kidney failure on dialysis starting in 2007. Patient exposed to 15 mL Gadovist in February 2008. GFR was 11 mL/min ~ 4 months prior to Gadovist exposure. Patient had multiple medical problems, eventually requiring amputation of toes and a finger. Thus, the tightening of skin on fingers and hands in 2009, finger disfiguration, and inability to bend fingers may or may not be attributed to NSF. Skin histology is also not convincing for NSF: although there is dermal thickening and perhaps septal involvement, there is no increase in CD34 positive cells.

Gadovist concentration is not reported. It is noted that the patient had prior exposure to Omniscan in June 2001 when the patient's GFR was > 60 mL/min.

►A fifth MedWatch report (200814121GPV) is notable for development of yellow dermopathy on palms and soles within 20 days following administration of two macrocyclic GBCAs separated by 3 days (7 mL Gadovist then 32 mL Prohance). Renal function status is not reported though the patient could have reduced renal function given the multiple myeloma history. Histology performed nearly 1 month after Gadovist exposure was reported as "compatible with NSF" though the specifics are not provided. Gadovist concentration is not reported.

Although this case cannot be attributed to Gadovist or Prohance given the close proximity in administration of the two drugs, it is important to note that administration of only macrocyclic GBCAs can result in NSF. Precedence for this is the NSF case from Switzerland which developed after 6 doses of 32 mL Prohance within 2 years (BRO-011796, AERS# 537428, [109, sponsored by Bracco]).There is also a possible NSF case after 1 dose of Prohance and 1 dose of Dotarem, both macrocyclic GBCAs, though not enough information was reported to be certain (CH-000003, AERS# 6328076CH-GUERBET-20070007).

►A sixth MedWatch report (CH-2007-025128) is notable for chronic renal failure on dialysis (renal function status not reported) as well as clinical and histology findings consistent with NSF after 7 GBCA administrations over 6 years, grouped into 2 clusters. In the first cluster, 15 mL Magnevist was administered in Feb 1999, unspecified GBCA in Oct 2000, and 15 mL Gadovist (concentration not stated) in Nov 2000. In the second cluster, Dotarem (20 mL each administration) was administered in Jan 2004, Aug 2004, and Jul 2005. Fifteen mL Gadovist 1.0 was administered in Oct 2005. The high cumulative gadolinium dose likely plays a causative role in this case. Of note, the second cluster of GBCA administrations was separated from the first cluster by 4 years and only included macrocyclic GBCAs, providing support that cumulative high doses of macrocyclic GBCAs could also cause NSF.

►A seventh MedWatch report (201021818GPV) was administered 21 mL Gadovist and, on the same day, developed hard skin, leg and foot pain, brownish leg discoloration, and stiff ankles and toes. Histology was reportedly consistent with NSF. However, this report lacks information on renal function status, prior GBCA administrations, and histology details.

►An eighth MedWatch report (200927399GPV) is a potential multi-agent case that also involves administration of a linear ionic GBCA. Two doses of Magnevist and one dose of Gadovist were administered within 21 months to a patient who started hemodialysis 3 months before the Gadovist dose. Renal function status is not reported, and histology was not entirely consistent with NSF.

6.4   University of Wisconsin Memo January 16, 2008

University of Wisconsin
**SCHOOL OF MEDICINE
AND PUBLIC HEALTH**

January 16, 2008

RE: Gadolinium Contrast Use in the Department of Radiology, University of Wisconsin

MEMO TO: Department of Radiology
FROM: MRI Safety Committee
                          Scott Reeder (Chair), Deborah Dasling, Aji Djamali, Gina Greenwood, Fred Kelcz, Tom
                          McKinlay, Frank Korosec, Howard Rowley, Elizabeth Sadowski, Mike Tuite

This following memo describes recent changes regarding the use and safety of gadolinium-based contrast agents in the UW Department of Radiology.

Background: Over the past two years a suspected link has arisen from the exposure of gadolinium-based contrast agents and the development of a rare but serious, life-threatening disease known Nephrogenic Systemic Fibrosis (NSF), in patients with renal failure. This is now a widely recognized problem implicated in patients receiving a variety of contrast agents, particularly gadodiamide (Omniscan), which previously was the sole gadolinium agent in use at UW. A total of 14 patients with renal failure and exposure to Omniscan have been diagnosed with NSF at UW. Patients considered to be at risk of NSF are those in renal failure with a coexisting pro-inflammatory condition (thrombosis, recent major surgery, and/or major systemic infection) (Sadowski *et al.*, Radiology 2007). Accordingly, NSF safety screening forms have been developed for the identification of patients at risk of developing NSF in our inpatient population.

