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

Template Version: March 6, 2009

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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).

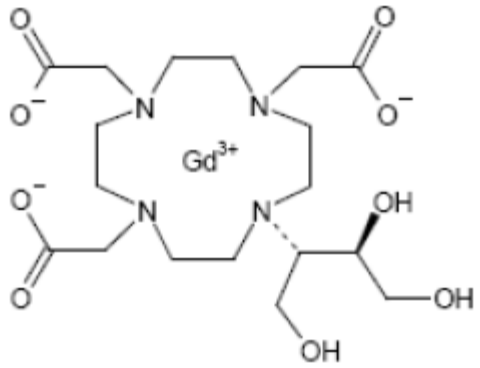
1.4 Recommendations for Postmarket Requirements and Commitments

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 4 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

A47570 22 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 fo**r** 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.

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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 =

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

	Unenhanced MRI		Combined unenhanced and gadobutrol-enhanced MRI		Combined unenhanced and comparator-enhanced MRI		Gadobutrol perfusion MRI
Variables	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

Pooled Efficacy Analyses

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	51.3%	71.2%	19.9%	12.7, 27.1
	Specificity	93.7%	94.0%	0.3%	-1.8, 2.3
	Accuracy	81.7%	87.5%	3.2%	3.2, 8.4
Exact Match of MR Diagnoses vs Final Clinical Diagnosis		55.0%	62.8%	7.8%	4.5, 11.1

<u>Pediatric PK Study</u> (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 **c**oncentration 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%) Investiga-tions 18, (4.5%) General disorders and administra-tion site conditions 17, (4.3%)	Gastrointest-inal 27, (6.9%) Nervous system 26, (6.6%) Investiga-tions 14, (3.6%) General disorders and administra-tion site conditions 18, (4.6%)	Nervous system 22. (6.4%) General disorders and administra-tion site conditions 16, (4.7%) Investiga-tions 16, (4.7%) Gastrointestinal 11, (3.2%)	Nervous system 35, (15.6%) Gastrointestinal disorders 16, (7.1%) General disorders and administrat-ion site conditions 13, (5.8%) Respiratory, thoracic,	Nervous system 23, (10.1%) Gastrointestinal disorders 8, (3.5%) General disorders and administra-tion site conditions 8, (3.5%) Musculo-

	Skin and subcutan-eous disorders 13, (3.3%) Infections and infestations 9, (2.3%)	Skin and subcutan-eous disorders 8, (2.0%) Respiratory, thoracic, mediastinal 7, (1.8%)		mediastinal 9, (4.0%) Skin and subcutan-eous tissue disorders 9, (4.0%)	skeletal and connective tissue disorders 6, (2.6%) Skin and subcutan-eous 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 Hospitaliza tion, both unrelated to study drug
Serious AEs	2 subjects, one SAE each, unrelated; brain metastasis *(Subject 100180001)* and aggravation of hydrocephal us, *(Subject 200030019)*	1 subject with 2 SAEs, unrelated; worsening of general condition and somno-lence *(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, hospital-lized prior to surgery *Subject 27006*-unrelated

Deaths Discontin-uations	None 3 (0.7%) S*ubject 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

S1 Pool, (Phase 1 Studies)

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.

S2 Pool, (Phase 2-4 Studies)

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	Gadoteridol 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) Gadoversetamide Nervous system disorders, (headache, dizziness, pareasthesia, dysguesia) Respiratory, thoracic, mediastinal, (wheezing) Skin and subcutaneous disorders, (pruritis) Gadopentate dimeglumine Nervous system disorders, (headache, dysguesia, dizziness, paresthesia) Gadodiamide Nervous system disorders, (dizziness, tremor)	Gadoteridol-555 subjects total, 104(18.7%) with 156 AEs Gadoversetamide-227 subjects total, 39 (17.2%) with 51 AEs Gadopentate dimeglumine-912 subjects total, 47 (5.2%) with 65 AEs Gadodiamide-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

Safety in Subjects With Renal Failure
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

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/s/

BARBARA A STINSON
01/27/2011