CLINICAL REVIEW

Application Type	Pediatric Supplemental New Drug Application
Application Number(s)	NDA 21357
Priority or Standard	Standard
Submit Date(s)	4/17/2009
Received Date(s)	4/20/2009
PDUFA Goal Date	2/26/2010
Reviewer Name(s)	Brenda Ye, MD
Review Completion Date	2/16/2010
Established Name	Gadobenate Dimeglumine Injection
(Proposed) Trade Name	MultiHance
Therapeutic Class	Gadolinium-based contrast agent
Applicant	Bracco Diagnostics Inc.
Formulation(s)	529 mg/ml Injection, solution
Dosing Regimen	0.1 mmol/kg, intravenous
Indication(s)	Magnetic resonance imaging of the central nervous system in pediatric patients 2 to <16 years of age
Intended Population(s)	Pediatric patients 2 to <16 years of age

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical reviewer recommends approval of the pediatric supplement for MultiHance to be used for intravenous use in children over 2 years of age for magnetic resonance imaging (MRI) of the CNS. The clinical reviewer agrees with the proposed dosing regimen of 0.1 mmol/kg.

1.2 Risk Benefit Assessment

The reviewer's recommendation is based on:

- Compared to unenhanced images, the use of MultiHance contributes to better visualization of lesions in the brain and spine.
- The improved visualization of CNS lesions provided by MultiHance in pediatric patients is comparable to that seen in adults.
- The safety profile of MultiHance is similar to that observed in adult subjects.

The efficacy data support the use of MultiHance as a magnetic resonance contrast agent for CNS imaging in the pediatric population. All efficacy analyses showed that the unenhanced images read together with the MultiHance-enhanced images provided better visualization scores compared to the predose images alone. The efficacy of MultiHance in imaging pediatric brain and spine disease of is comparable to that seen in adults.

The safety profile of MultiHance in children ages 2 years and above is comparable to that seen in adults. The overall incidence of adverse events reported following administration to the pediatric population was 11.1%, similar to that reported for the adult population (14.4%). The most commonly reported adverse events were vomiting (1.8%), pyrexia (1.4%), abdominal pain (0.9%), headache (0.9%), and hyperhidrosis (0.9%).

Overall, the benefit-to-risk profile for MultiHance in children ages two years and above is favorable.

1.3 Recommendations for Postmarket Risk Management Activities

Currently the MultiHance Package Insert contains the following boxed warning on nephrogenic systemic fibrosis (NSF):

> Gadolinium-based contrast agents increase the risk for nephrogenic systemic fibrosis (NSF) in patients with:
> • Acute or chronic severe renal insufficiency (glomerular filtration rate <30 L/min/1.73m2)

- Acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period

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

On December 8, 2009, FDA held an Advisory Committee meeting on gadolinium-based contrast agents (GBCA) and NSF (b) (4) The reviewer does not recommend any other actions.

1.4 Recommendations for Postmarket Studies/Clinical Trials

1) Post-marketing commitments under Pediatric Research Equity Act (PREA) issued with the original NDA Approval Letter on Nov 23, 2004:
There are two post-marketing commitments (PMC) under Pediatric Research Equity Act (PREA) issued with the original NDA Approval Letter on Nov 23, 2004:

1) A pediatric safety and efficacy study under PREA for the evaluation of known or suspected CNS disease in pediatric patients ages 2 to 16
2) A pediatric pharmacokinetic study under PREA for the evaluation of known or suspected CNS disease in pediatric patients age 2 to 5

The reviewer recommends updating the status of the two PMCs to fulfilled status.

1) Study MH-110 entitled: *"A Phase III, Multi-Center Open-Label Study to Evaluate Safety and Efficacy of MultiHance at the Dose of 0.10 mmol/kg in Magnetic Resonance Imaging of the Central Nervous System in Pediatric Patients"*, fulfills PMC #1
2) Study MH-119 entitled: *"A Clinical Investigation on the Pharmacokinetics and Safety of MultiHance® in Patients From 2 to 5 Years of Age Undergoing a Clinically Indicated MRI of the CNS"*, fulfills PMC #2

2) Pediatric Research Equity Act (PREA) of 2003 expectations:
Incorporating inputs from the FDA Pediatric Research Committee (PeRC), a pediatric clinical study for children under 2 years of age was not conducted due to concerns on increased risk of developing NSF given immature renal function in this patient population. The reviewer recommends that preclinical studies in immature animals be conducted before conducting clinical studies in neonates and infants.

2 Introduction and Regulatory Background

2.1 Product Information

MultiHance (gadobenate dimeglumine injection) is a gadolinium-based MR contrast agent marketed by Bracco Diagnostics Inc. It was approved by the FDA on November 23, 2004.

Established name: Gadobenate dimeglumine Injection
Proprietary name: MultiHance
Dosage form: injection, solution
Strengths: 529 mg/ml
Route of administration: intravenous

MultiHance is currently indicated for intravenous use in magnetic resonance imaging (MRI) of the CNS in adults to visualize lesions with abnormal blood brain barrier or abnormal vascularity of the brain, spine, and associated tissues.

This pediatric supplement proposes to extend the above indication to pediatric population between 2 and 16 years of age.

2.2 Tables of Currently Available Treatments for Proposed Indications

In addition to MultiHance, the MRI contrast agents currently used for imaging the CNS are gadopentetate dimeglumine (Magnevist), gadodiamide (Omniscan), gadoversetamide (OptiMARK), and gadoteridol (ProHance). Magnevist, Omniscan, and ProHance are approved in both adults and children (2 years of age and above) for MR imaging of the CNS (Table 1).

Table 1: Currently Available Contrast Agents for MRI of CNS

Trade Name	**Established Name**	**Approved for Pediatric Use**
MultiHance	Gadobenate dimeglumine	No – Adults only
OptiMark	Gadoversetamide	No – Adults only
Magnevist	Gadopentetate dimeglumine	Yes – Adults and pediatric patients (2 years of age and older)
Omniscan	Gadodiamide	Yes – Adults and pediatrics 2-16 years of age
ProHance	Gadoteridol	Yes – Adults and children over 2 years of age

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient, gadobenate dimeglumine, is only available in MultiHance (gadobenate dimeglumine) Injection, 529 mg/mL.

2.4 Important Safety Issues with Consideration to Related Drugs

Currently the MultiHance Package Insert and other gadolinium-based contrast agents (GBCA) contain the following boxed warning on nephrogenic systemic fibrosis (NSF):

> Gadolinium-based contrast agents increase the risk for nephrogenic systemic fibrosis (NSF) in patients with:
> - Acute or chronic severe renal insufficiency (glomerular filtration rate <30 L/min/1.73m2)
> - Acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period.
>
> In these patients, avoid use of gadolinium-based contrast agents unless the diagnostic information is essential and not available with non-contrast magnetic resonance imaging (MRI). NSF may result in fatal or debilitating systemic fibrosis affecting the skin, muscle and internal organs. Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests. When administering a gadolinium-based contrast agent, do not exceed the recommended dose and allow a sufficient period of time for elimination of the agent from the body prior to any readministration

On December 8, 2009, FDA held an Advisory Committee meeting on GBCA and NSF. (b) (4)

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2.5 Summary of Presubmission Regulatory Activity Related to Submission

On April 27, 2001, Bracco submitted a new drug application (NDA) for MultiHance. As part of the NDA submission, data were provided for the pharmacokinetics and safety of 25 normal pediatric subjects who received MultiHance (Study 43,779-10), as well as efficacy and safety data for 85 pediatric subjects with CNS lesions who received MultiHance (Study B19036/036).

On May 24, 2002, FDA issued an Approvable Letter, indicating that the application lacked sufficient data to establish the safe and effective use of MultiHance for pediatric patients. It was indicated that there were insufficient numbers of enrolled patients between 2 and 5 years in both the pharmacokinetic study 43,779-10 and the efficacy study B19036/036. In addition, results of the pediatric efficacy study B19036/036 were inconclusive, as the study contained design flaws (i.e., lack of a truth standard, lack of sufficient lesion tracking, inconsistency between readers, insufficiently defined statistical methods).

In the response to the Approvable Letter, on October 10, 2003 Bracco submitted additional data conducted under protocol MH-112 to address the deficiencies cited above for the pediatric efficacy study B19036/036. The additional data were based on blinded re-read of MRI images from patients in Study B19036/036 with neoplastic enhancing lesions.