In the summer of 2007, we switched gadolinium agents from Omniscan to gadobenate dimeglumine (Multihance), the only FDA-approved gadolinium agent not linked with NSF (to date). Multihance has several diagnostic advantages over other available FDA-approved contrast agents, including improved visualization of CNS tumors, improved MR Angiography, and partial hepatic excretion, which has important diagnostic features for liver and biliary imaging. For this combination of reasons, the use of Omniscan was discontinued and all protocols requiring gadolinium-based contrast agents were switched to Multihance.

However, since that time we have witnessed an apparent increase in adverse reactions associated with contrast-enhanced MRI/MRA. Specifically, there have been reports of nausea and vomiting and anaphylactoid reactions associated with Multihance.   Several of these reactions have required pharmacological intervention with diphenhydramine and epinephrine, and subsequent admission to the Emergency Department. No long-term complications or fatalities have resulted. All reactions have been logged within our own internal QA system as well as the UW patient safety network (PSN). During the period from 10/15/07 through 12/17/07, a total of 14 documented reactions to Multihance (6 minor, 8 serious) were documented. During this same period, a total of 1759 patients were administered Multihance, for an approximate adverse reaction rate of 0.8%.

This rate of adverse reactions at UW is higher than that reported in the literature. Reports from double-blinded and cross-over studies with other contrast agents and placebo have demonstrated no increased rate of adverse reactions from Multihance compared to placebo or other contrast agents. A recent study by Kanal *et al.* at RSNA 2007 in 25,244 patients demonstrated adverse reactions (minor and serious) in 0.3% of patients, with no fatalities or complications.

Department of Radiology

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After the identification of three anaphylactoid reactions during one week in December, the contrast agent packages containing lot numbers associated with these reactions were pulled from the shelves, and these reactions were reported to Bracco (manufacturer of Multihance). In addition, the MRI Safety Committee met on 1/11/08 to develop the following policies regarding the use of Multihance. These policies reflect our attempt to balance the importance of these recent adverse reactions with the high safety profile of Multihance (with regard to NSF) and the important diagnostic advantages of Multihance.

New Gadolinium Contrast Agent Policy:

1. **Outpatient Facilities** (Research Park, Waisman Center, East Clinic): Multihance will be discontinued as the primary gadolinium agent at our outpatient facilities, and replaced with Omniscan. However, patients who identify themselves as having "renal disease" on their MR screening forms will be administered Multihance, in light of the apparent association of Omniscan with NSF in patients with renal disease. Patients with *known* eGFR < 30 also will be given Multihance. It is *neither required nor recommended* to obtain serum creatinine/eGFR's for outpatients prior to contrast enhanced MRI. If there is a specific diagnostic need for Multihance, it may be used with specific approval from the attending radiologist. We expect only a small handful of patients to receive Multihance at the outpatient facilities. When a patient is to receive Multihance at these sites, particularly the Waisman Center, it is recommended that the technologist alert the responsible fellow or attending, 10-15 minutes prior to injection.

2. **UW Hospital and Clinics**: Data indicate that the inpatient population is at significantly higher risk of developing NSF from exposure to Omniscan. Therefore, Multihance will continue to be the gadolinium agent of choice during regular hours (7:00AM-11:00PM Monday-Friday, 7:00AM-3:00PM Saturday). Omniscan will be used after 11:00PM on weekdays, after 3:00PM on Saturday and all day Sunday with the following exceptions:
   - A. contrast-enhanced MRA
   - B. brain imaging for the identification for CNS tumors
   - C. liver imaging
   - D. patients with renal failure (eGFR<30) and/or those identified to be at risk for NSF

   based on NSF screening forms. Please see following link for more detail:

   (http://www.radiology.wisc.edu/fileShelf/forReferring/NSF_infoSheet_forPhysicians.pdf).

   Technologists should ask the resident, fellow or attending if there are questions or confusion on which patients should receive Multihance based on the above criteria. In addition, when Multihance is used after hours, it is recommended that the technologists alert the on-call resident 10-15 minutes prior to injection.

3. **Contrast Warmers:** Anecdotal evidence from other institutions suggests that contrast warmers may be helpful in reducing adverse reactions to Multihance. No definitive data exists to demonstrate this reduction in adverse reactions. As of 1/14/08, we have installed two contrast warmers located within the hospital. Based on our future experience with adverse reactions and contrast warmers, we may expand the use of contrast warmers to other locations.

4. **NPO Status:** It is now *recommended, but not required* that all patients who are to receive any intravenous gadolinium agents (Multihance or Omniscan) be NPO 2-4 hours prior to the exam. This may alleviate the rate of nausea and vomiting and will reduce the risk of aspiration in patients who do vomit. Schedulers and technologists will be advised to convey this recommendation when scheduling patients for scanning. However, this recommendation should not be communicated as an absolute requirement and should not interfere with patient scheduling, particularly for inpatients.