On November 23, 2004, FDA approved MultiHance for intravenous use in MR imaging of the CNS in adults. As indicated in the Approval Letter of November 23, 2004, Bracco was required to perform two additional studies in pediatric patients as Postmarketing Commitments:

- A pediatric pharmacokinetic study for the evaluation of known or suspected central nervous system (CNS) disease in pediatric patients ages 2 to 5
- A pediatric safety and efficacy study for the evaluation of known or suspected CNS disease in pediatric patients ages 2 to 16

In order to meet these commitments, Bracco conducted two studies in pediatric patients:

- Study MH-110 entitled: *"A Phase III, Multi-Center Open-Label Study to Evaluate Safety and Efficacy of MultiHance at the Dose of 0.10 mmol/kg in Magnetic Resonance Imaging of the Central Nervous System in Pediatric Patients"*, and
- Study MH-119 entitled: *"A Clinical Investigation on the Pharmacokinetics and Safety of MultiHance® in Patients From 2 to 5 Years of Age Undergoing a Clinically Indicated MRI of the CNS"*.

The design for Study for MH-110 is based on discussions between Bracco and the Agency that occurred from February 2005 to January 2006. A meeting between Bracco and the Agency on July 8, 2008 reached agreements to terminate study MH-110 prior to the enrollment of the protocol-specified 150 evaluable patients. Enrollment was terminated after 94 patients were enrolled. The reasons provided by Bracco for the early termination were:

a) A new sample size calculation was conducted based on new knowledge about the effect size of MultiHance-enhanced MRI over plain MRI
b) The distribution of CNS pathology in the patient population already available in Study MH-110 is representative of the patient population seen in routine clinical practice
c) The distribution of patients by age classes already available in Study MH-110 is also representative of the pediatric population seen in routine practice, with a relative large group of patients < 5 years of age

Subsequently, a pre-NDA meeting was held between the Agency and Bracco on January 23, 2009, at which time an overview of the 5 studies to be included in the submission as well as the plan for the supplemental NDA submission were discussed.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

No major protocol deviations/violations were recorded in the pivotal controlled trial MH-110. The quality of the submission was acceptable. No site inspection was deemed necessary.

3.2 Compliance with Good Clinical Practices

The clinical trials were conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and in compliance with the regulations and guidelines released by the U.S. Food and Drug Administration (FDA), the European Union (EU), and the International Conference on Harmonization.

3.3 Financial Disclosures

The applicant has certified that no financial arrangements were made with clinical investigators. The applicant's financial disclosure was adequate.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Clinical Pharmacology

4.1.1 Mechanism of Action

Gadobenate dimeglumine is a paramagnetic agent and develops a magnetic moment when placed in a magnetic field. The relatively large magnetic moment produced by the paramagnetic agent results in a relatively large local magnetic field, which can enhance the relaxation rates of water protons in the vicinity of the paramagnetic agent. In MRI, visualization of normal and pathological tissue depends in part on variations in the radiofrequency signal intensity that occur with 1) differences in proton density; 2) differences of the spin-lattice or longitudinal relaxation times (T1); and 3) differences in the spin-spin or transverse relaxation time (T2). When placed in a magnetic field, gadobenate dimeglumine decreases the T1 and T2 relaxation time in target tissues. At recommended doses, the effect is observed with greatest sensitivity in the T1-weighted sequences.

4.1.2 Pharmacodynamics

Gadolinium-based contrast agents increase contrast on conventional MRI studies by shortening the T1 relaxation time of adjacent water molecules. Gadobenate dimeglumine does not cross the intact blood brain barrier and, therefore, does not accumulate in normal brain or in lesions that have a normal blood brain barrier, e.g., cysts, mature post-operative scars, etc.; while it enhances normal tissues lacking a blood brain barrier. Abnormalities of the blood brain barrier or abnormal vascularity allow preferential distribution of gadobenate dimeglumine in lesions such as neoplasms, abscesses, and subacute infarcts. The main reason why gadolinium-based contrast agents are administered when imaging the central nervous system is to detect a breakdown of the blood brain barrier or to identify abnormal vascularity of the pathological tissue. The enhancement patterns expected in lesions of children over 1 year of age are similar to those in adults.

4.4.3 Pharmacokinetics

In adult subjects, gadobenate ion is eliminated predominately via the kidneys. The clearance is similar to that of substances that are subject to glomerular filtration. The mean elimination half-life ranged from 1.17 to 2.02 hours. A small percentage of the administered dose (0.6% to 4%) is eliminated via the biliary route and recovered in feces. There was no detectable biotransformation of gadobenate ion. Volume of distribution is approximately equivalent to the average volume of extracellular body water in man. In vitro studies showed no appreciable binding of gadobenate ion to human serum proteins.

The pharmacokinetics of MultiHance was evaluated in the pediatric population in the following two studies:

Study MH-119 investigated the pharmacokinetics and safety of intravenously administered MultiHance to pediatric patients aged 2 to 5 years. A total of 15 patients scheduled to undergo MRI of the CNS were evaluated.

Study 43,779-10 (submitted with original NDA) investigated the pharmacokinetics and safety of intravenously administered MultiHance in healthy pediatric subjects. A total of 25 healthy subjects from 3 to 16 years of age were evaluated.

Review by the FDA Clinical Pharmacology team showed that there is a 21% decrease in the clearance and central volume of distribution of MultiHance in children 2 to 5 years of age, compared to children older than 5 years of age. Despite this difference in pharmacokinetics, the FDA Clinical Pharmacology review team does not recommend a dose adjustment in children 2 to 5 years of age. This is because the observed decreased clearance and central volume of distribution of MultiHance in children 2 to 5 years of age are corrected by the mmol/kg based dosing regimen of MultiHance. Therefore, the adult 0.1 mmol/kg dose of MultiHance is appropriate in all pediatric patients 2 years and older.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The clinical program to assess the pharmacokinetics, safety, and efficacy of MultiHance in pediatric patients was conducted in the North America, Europe, and China and comprises 5 clinical studies (Table 2):

- A pharmacokinetic study (MH-119) in 15 patients aged 2 to 5 years administered 0.1 mmol/kg MultiHance undergoing MRI of the CNS (post-marketing commitment)
- A pharmacokinetic study (43,779-10) in 25 healthy subjects aged 3 to 16 years administered 0.1 mmol/kg MultiHance (submitted with the original NDA 21-357 in April 2001)
- A Phase III study (MH-110, confirmatory study) in 92 patients aged 2 to 17 years with known or suspected CNS diseases to assess the safety and efficacy of an 0.1 mmol/kg dose of MultiHance (post-marketing commitment)
- A Phase III study (B19036/036, supportive study) in 174 patients aged 4 days to 17 years with known or suspected CNS diseases to compare the safety and activity of 0.1 mmol/kg dose of MultiHance (85 patients) with the same dose of Magnevist (89 patients) (submitted with the original NDA 21-357 in April 2001)
- A blinded re-read of images (MH-112, supportive study) from a subgroup 63 patients with CNS neoplastic enhancing lesions enrolled in the Phase III study B19036/036 to compare MultiHance (29 patients) with Magnevist (34 patients) (resubmitted in October 2003 with response to FDA Approvable Letter)

Table 2: Overview of Clinical Studies Conducted in Pediatric Subjects

Study Identifier	Objective of the Study	Study Design	Test Product(s), Dose, Route of Administration	Number of Subjects
Pharmacokinetic Studies				
MH-119 Postmarketing Commitment	To assess the pharmacokinetics in pediatric patients age 2 to 5 years undergoing MRI of the CNS	Single-center, open-label	MultiHance 0.1 mmol/kg IV	15
43,779-10 Submitted With Original NDA 21-357 April 2001	To assess the pharmacokinetics in healthy pediatric subjects age 3 to 16 years	Single-center, open-label	MultiHance 0.1 mmol/kg IV	25
Confirmatory Efficacy Study				
MH-110 Postmarketing Commitment	To assess the efficacy of MultiHance MRI of the CNS in pediatric patients in terms border delineation of lesions, visualization of internal morphology of lesions, and contrast enhancement of lesions.	Multicenter, within-patient comparison of contrast-enhanced and unenhanced MRI	MultiHance 0.1 mmol/kg IV	92
Supportive Efficacy Studies				
B19036/036 Submitted With Original NDA 21-357 April 2001	To compare MultiHance and Magnevist in MRI detection and evaluation of CNS abnormalities in pediatric patients.	Multicenter, randomized, double-blind, parallel-group	Total MultiHance 0.1 mmol/kg IV Magnevist 0.1 mmol/kg IV	174 85 89
MH-112 (re-read of images from B19036/036)* Submitted With Responses to Approvable Letter October 2003	To compare MultiHance and Magnevist in terms of qualitative and quantitative assessment of unenhanced and contrast-enhanced MRI for visualization of brain and spine in pediatric disease.	Blinded re-read of patients with enhancing brain/spine neoplastic enhancing lesions included in the original study B19036/036	Total MultiHance 0.1 mmol/kg IV Magnevist 0.1 mmol/kg IV	63* 29* 34*

* Study MH-112 was a re-read of images from patients with neoplastic enhancing lesions enrolled in study B19036/036 and does not contribute to the total number of patients.

Table data derived from *Individual Clinical Trial Reports*.

5.2 Review Strategy

The reviewer focused on the confirmatory safety and efficacy trial MH-110, with the re-read study MH-112 as supportive efficacy evidence. Study B19036/036 has fundamental design flaws, and deficiencies of the study were thoroughly discussed by the FDA review team of the original NDA submission in 2002, therefore only the study's safety data are included in this review.

The submission contains results from pharmacokinetic studies and clinical efficacy and safety trials. No data were submitted on chemistry/manufacturing, clinical microbiology, or preclinical pharmacology and toxicology, therefore these subsections are omitted from the standard NDA review template. In addition, for the safety review, exploration for dose response, special animal and/or in vitro testing, metabolic/clearance/interaction workup, evaluation for potential adverse events for similar drugs in drug class, immunogenicity, dose- and time-dependency for adverse events, and human carcinogenicity are irrelevant to this submission, and therefore omitted from the standard NDA review template.

5.3 Discussion of Individual Studies/Clinical Trials

Study MH-110 (Confirmatory efficacy and safety trial, Postmarketing Commitment)
Study Title - *"A Phase III, Multi-Center Open-Label Study to Evaluate Safety and Efficacy of MultiHance at the Dose of 0.10 mmol/kg in Magnetic Resonance Imaging of the Central Nervous System in Pediatric Patients"*

Study MH-110 is a Phase III, prospective, multi-national, multicenter, within-patient comparison of the efficacy of contrast-enhanced MRI with 0.1 mmol/kg MultiHance versus unenhanced MRI of brain and spine of pediatric patients. Male or female patients between 2 and 17 years old with known or highly suspected disease of the CNS (brain/spine) and referred for cranial or spinal MR examination requiring an injection of MR contrast agent were enrolled in the study. All patients were imaged using the same imaging sequences and parameters. The brain and spine were imaged with T1wSE, T2wFSE, and FLAIR imaging sequences prior to the administration of the investigational product MultiHance. A T1wSE sequence was acquired postdose.

An off-site assessment of all MR image sets, i.e., predose, postdose, and predose + postdose was conducted by three independent neuroradiologists, who were blinded to all patients' clinical and radiological information:

- Images were masked for all patient identifiers
- The test image sets were presented to the readers in a random order
- All image sets obtained from study investigators were included in the blinded read
- Each reader viewed all the images in a given study

Study MH-112
Study MH-112 is a re-read study of a subset of patients from Study B190361036. Study B190361036 was originally submitted to the original NDA in 2001 and FDA review team concluded that the study had fundamental design flaws. After discussion with FDA, Bracco included results from a subset of 29 pediatric tumor patients from the original Study B 190361036 (as defined by the presence of a known CNS tumor) and submitted for re-read under Study MH 112 in October 2003 with response to FDA Approvable Letter. This was a re-read study aimed at comparing MultiHance and Magnevist at a dose of 0.1 mmol/kg in improvement of visualization of brain and spine lesions on pediatric MRI, using 3 co-primary efficacy endpoints (lesion border delineation, visualization of lesion internal morphology, and lesion contrast enhancement).

One blinded reader (unaffiliated with the study sites and blinded to all patient information and type of study agent, and not involved with blinded read of study MH-110) read the images. Only patients with brain/spine neoplastic enhancing lesions from the original patient population of study B19036/036 were included. A total of 63 children (29 in the MultiHance group and 34 in the Magnevist group) with a final diagnosis of an enhancing CNS neoplastic lesion were selected from study B19036/036 to be included in this re-read study. Of the 63 patients, an experienced neuroradiologist confirmed that 59 of those had tumor (26 in the MultiHance group and 32 in the Magnevist group).

Reviewer's comments: The images were re-read by a single blinded reader in Study MH 112, which does not provide reproducibility of results.

6 Review of Efficacy

Efficacy Summary

1. Based on all lesion analysis comparing precontrast vs. precontrat+postcontrast paired images, the pivotal trial (Study MH-110) demonstrates statistically significant improvement in visualization of brain and spine lesions with MultiHance for all 3 co-primary endpoints for all 3 blinded readers. The efficacy (improvement in brain and spine lesion visualization) for pediatric patients of 2-17 years of age is comparable to that of adults.

2. Most secondary analyses in the pivotal trial (MH-110), including the common lesion analysis and patient level analysis, show statistically significant improvement of lesion visualization with MultiHance. It is however noted that all lesion analysis comparing precontrast vs. postcontrast images (one of the secondary analyses) failed to show statistically significant improvement of lesion visualization with MultiHance.

3. The re-read study (MH-112) shows supportive evidence of improvement in brain and spine lesion visualization with MultiHance.

4. Study B19036/036 has major deficiencies and design flaws and does not directly provide efficacy evidence. It provided raw data (MR images) for the re-read study MH-112.

6.1 Indication

MultiHance is currently indicated for intravenous use in magnetic resonance imaging (MRI) of the CNS in adults to visualize lesions with abnormal blood brain barrier or abnormal vascularity of the brain, spine, and associated tissues.

The applicant’s proposed indication is as follows (italic font style indicates proposed changes):
MultiHance is indicated for intravenous use in magnetic resonance imaging (MRI) of the CNS

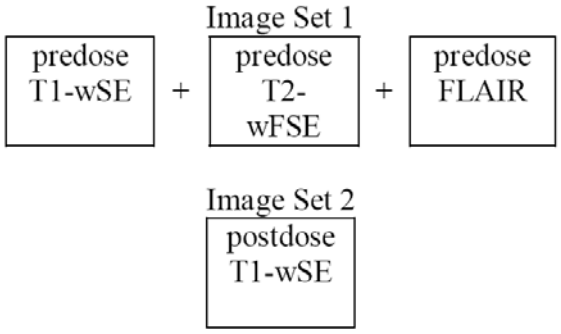
in adults *and children over 2 years of age* to visualize lesions with abnormal blood brain barrier or abnormal vascularity of the brain, spine, and associated tissues.

6.1.1 Methods

Efficacy assessment relies on the confirmatory trial MH-110 and the supportive re-read study MH-112. Study MH-110 is a Phase III, prospective, multi-national, multicenter, within-patient comparison of the efficacy of contrast-enhanced MRI with 0.1 mmol/kg MultiHance versus unenhanced MRI of brain and spine of pediatric patients. Study MH-112 is a re-read study of a subset of pediatric patients from Study B190361036. Twenty-nine patients with neoplastic lesions who were given MultiHance were included in the study.

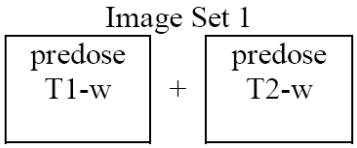
The blinded off-site assessment of all MR image sets was performed in two separate sessions for both Study MH-110 and MH-112. The separate predose and postdose image sets (Image Set 1 and Image Set 2) were read in one session and the predose + postdose paired image set was read in a second session. The test image sets (predose, postdose, and predose + postdose) were presented to the reader in an order determined by a randomization schedule.

Study MH-110
Session 1 (Unpaired - Predose or Postdose Images Alone)



Session 2 (Paired - Predose+Postdose Images Together)

Study MH-112
Session 1 (Unpaired - Predose or Postdose Image Alone)



Session 2 (Paired – Predose+Postdose Images Together)

Reviewer's comments: In both studies, the postcontrast image set is comprised of postdose T1 sequence alone. It is worth noting that in clinical radiology practice, postcontrast MR images (T1 postcontrast) are always acquired and interpreted in conjunction with a precontrast T1 sequence and precontrast T2 sequence. So a clinical radiologist rarely reads T1 postcontrast MR images alone (i.e. leaving out T2 information altogether). This is because gadolinium's effect is T1 shortening, and has little effect on T2 or FLAIR at clinically relevant concentrations of MultiHance (or other gadolinium-based contrast agents), therefore postcontrast T2 images are not routinely obtained in clinical practice. In other words, noncontrast T2 and FLAIR images provide valuable information that are absent in a 'purely postcontrast MR exam' (as defined by Image Set 2 in both MH-110 and MH-112). Therefore comparing the precontrast image set (precontrast T1, precontrast T2, +/- FLAIR) with the postcontrast image set (postcontrast T1) may appear to isolate the 'theoretical' contribution of the contrast agent, but in fact this is not clinically relevant. In the opinion of the reviewer, comparing precontrast image set (precontrast T1, precontrast T2, +/- FLAIR) with the paired precontrast and postcontrast image sets (precontrast T1, precontrast T2, postcontrast T1, +/- FLAIR) provides the most clinically relevant efficacy assessment. This is indeed the primary efficacy comparison used for both MH-110 and MH-112.

6.1.2 Demographics

Male or female patients between 2 and 17 years old with known or highly suspected disease of the CNS (brain/spine) and referred for cranial or spinal MR examination requiring an injection of MR contrast agent were enrolled in studies MH-110 and B19036/036. The patient population enrolled was representative of the population in which MultiHance is intended to be used, i.e., mostly children with brain or spine neoplasms, but also infection, inflammation, phakomatoses, degenerative abnormalities, and other disorders.