Department of Radiology

University of Wisconsin
**SCHOOL OF MEDICINE
AND PUBLIC HEALTH**

5. **Contrast Reaction Boxes:** All contrast reaction and airway boxes will be double-checked to ensure that they are up to the same standard as those found within the CT scanning area. Please note that gadolinium reactions should be treated with the same level of seriousness as CT contrast reactions. For those physicians that have not completed their contrast reaction training, please visit the contrast reaction tutorial located at the Department of Radiology website (http://www.radiology.wisc.edu/intranet/filebin/ContrastAgentsTutorial.pdf), or contact Dr. Myron Pozniak for further details. It is highly recommended that all faculty, residents and staff working in the MRI-related sections take the time to refresh their knowledge of contrast reaction management, and be familiar with the location of the nearest contrast reaction box near the MRI suites.

6. **Research Contrast Injections:** All research contrast injections must be performed during regular hours (7:00AM-6:00PM) at UWHC. No contrast will be given for research at the outpatient facilities (Research Park, Waisman Center, East Clinic). A radiologist must be informed prior to injection and must be within the vicinity. No research contrast injections should be performed at night or on weekends or at outpatient facilities except in special circumstances that require explicit permission from the PI of the study and Dr. Reeder. Both Omniscan and Multihance will be available for use in research subjects. Unless otherwise specified, Omniscan will be the agent of choice although there may be applications where Multihance is preferred. Per routine, all research subjects who indicate a history of renal disease will not be permitted to undergo gadolinium injection, unless there is approval under a specific IRB protocol. There will be no NPO requirement for research subjects receiving contrast.

7. **Adverse Reaction Monitoring**: We will begin a formal, *prospective tracking of all contrast injections* performed at UWHC and the three outpatient clinics (Research Park, Waisman Center, East Clinic), to determine with greater accuracy, the rate and nature of adverse reactions. All reactions will continue to be reported through the patient safety network (PSN) and also tracked with the new prospective tracking forms. Specific information recorded in patients experiencing adverse reactions will include: patient identification, type of contrast agent (Omniscan vs. Multihance), volume of contrast, rate of injection, lot number, and a detailed description of the reaction, treatment (if any), and patient disposition (eg. admitted to ED). We will closely follow all adverse reactions with gadolinium agents and respond accordingly. Results will be tabulated quarterly to better understand the rate of reactions, and a detailed report from the MRI Safety Committee will be presented in six months detailing a summary of additional adverse reactions.

8. **Documentation of Contrast Agent and Dose within Radiology Reports**: Contrast agents are drugs. The type, dose, and route of delivery of this drug must be recorded in the patient's medical record. Currently, the technologists record the type and volume of contrast agent administered, in the DICOM header of the images acquired during and after administration of a contrast agent. However, it is recommended that this information be reported directly in the "technique" section of all radiology reports on MRI studies.

Finally, the MRI Safety Committee would like to commend all of the nurses, technologists, and radiologists who have been involved in responding to recent contrast reactions. They have all demonstrated an exceptional level of professionalism and competency, of which we are very proud.

Scott B. Reeder, MD, PhD
Division Chief of MRI
MRI Safety Committee Chair

Department of Radiology

69

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-19596	ORIG-1	BAYER HEALTHCARE PHARMACEUTICALS INC	MAGNEVIST
NDA-20123	ORIG-1	GE HEALTHCARE	OMNISCAN (GADODIAMIDE)
NDA-20131	ORIG-1	BRACCO DIAGNOSTICS INC	PROHANCE
NDA-20937	ORIG-1	MALLINCKRODT INC	OPTIMARK
NDA-20975	ORIG-1	MALLINCKRODT INC	OPTIMARK
NDA-20976	ORIG-1	MALLINCKRODT INC	OPTIMARK IN PLASTIC CONTAINER
IND-56410	ORIG-1	BERLEX LABORATORIES INC	GADOBUTROL INJECTION
NDA-21037	ORIG-1	BAYER HEALTHCARE PHARMACEUTICALS INC	MAGNEVIST
NDA-21357	ORIG-1	BRACCO DIAGNOSTICS INC	MULTIHANCE(GADOBENATE DIMEGLUMINE INJ)
NDA-21358	ORIG-1	BRACCO DIAGNOSTICS INC	MULTIHANCE (GADOBENATE DIMEGLUMINE INJ)
NDA-21489	ORIG-1	BRACCO DIAGNOSTICS INC	PROHANCE MULTIPACK(GADOTERIDOL)INJECTION
(b) (4)	ORIG-1	GUERBET LLC	DOTAREM(GADOTERATE MEGLAMINE) INJECTION
NDA-21711	ORIG-1	LANTHEUS MEDICAL IMAGING INC	GADOFOSVESET TRISODIUM (Ablavar)
NDA-22066	ORIG-1	GE HEALTHCARE	OMNISCAN INJ
NDA-22090	ORIG-1	BAYER HEALTHCARE PHARMACEUTICALS INC	EVOIST INJECTION
NDA-201277	ORIG-1	BAYER HEALTHCARE PHARMACEUTICALS INC	GADOBUTROL INJECTION

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