The age of the patients evaluated for efficacy ranged from 4 days to 17.8 years. Of the 177 patients dosed with MultiHance (Table 3):
– 15 (8.5%) were <2 years,
– 37 (20.9%) were between 2 to 5 years,
– 60 (33.9%) were between 6 and 10 years,
– 65 (36.7%) were between 11 and 17 years.

Table 3: Age Distribution for Pediatric Subjects Evaluated for Efficacy

Age group (years)	Study MH-110 (Confirmatory Study)	Study B19036/036 (Supportive Study)		Re-read Study MH-112* (Supportive Study)		
	MultiHance 0.1 mmol/kg	MultiHance 0.1 mmol/kg	Magnevist 0.1 mmol/kg	MultiHance 0.1 mmol/kg	Magnevist 0.1 mmol/kg	Total*
< 2	0	15	12	3	4	27
2 to 5	13	24	55	9	8	92
6 to 10	34	26	20	9	10	80
11 to 17	45	20	2	8	12	67
Total*	92	85	89	29	34	266

* Study MH-112 was a re-read of images from patients with neoplastic enhancing lesions enrolled in study B19036/036 and does not contribute to the total number of patients.

The distribution of patients with brain or spine lesions, and the distribution of patients with tumor or non-tumor disorders, and within tumor patients, benign or malignant tumor, are shown in Table 4 below.

Table 4: Distribution of Tumor and Non-tumor Patients, Patients Evaluated for Efficacy

	MH-110 (Confirmatory Study)	B19036/036 (Supportive Study)		MH-112 (Supportive Study)	
	MultiHance 0.1 mmol/kg	MultiHance 0.1 mmol/kg	Magnevist 0.1 mmol/kg	MultiHance 0.1 mmol/kg	Magnevist 0.1 mmol/kg
Location	(N=92)	(N=85)	(N=89)	(N=29)	(N=34)
Brain	88 (95.7%)	75 (88.2%)	81 (91.0%)	25 (86.2%)	31 (91.2%)
Spine	4 (4.3%)	10 (11.8%)	8 (9.0%)	4 (13.8%)	3 (8.8%)
Condition	(N=92)	(N=85)	(N=89)	(N=29)	(N=34)
Normal Parenchyma	4 (4.3%)	22 (25.9%)	18 (20.2%)	0	0
Non-tumor	28 (30.4%)	25 (29.4%)	21 (23.6%)	0	0
Tumor*	60 (65.2%)	38 (44.7%)**	50 (56.2%)**	29 (100.0%)**	34 (100.0%)**
Tumor Type	(N=60)	(N=38)**	(N=50)**	(N=29)**	(N=34)**
Intra-axial	43 (71.7%)	34 (89.5%)	45 (90.0%)	24 (82.3%)	31 (91.2%)
Extra-axial	17 (28.3%)	4 (10.5%)	4 (8.0%)	5 (17.2%)	2 (5.9%)
Not applicable	0	0	1 (2.0%)	0	1 (2.9%)
Tumor Nature	(N=60)	(N=38)**	(N=50)**	(N=29)**	(N=34)**
Benign	25 (41.7%)	5 (13.2%)	8 (16.0%)	5 (17.2%)	5 (14.7%)
Malignant	35 (58.3%)	33 (86.8%)	42 (84.0%)	24 (82.3%)	29 (85.3%)

* Tumor classification includes patients who were being imaged for detection and assessment of tumors as well as patients imaged for follow-up after the surgical removal of a tumor.

** Although 88 patients (38 for MultiHance and 50 for Magnevist) from Study B19036/036 were classified as "tumor patients" only 63 patients (29 for MultiHance and 34 for Magnevist) had enhancing neoplastic lesions and were included in Re-read Study MH-112.

Table data derived from *Individual Clinical Trial Reports*.

Reviewer's comments: Although the number of patients enrolled with an indication for a spine MRI is low (n = 4 in study MH-110 and n = 10 patients given MultiHance in study B19036/036), this is relatively consistent with the distribution seen in clinical practice in the pediatric population. The majority of spine MRI performed in clinical practice are noncontrast MRI, for indications such as degenerative spine disease (in adults) and trauma. In both adults and children, contrast is indicated when the clinical question involves neoplasm or infection.

6.1.3 Subject Disposition

The number of pediatric patients included in the efficacy evaluation is shown in the following table:

Table 5: Pediatric Patients with CNS Lesions Included in the Evaluation of Efficacy

Study Number	Dose (mmol/kg)	Number of Patients		
		MultiHance	Magnevist	Total
Confirmatory Study				
MH-110 Postmarketing Commitment	0.1 mmol/kg	92	--	92
Supportive Studies				
B19036/036 Submitted With Original NDA 21-357, April 2001	0.1 mmol/kg	85	89	174
MH-112* With Responses to Approvable Letter October 2003	0.1 mmol/kg	29*	34*	63*
TOTAL		177	89	266

* Study MH-112 was a re-read of images from patients with neoplastic enhancing lesions enrolled in study B19036/036 and does not contribute to the total number of patients.
Table data derived from *Individual Clinical Trial Reports*.

A total of 94 patients were enrolled in Study MH-110. Two patients discontinued prior to dosing (screening failure), and 92 patients were dosed with MultiHance. All 92 (100%) were included in both efficacy and safety analysis.

Study MH-112 was a re-read study of images from patients with enhancing neoplastic lesions enrolled in study B19036/036 and does not contribute to the total number of patients. Although 88 patients (38 for MultiHance and 50 for Magnevist) from Study B19036/036 were classified as "tumor patients" only 63 patients (29 for MultiHance and 34 for Magnevist) had enhancing neoplastic lesions and were included in re-read study MH-112.

Reviewer's comments: During the Pre-NDA meeting between the Agency and Bracco on January 23, 2009, the reviewer questioned Bracco why some of the tumor patients from Study B19036/036 were not included in the re-read study of MH-112. Bracco clarified that the excluded tumor patients were post-operative follow-up patients who already had the tumor resected prior to the MRI scan, and therefore not included in the re-read study of MH-112.

6.1.4 Analysis of Primary Endpoint(s)

For studies MH-110 and MH-112, there were three co-primary endpoints of efficacy that were discussed and agreed upon with the Division and were related to the comparison of objective image features, i.e., lesion border delineation, visualization of internal lesion morphology, and

contrast enhancement of lesions, with and without the administration of contrast. Each reader is asked to score images on a scale of 0-4 with 0 being none, 1 being poor, and 4 being excellent.

The three co-primary measures are:

- **degree of lesion border delineation:**
  - 0 = no delineation of lesion borders: assigned by default when a lesion is not identified in an image set and therefore lesion borders not visible and evaluable (option not available to the reader but imputed by default when a lesion is not observed in an image set);
  - 1 = poor border delineation: all lesion borders poorly distinct, lesion not separated from surrounding tissues/structures/edema;
  - 2 = moderate border delineation: the delineation of lesion borders fair and not complete, lesion not clearly separated from surrounding tissues/structures/edema;
  - 3 = good border delineation: the delineation of lesion borders complete, lesion adequately separated from surrounding tissues/structures/edema;
  - 4 = excellent border delineation: lesion borders sharp and clearly distinct, lesion sharply separated from surrounding tissues/structures/edema

- **visualization of lesion internal morphology:**
  - 0 = no visualization of lesion internal morphology: assigned by default when a lesion is not identified in the image set and therefore lesion internal morphology not visible and assessable (option not available to the reader but imputed by default when a lesion is not observed in an image set);
  - 1 = poor visualization of lesion internal morphology: lesion internal morphology insufficiently depicted and intralesional features poorly identified;
  - 2 = moderate visualization of lesion internal morphology: some intralesional features visible, but internal morphology of the lesion not completely depicted;
  - 3 = good visualization of lesion internal morphology: lesion internal morphology completely depicted and intralesional features adequately identified;
  - 4 =excellent visualization of lesion internal morphology: lesion internal morphology optimally depicted and intralesional features clearly identified and characterized

- **degree of lesion contrast enhancement:**
  - 0 = no lesion contrast enhancement: assigned by default when a lesion is not identified in the image set and therefore no contrast between the lesion and surrounding normal brain/spine tissue (option not available to the reader but imputed by default when a lesion is not observed in an image set);
  - 1 = poor lesion contrast enhancement: the difference in signal intensity between the lesion and the surrounding normal brain/spine tissue poor, lesion barely identified, not possible to evaluate and measure the size (maximum diameter) of the lesion;
  - 2 = moderate lesion contrast enhancement: the difference in signal intensity between the lesion and the surrounding normal brain/spine tissue fair, the lesion identified, but not possible to evaluate and measure the size (maximum diameter) of the lesion;

- 3 = good lesion contrast enhancement: the difference in signal intensity between the lesion and surrounding normal brain/spine tissue adequate, lesion identified and size (maximum diameter) evaluated and measured;
- 4 = excellent lesion contrast enhancement: the difference in signal intensity between lesion and surrounding parenchyma marked, the lesion optimally identified and size (maximum diameter) easily measured

Delineation of lesion borders, contrast enhancement, and visualization of lesion internal morphology are clinically important diagnostic features related to MR visualization of any type of CNS lesion. Both study MH-110 and MH-112 use the same three co-primary endpoints.

Study MH-110

The primary efficacy analysis in study MH-110 is conducted on "*Lesion-Level All Lesion Analysis*", comparing predose vs. predose + postdose and including all lesions detected on **either** of the image sets (i.e., the predose image set or the predose + postdose paired image set). If a lesion was not detected on one of the image sets, the score "0" was assigned by default programmatically for that lesion and for the image set at which the lesion was not detected.

There is statistically significant improvement from the predose image set to the predose + postdose image set for each of the 3 co-primary variables for all 3 readers. The mean changes ranged from 0.7 to 1.3 for lesion border delineation, from 0.6 to 1.3 for visualization of lesion internal morphology, and from 0.8 to 1.2 for lesion contrast enhancement. For purposes of comparison, results from the pediatric population are compared with those from the adult population in Table 6. The results are comparable between the two populations.

Table 6: Mean Summary Statistics of the 3 Co-Primary Variables, Lesion-Level, All Lesion Analysis, Predose vs. Predose + Postdose Comparison of Pediatric Data (Study MH-110) and Adult Data

		MultiHance 0.1 mmol/kg		
		Reader 1	**Reader 2**	**Reader 3**
Pediatric Study MH-110				
Lesion Border Delineation	**No. of Lesions**	148	135	131
	Predose ±SD	1.7 ±1.16	1.9 ±1.15	1.7 ±1.19
	Pre + Postdose ±SD	3.0 ±1.20	3.1 ±1.11	2.4 ±1.12
	Change ±SD	1.3 ±1.46	1.2 ±1.45	0.7 ±1.42
	p-value[a]	<0.0001	<0.0001	<0.0001
Visualization of Lesion Internal Morphology	**No. of Lesions**	148	135	131
	Predose ±SD	1.9 ±1.18	2.1 ±1.17	1.4 ±1.06
	Pre + Postdose ±SD	3.2 ±1.19	3.2 ±1.13	2.0 ±1.23
	Change ±SD	1.3 ±1.56	1.1 ±1.49	0.6 ±1.20
	p-value[a]	<0.0001	<0.0001	<0.0001
Lesion Contrast Enhancement	**No. of Lesions**	148	135	131
	Predose ±SD	1.8 ±1.16	2.0 ±1.20	1.4 ±0.96
	Pre + Postdose ±SD	3.0 ±1.19	3.2 ±1.12	2.2 ±1.41
	Change ±SD	1.2 ±1.57	1.2 ±1.49	0.8 ±1.54
	p-value[a]	<0.0001	<0.0001	<0.0001
Adult Study MH-105				
Lesion Border Delineation	**No. of Lesions**	395	384	299
	Predose ±SD	1.5 ±1.09	1.7 ±1.00	1.6 ±1.25
	Pre + Postdose ±SD	2.3 ±0.84	2.2 ±1.07	2.4 ±1.13
	Change ±SD	0.8 ±1.32	0.6 ±1.42	0.8 ±1.73
	p-value[a]	<0.001	<0.001	<0.001
Visualization of Lesion Internal Morphology	**No. of Lesions**	395	384	299
	Predose ±SD	1.6 ±1.10	1.7 ±1.06	1.7 ±1.28
	Pre + Postdose ±SD	2.4 ±0.88	2.4 ±1.15	2.5 ±1.13
	Change ±SD	0.8 ±1.29	0.6 ±1.51	0.7 ±1.77
	p-value[a]	<0.001	<0.001	<0.001
Lesion Contrast Enhancement	**No. of Lesions**	395	384	299
	Predose ±SD	1.9 ±1.27	1.8 ±1.10	2.0 ±1.42
	Pre + Postdose ±SD	2.6 ±0.88	2.3 ±1.13	2.8 ±1.11
	Change ±SD	0.7 ±1.52	0.5 ±1.51	0.8 ±1.94
	p-value[a]	<0.001	<0.001	<0.001

a p-value based on paired t-test for change from predose to predose + postdose.

Study MH-112

Similarly to Study MH-110, in this study, the primary efficacy measurements are visualization of lesions (in terms of lesion border delineation, visualization of internal lesion morphology, and contrast enhancement of lesions) based on an all lesion analysis. One blinded reader assessed all the images. The changes from predose to predose + postdose were statistically significant for all three co-primary endpoints (Table 7).

Table 7: Summary Statistics of the 3 Co-Primary Variables, Lesion-Level, All Lesion Analysis, Predose vs. Predose + Postdose, Re-read Study MH-112

	Lesion Border Delineation	Visualization Lesion Internal Morphology	Lesion Contrast Enhancement
No. of Lesions	N = 33	N = 33	N = 33
Predose +/- SD	2.0 +/- 1.1	2.1 +/- 1.1	2.1 +/- 1.1
Pre+Postdose +/- SD	3.3 +/- 0.7	3.2 +/- 0.8	3.4 +/- 0.6
Change +/- SD	1.2 +/- 1.2	1.2 +/- 1.0	1.4 +/- 1.2

Study B19036/036
The primary efficacy measurement in Study B19036/036 was the level of diagnostic information provided by the unenhanced and contrast-enhanced images. The study contains design flaws (i.e., lack of a truth standard, lack of sufficient lesion tracking, inconsistency between readers, insufficiently defined statistical methods). The primary endpoint of 'level of diagnostic information' is subjective. The study is fundamentally flawed, and data from this study is not relied upon in this review and is not discussed here.

6.1.5 Analysis of Secondary Endpoints(s)

Secondary efficacy analyses in studies MH-110 and MH-112 include:

- "*Lesion-Level, All Lesion Analysis*" comparing **predose vs. postdose** and including all lesions detected on **either** image set
- "*Lesion-Level, Common-Lesion Analysis*": compared predose vs. postdose and predose vs. predose + postdose and included all lesions detected on **both** image sets.
- "*Patient-Level Analysis*": compared predose vs. postdose and predose to predose + postdose.

a) Lesion-Level, All Lesion Analysis, Predose vs. Postdose
Study MH-110
For "all lesion" analysis comparing predose vs. predose, all lesions detected on **either** the predose image set or the postdose image set are included. If a lesion was not detected on one of the image sets, the score "0" was assigned by default programmatically for that lesion and for the image set at which the lesion was not detected. Since predose + postdose paired image set generally allows detection of the highest number of lesions, the number of 'all lesions' from the predose vs. postdose comparison are *lower* than the number of 'all lesions' from the predose vs. predose + postdose comparison used in the primary efficacy analysis. Refer to Section 6.1.6 Other endpoints – Number of Lesions Detected and Table 17 for more detail. The postdose mean lesion-level scores were generally higher than the predose scores.

Table 8: Mean Summary Statistics of the 3 Co-Primary Variables, Lesion-Level, All Lesion Analysis, Predose to Postdose, Off-site Read, Study MH-110

	MULTIHANCE 0.1 mmol/kg		
	Reader 1	**Reader 2**	**Reader 3**
Lesion Border Delineation			
No. of Lesions*	131	132	132
Predose ±SD	2.0 ±1.04	2.0 ±1.13	1.7 ±1.20
Postdose ±SD	2.4 ±1.57	2.0 ±1.47	1.9 ±1.36
Change ±SD	0.4 ±1.76	0.0 ±1.79	0.2 ±1.72
p-value[a]	0.0108	0.8457	0.1592
95% CI of Change	(0.1, 0.7)	(-0.3, 0.3)	(-0.1, 0.5)
Visualization of Lesion Internal Morphology			
No. of Lesions*	131	132	132
Predose ±SD	2.1 ±1.02	2.1 ±1.14	1.4 ±1.06
Postdose ±SD	2.4 ±1.55	1.9 ±1.38	1.6 ±1.32
Change ±SD	0.2 ±1.78	-0.2 ±1.77	0.2 ±1.26
p-value[a]	0.1314	0.2408	0.0398
95% CI of Change	(-0.1, 0.5)	(-0.5, 0.1)	(0.0, 0.4)
Lesion Contrast Enhancement			
No. of Lesions*	131	132	132
Predose ±SD	2.1 ±1.02	2.0 ±1.17	1.3 ±0.96
Postdose ±SD	2.5 ±1.64	2.1 ±1.52	2.0 ±1.63
Change ±SD	0.4 ±1.94	0.1 ±1.82	0.6 ±1.78
p-value[a]	0.0166	0.5990	0.0001
95% CI of Change	(0.1, 0.7)	(-0.2, 0.4)	(0.3, 0.9)

* With imputations of zero scores for the lesions not detected in an image set.
[a] p-value based on paired t-test for change from predose to postdose.

MH-112

When predose was compared to postdose alone, the difference favored postdose for all 3 variables in the Re-Read Study MH-112 (Table 9).

Table 9: Summary Statistics of the 3 Co-Primary Variables, Lesion-Level, All Lesion Analysis, Predose vs. Postdose, Re-read Study MH-112

	Lesion Border Delineation	Visualization Lesion Internal Morphology	Lesion Contrast Enhancement
No. of Lesions	N = 33	N = 33	N = 33
Predose +/- SD	2.0 +/- 1.1	2.1 +/- 1.1	2.1 +/- 1.1
Postdose +/- SD	3.2 +/- 1.0	3.1 +/- 1.1	3.2 +/- 1.0
Change +/- SD	1.1 +/- 1.6	1.0 +/- 1.4	1.2 +/- 1.5

b) Common Lesion Analysis, Predose vs. Predose + Postdose

A ‘common lesion” is a lesion that was detected on both the predose image set and the predose + postdose paired image set. This analysis compares changes in lesion visualization from the predose to predose + postdose image set for the 3 co-primary endpoints for those lesions visible in both image sets (“common lesions”). An improvement was demonstrated for each of the 3 co-

primary variables for all 3 readers in Study MH-110 and for the one blinded reader for the Re-read study MH-112 (Table 10). The results support the efficacy results of the primary analysis.

Table 10: Mean Summary Statistics of the 3 Co-Primary Variables, Lesion Level, Common Lesion Analysis, Predose to Predose + Postdose, Study MH-110 and Re-Read Study MH-112

	MH-110			MH-112
	Reader 1	Reader 2	Reader 3	Blinded Reader
Lesion Border Delineation				
No. of Lesions*	100	98	91	27
Predose +/- SD	2.3 +/- 0.75	2.5 +/- 0.69	2.2 +/- 0.93	2.5 +/- 0.6
Pre+Postdose +/- SD	3.5 +/- 0.66	3.4 +/- 0.61	2.7 +/- 0.78	3.3 +/- 0.7
Change +/- SD	1.1 +/- 0.75	1.0 +/- 0.69	0.5 +/- 0.91	0.8 +/- 0.8
95% CI of Change	(1.0, 1.3)	(0.8, 1.1)	(0.3, 0.7)	
Visualization of Lesion Internal Morphology				
No. of Lesions*	100	98	91	27
Predose +/- SD	2.5 +/- 0.63	2.7 +/- 0.58	1.8 +/- 0.91	2.6 +/- 0.6
Pre+Postdose +/- SD	3.7 +/- 0.50	3.5 +/- 0.60	2.3 +/- 1.06	3.4 +/- 0.6
Change +/- SD	1.1 +/- 0.68	0.8 +/- 0.66	0.5 +/- 0.82	0.9 +/- 0.8
95% CI of Change	(1.0, 1.3)	(0.7, 1.0)	(0.3, 0.7)	
Lesion Contrast Enhancement				
No. of Lesions*	100	98	91	27
Predose +/- SD	2.4 +/- 0.64	2.5 +/- 0.74	1.7 +/- 0.80	2.5 +/- 0.6
Pre+Postdose +/- SD	3.4 +/- 0.67	3.5 +/- 0.58	2.4 +/- 1.25	3.4 +/- 0.5
Change +/- SD	1.0 +/- 0.80	1.0 +/- 0.76	0.7 +/- 1.03	0.9 +/- 0.8
95% CI of Change	(0.8, 1.2)	(0.8, 1.1)	(0.5, 0.9)	

*A lesion had to be detected in both of the image sets.

c) Common Lesions Analysis, Predose vs. Postdose Alone

The postdose lesion-level scores are generally higher than the predose scores (Table 11).

Table 11: Mean Summary Statistics of the 3 Co-Primary Variables, Lesion Level, Common Lesion Analysis, Predose to Postdose, Study MH-110 and Re-Read Study MH-112

	MH-110			MH-112
	Reader 1	Reader 2	Reader 3	Blinded Reader
Lesion Border Delineation				
No. of Lesions*	79	71	72	25
Predose +/- SD	2.4 +/- 0.69	2.6 +/- 0.67	2.4 +/- 0.86	2.5 +/- 0.7
Postdose +/- SD	3.3 +/- 0.76	2.9 +/- 0.85	2.5 +/- 0.93	3.3 +/- 0.6
Change +/- SD	0.8 +/- 0.92	0.3 +/- 0.87	0.2 +/- 1.07	0.8 +/- 0.8
95% CI of Change	(0.6, 1.0)	(0.1, 0.5)	(-0.1, 0.4)	
Visualization of Lesion Internal Morphology				
No. of Lesions*	79	71	72	25

Predose +/- SD	2.6 +/- 0.56	2.7 +/- 0.55	2.0 +/- 0.95	2.6 +/- 0.7
Postdose +/- SD	3.3 +/- 0.67	2.8 +/- 0.72	2.4 +/- 1.07	3.3 +/- 0.7
Change +/- SD	0.6 +/- 0.74	0.0 +/- 0.74	0.4 +/- 0.83	0.9 +/- 0.9
95% CI of Change	(0.5, 0.8)	(-0.1, 0.2)	(0.2, 0.6)	
Lesion Contrast Enhancement				
No. of Lesions*	79	71	72	25
Predose +/- SD	2.5 +/- 0.62	2.7 +/- 0.69	1.8 +/- 0.84	2.5 +/- 0.6
Postdose +/- SD	3.3 +/- 0.81	3.0 +/- 0.88	2.6 +/- 1.35	3.5 +/- 0.6
Change +/- SD	0.9 +/- 0.96	0.3 +/- 0.92	0.9 +/- 1.20	1.0 +/- 0.8
95% CI of Change	(0.6, 1.1)	(0.1, 0.6)	(0.6, 1.1)	

* A lesion had to be detected in both of the image sets.
[a] p-value based on paired t-test for change from predose to postdose.

d) Patient-Level Analysis, Predose vs. Predose + Postdose

The efficacy data were also analyzed at a patient level. To perform this analysis, average scores of the three co-primary endpoints for an image set of a given patient were calculated as the sum of all the individual lesion scores divided by the total number of lesions in that image set. Patients with no lesions detected at both image sets were excluded from this analysis. There is a improvement from the predose image set to the predose + postdose paired image set demonstrated for all 3 co-primary variables (lesion border delineation, visualization of lesion internal morphology, lesion contrast enhancement) for all 3 readers in Study MH-110. The mean changes ranged from 0.6 to 1.2 for lesion border delineation, from 0.5 to 1.2 for visualization of lesion internal morphology, and from 0.8 to 1.1 for lesion contrast enhancement. The results are comparable to those seen in the adult study (Table 12).

Table 12: Mean Summary Statistics of the 3 Co-Primary Variables, Patient-Level Analysis, Predose vs. Predose + Postdose Comparison of Pediatric Data (Study MH-110) and Adult Data

		MultiHance 0.1 mmol/kg		
		Reader 1	Reader 2	Reader 3
Pediatric Study MH-110				
Lesion Border Delineation	No. of Patients	77	74	74
	Predose ±SD	2.3 ±0.68	2.5 ±0.66	2.2 ±0.85
	Pre + Postdose ±SD	3.5 ±0.56	3.5 ±0.56	2.8 ±0.58
	Change ±SD	1.2 ±0.68	1.0 ±0.72	0.6 ±0.88
	p-value[a]	<0.0001	<0.0001	<0.0001
Visualization of Lesion Internal Morphology	No. of Patients	77	74	74
	Predose ±SD	2.5 ±0.60	2.7 ±0.53	1.9 ±0.92
	Pre + Postdose ±SD	3.7 ±0.45	3.6 ±0.57	2.4 ±1.00
	Change ±SD	1.2 ±0.63	0.9 ±0.66	0.5 ±0.78
	p-value[a]	<0.0001	<0.0001	<0.0001
Lesion Contrast Enhancement	No. of Patients	77	74	74
	Predose ±SD	2.4 ±0.65	2.6 ±0.68	1.7 ±0.75
	Pre + Postdose ±SD	3.5 ±0.55	3.6 ±0.54	2.6 ±1.14
	Change ±SD	1.1 ±0.77	1.0 ±0.77	0.8 ±0.98
	p-value[a]	<0.0001	<0.0001	<0.0001
Adult Study MH-105				
Lesion Border Delineation	No. of Patients	104	94	91
	Predose ±SD	2.1 ± 0.57	2.3 ±0.51	2.3 ±0.66
	Pre + Postdose ±SD	2.7 ± 0.68	2.7 ±0.86	2.9 ±0.78
	Change ±SD	0.6 ± 0.77	0.4 ±0.76	0.6 ±0.85
	p-value[a]	<0.001	<0.001	<0.001
Visualization of Lesion Internal Morphology	No. of Patients	104	94	91
	Predose ±SD	2.3 ±0.50	2.4 ±0.60	2.5 ±0.56
	Pre + Postdose ±SD	2.9 ±0.64	3.0 ±0.91	2.9 ±0.76
	Change ±SD	0.6 ±0.67	0.5 ±0.81	0.5 ±0.83
	p-value[a]	<0.001	<0.001	<0.001
Lesion Contrast Enhancement	No. of Patients	104	94	91
	Predose ±SD	2.7 ±0.45	2.5 ±0.57	2.8 ±0.51
	Pre + Postdose ±SD	2.8 ±0.62	2.9 ±0.92	3.2 ±0.59
	Change ±SD	0.2 ±0.71	0.3 ±0.77	0.4 ±0.64
	p-value[a]	<0.001	<0.001	<0.001

a p-value based on paired t-test for change from predose to predose + postdose.

e) Patient-Level Analysis, Predose vs. Postdose AloneThe postdose scores are generally higher than the predose scores at the patient-level (Table 13).

Table 13: Mean Summary Statistics of the 3 Co-Primary Variables, Patient-Level Analysis, Predose to Postdose, Off-site Read, Study MH-110

	MULTIHANCE 0.1 mmol/kg		
	Reader 1	**Reader 2**	**Reader 3**
Lesion Border Delineation			
No. of Patients	70	66	68
Predose ±SD	2.3 ±0.66	2.5 ±0.64	2.2 ±0.83
Postdose ±SD	3.3 ±0.70	2.9 ±0.71	2.6 ±0.82
Change ±SD	1.0 ±0.83	0.4 ±0.80	0.4 ±1.10
p-value[a]	<0.0001	0.0004	0.0078
95% CI of Change	(0.8, 1.2)	(0.2, 0.6)	(0.1, 0.6)
Visualization of Lesion Internal Morphology			
No. of Patients	70	66	68
Predose ±SD	2.6 ±0.54	2.7 ±0.53	1.9 ±0.93
Postdose ±SD	3.3 ±0.66	2.8 ±0.69	2.3 ±1.05
Change ±SD	0.7 ±0.68	0.1 ±0.76	0.4 ±0.85
p-value[a]	<0.0001	0.3074	0.0001
95% CI of Change	(0.5, 0.9)	(-0.1, 0.3)	(0.2, 0.6)
Lesion Contrast Enhancement			
No. of Patients	70	66	68
Predose ±SD	2.4 ±0.61	2.6 ±0.64	1.7 ±0.76
Postdose ±SD	3.4 ±0.75	3.1 ±0.78	2.6 ±1.27
Change ±SD	1.0 ±0.90	0.4 ±0.91	0.9 ±1.19
p-value[a]	<0.0001	0.0002	<0.0001
95% CI of Change	(0.7, 1.2)	(0.2, 0.7)	(0.6, 1.2)

[a] p-value based on paired t-test for change from predose to postdose.

Patient Level Analysis in the Re-Read Study MH-112

The data were analyzed at a patient level for the Re-read study MH-112. In both the predose vs. predose + postdose comparison and the predose vs. postdose comparison, the changes from predose favored the pre+ post dose and the postdose for all 3 lesion visualization parameters (Table 14).

Table 14: Summary Statistics of the 3 Co-Primary Variables, Patient-Level Analyses, Re-read Study MH-112

	Lesion Border Delineation	Visualization of Lesion Internal Morphology	Lesion Contrast Enhancement
Predose vs. Predose + Postdose			
No. of Patients	25	25	25
Predose +/- SD	2.5 +/- 0.7	2.5 +/- 0.6	2.5 +/- 0.6
Pre + Postdose +/- SD	3.3 +/- 0.6	3.4 +/- 0.7	3.4 +/- 0.5
Change +/- SD	0.8 +/- 0.8	0.8 +/- 0.8	0.9 +/- 0.8

P-value [a]	p < 0.001	p < 0.001	p < 0.001
Predose vs. Postdose			
No. of Patients	24	24	24
Predose +/- SD	2.5 +/- 0.7	2.5 +/- 0.7	2.5 +/- 0.6
Postdose +/- SD	3.3 +/- 0.6	3.4 +/- 0.6	3.4 +/- 0.6
Change +/- SD	0.8 +/- 0.8	0.8 +/- 0.9	0.9 +/- 0.9
P-value [a]	p < 0.001	p < 0.001	p < 0.001

a P-value based on paired t-test for change from predose to postdose.

6.1.6 Other endpoint(s)

Number of Lesions Detected

The majority of the patients had only 1 lesion for the primary analysis of predose versus predose + postdose; the number of patients with a single lesion ranged from 74.4% to 83.5% across the 3 readers. One subject had 6 lesions, and two subjects had 5 lesions. As shown in Table 15, the greatest numbers of lesions were detected in the predose + postdose image set (116 to 134) across the 3 readers, while the fewest numbers of lesions were detected in the postdose image set (95 to 98). In addition, lesions identified on the predose image set may not be visualized on the postdose image set for the same patient, and vice versa.

Table 15: Number of Lesions Detected by Image Set, Off-site Read (MH-110)

	Reader 1	**Reader 2**	**Reader 3**
Predose Image Set	114	108	106
Postdose Image Set	96	95	98
Predose + Postdose Paired Image Set	134	125	116
"All Lesion" - seen on either predose or predose+postdose paired image set	148	135	131
"All Lesion" - seen on either predose or postdose image set	131	132	132
"Common Lesion" - seen on both predose and predose + postdose paired image sets	100	98	91
"Common Lesion" – seen on both predose and postdose image sets	79	71	72

6.1.7 Subpopulations

Efficacy data were analyzed for the tumor subgroup and non-tumor subgroup of patients from Study MH-110. Because the underlying pathophysiology for neoplastic process is different from that of non-neoplastic process, it is conceivable that the degree of blood-brain-barrier (BBB) disruption, and therefore the improvement in lesion visualization afforded by MultiHance, which does not cross intact BBB, could potentially differ. The subgroup analysis was performed with all-lesion analysis, comparing predose vs. predose + postdose in terms of the three co-primary

efficacy endpoints. Table 16 shows that in both subgroups, there is improvement in lesion visualization from predose to predose + postdose at the lesion level for all 3 readers.

Table 16: Primary Efficacy by Final Diagnosis - All Lesion Analysis, Mean change from Predose to Predose+Postdose (Study MH-110)

	Reader 1		Reader 2		Reader 3	
	Tumor	Non-Tumor	Tumor	Non-Tumor	Tumor	Non-Tumor
Lesion Border Delineation						
No. of Lesions	93	54	92	42	93	35
Change ± SD	1.4± 1.22	1.0 ± 1.77	1.3±1.39	0.8±1.52	0.8±1.45	1.0±1.43
95% CI on Change	(1.2 , 1.7)	(0.5 , 1.5)	(1.0,1.6)	(0.3, 1.3)	(0.4,1.1)	(0.5,1.5)
Visualization of Lesion Internal Morphology						
No. of Lesions	93	54	92	42	93	35
Change ± SD	1.4± 1.31	1.1 ± 1.91	1.2±1.41	0.8±1.65	0.6±1.21	0.6±1.19
95% CI on Change	(1.2 , 1.7)	(0.6 , 1.6)	(0.9,1.5)	(0.3, 1.3)	(0.3,0.8)	(0.2,1.0)
Lesion Contrast Enhancement						
No. of Lesions	93	54	92	42	93	35
Change ± SD	1.4± 1.26	0.8 ± 1.94	1.3±1.47	0.9±1.61	0.9±1.53	0.6±1.56
95% CI on Change	(1.2 , 1.7)	(0.3 , 1.3)	(1.0,1.6)	(0.4, 1.4)	(0.6,1.3)	(0.4,1.1)

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

In full-term infants, glomerular filtration rate usually reaches adult levels by 6 months of age. Renal tubular maturation is delayed somewhat as compared with the glomerular filtration rate, resulting in a functional glomerular-tubular imbalance until renal tubular maturation is complete at about 1 year of age. MultiHance is not metabolized.

The two pharmacokinetic studies (MH-119 and 43,779-10) confirmed that distribution and elimination of MultiHance in children between 2 years and 17 years of age are superimposable to those in adults. The choice of a 0.1 mmol/kg dose is based on the dose recommended in the adult population for the same CNS indication, the superimposable pharmacokinetic behavior between adults and children, and the dose at which other gadolinium chelates have been approved for use in the pediatric CNS population. In particular, MultiHance provides efficacy results in children that are similar to those achieved in adults. The similar pharmacokinetics and safety profile observed between adults and children further confirm the appropriateness of 0.1 mmol/kg dose as the selected dose for MRI of pediatric CNS diseases and that a dose adjustment in children is not necessary.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

MultiHance is administered as a single injection in a single MR imaging session; therefore, evaluation of long-term efficacy to assess persistence of effect or tolerance is not relevant.

7 Review of Safety

Safety Summary

There is no overall difference in the safety profile of MultiHance between pediatric subjects 2-17 years of age and adults. Safety has been evaluated in a total of 217 pediatric subjects who received MultiHance in clinical trials. A total of 31 adverse events were reported for 24 (11.1%) of the 217 subjects dosed with MultiHance in the pediatric population. Related adverse events were reported for 14 (6.5%) of the subjects in the pediatric population. The majority of adverse events were mild or moderate in intensity and resolved without intervention. No subject died or discontinued as a result of adverse events during study participation. Serious adverse events were reported for 2 (0.9%) subjects:

- 1 patient with a brain tumor (glioma) experienced worsening of vomiting that was considered by the Investigator to be possibly related to the study contrast agent
- 1 patient with a posterior fossa tumor with hydrocephalus experienced oxygen saturation abnormal that was considered to be not related to the study contrast agent.

7.1 Methods

The safety and tolerability of MultiHance were evaluated in clinical studies by means of:

- Complete physical examination on screening and at least 24 hours after study agent injection;
- Continuous patient monitoring for adverse events for at least 24 hours (up to 72 hrs) following the study agent administration;
- Measurement and recording of vital signs (blood pressure and heart rate) predose and at different timepoints for at least 24 hours postdose;
- 12-lead electrocardiographic controls on screening as well as at different timepoints up to 24 hours postdose;
- Clinical laboratory investigations (hematology, blood chemistry, and urinalysis) conducted predose and at least 24 hours postdose.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The two pharmacokinetic studies (MH-119 and 43,779-10) and phase 3 clinical trials MH-110 and B19036/036 were used in safety evaluation. Study MH-112 is a re-read study of a subset of patients from study B19036/036 and does not contribute additional safety information. The 217 pediatric subjects dosed with MultiHance in clinical studies comprised 25 healthy subjects in the pharmacokinetic study 43,779-10 and 192 pediatric patients with clinical indications for a cranial or spine MRI in the other 4 submitted clinical studies. Age distribution of the pediatric subjects in clinical studies is shown in the following table.

Table 17: Distribution of Pediatric Subjects Given MultiHance

	Pharmacokinetic Studies		Phase 3 Efficacy and Safety Studies		
Age Group	**MH-119**	**43,779-10**	**MH-110**	**B19036/036**	**Total**
<2 years	0	0	0	15	15
2 to 5 years	15	3	13	24	55
6 to 10 years	0	11	34	26	71
11 to 17 years	0	11	45	20	76
Total	15	25	92	85	217

7.1.2 Categorization of Adverse Events

Adverse events were categorized by MedDRA System Organ Class (SOC) and Preferred Terms (PT).

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

A total of 217 pediatric subjects were administered MultiHance at a dose of 0.1 mmol/kg in 5 clinical studies – two pharmacokinetic studies (MH-119 and 43779-10) and two phase 3 clinical trials (MH-110 and B19036/036).

Study MH-110
A total of 9 adverse events were reported for 8 (8.7%) patients. All adverse events were mild or moderate in intensity. Three related adverse events were reported for 2 patients (2.2%). No patient died, had a serious adverse event, or discontinued as a result of an adverse event. Headache was reported by 2 patients (2.2%). Eyelid edema, abdominal discomfort, constipation, vomiting, otitis media, somnolence, and epistaxis were each reported by 1 patient (1.1%); eyelid edema, abdominal discomfort, and vomiting were considered related to MultiHance administration.

Table 18: Adverse Events by System Organ Class and Preferred Term (MH-110)

MedDRA System Organ Class[b] / Preferred Term[c]	MULTIHANCE 0.1 mmol/kg Number (%) of Patients (N = 92)	
	All Adverse Events	Related Adverse Events[a]
Number (%) of Patients With Adverse Events[d]	8 (8.7)	2 (2.2)
Eye Disorders	1 (1.1)	1 (1.1)
Eyelid oedema	1 (1.1)	1 (1.1)
Gastrointestinal Disorders	3 (3.3)	2 (2.2)
Abdominal discomfort	1 (1.1)	1 (1.1)
Constipation	1 (1.1)	0
Vomiting	1 (1.1)	1 (1.1)
Infections and Infestations	1 (1.1)	0
Otitis media	1 (1.1)	0
Nervous System Disorders	3 (3.3)	0
Headache	2 (2.2)	0
Somnolence	1 (1.1)	0
Respiratory, Thoracic, and Mediastinal Disorders	1 (1.1)	0
Epistaxis	1 (1.1)	0

a Includes adverse events with a probable, possible, unknown, or missing relationship to investigational product.
b Patients with more than one event within a MedDRA system organ class were counted once.
c Patients with more than one event assigned to the same MedDRA preferred term were counted once.
d Patients with more than one event were counted once.

Study B19036/036

A total of 85 patients received MultiHance (54% male, 46% female). Eleven patients (13%) in the MultiHance group experienced adverse events. The most frequently reported adverse event was fever (3 patients). Two patients had serious adverse events. One patient was hospitalized for an episode of worsening of vomiting 4.5 hours after completion of contrast agent administration. The adverse event was considered to have a possible relationship to contrast agent. The patient recovered without sequelae. Another patient experienced a 3-hour long episode of hypoxia that required hospitalization. The event was not considered to be related to the test agent. The patient recovered without sequelae.

7.2 Adequacy of Safety Assessments

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

All 217 subjects were scheduled to receive a dose of MultiHance 0.1 mmol/kg. The mean dose of MultiHance administered was 0.096 mmol/kg (range 0.056 to 0.190 mmol/kg).

Demographic and baseline characteristics for the Pediatric Population are provided in Table 19. Of the 217 dosed pediatric subjects, there were 112 males (51.6%) and 105 females (48.4%). The majority of the subjects were white (77.4% of the 217 subjects). The mean age was 8.3 years; the age range was 4 days to 17 years. There were 15 subjects <2 years, 55 subjects between 2 and 5 years, 71 subjects between 6 to 10 years, and 76 subjects between 11 and 17 years. The mean weight was 34.6 kg (range 4 to 114 kg), and the mean height was 128.4 cm (range 49 to 188 cm).

Table 19: Demographics and Baseline Characteristics, MultiHance, Pediatric Population

Categories n (%)	**MultiHance 0.1 mmol/kg (N=217)**
Sex, n (%)	
Male	112 (51.6)
Female	105 (48.4)
Age (years)	
Mean (SD)	8.3 (4.72)
Range	4 days to 17 years
Categories n (%)	
< 2 years	15 (6.9)
2 to 5 years	55 (25.3)
6 to 10 years	71 (32.7)
11 to 17 years	76 (35.0)
Race, n (%)	
White	168 (77.4)
Black	12 (5.5)
Hispanic	24 (11.1)
Asian	12 (5.5)
Other	1 (0.5)
Weight (kg)	
Mean (SD)	34.6 (21.18)
Range	4 to 114
Height (cm)	(N=213)
Mean (SD)	128.4 (30.36)
Range	49 to 188

7.2.2 Routine Clinical Testing

The safety and tolerability of MultiHance were evaluated in clinical studies by means of:

- Complete physical examination on screening and at least 24 hours after study agent injection;
- Continuous patient monitoring for adverse events for at least 24 hours (up to 72 hrs) following the study agent administration;
- Measurement and recording of vital signs (blood pressure and heart rate) predose and at different timepoints for at least 24 hours postdose;

- 12-lead electrocardiographic controls on screening as well as at different timepoints up to 24 hours postdose;
- Clinical laboratory investigations (hematology, blood chemistry, and urinalysis) conducted predose and at least 24 hours postdose.

The reviewer finds the routine clinical testing of trial subjects adequate.

7.3 Major Safety Results

There is no overall difference in the safety profile of MultiHance between pediatric subjects 2-17 years of age and adults. As shown in Table 20, a total of 31 adverse events were reported for 24 (11.1%) of the 217 subjects dosed with MultiHance in the pediatric population. Related adverse events were reported for 14 (6.5%) of the subjects in the pediatric population. The majority of adverse events were mild or moderate in intensity and resolved without intervention. No subject died during study participation. No subject discontinued as a result of an adverse event. Serious adverse events were reported for 2 (0.9%) subjects (1 of which was considered unrelated to MultiHance administration): 1 patient with a brain tumor (glioma) experienced worsening of vomiting that was considered by the Investigator to be possibly related to the study contrast agent and another patient with a posterior fossa tumor with hydrocephalus experienced oxygen saturation abnormal that was considered to be not related to the study contrast agent.

Table 20: Summary of Adverse Events, MultiHance, Pediatric Population

	(N = 217)	
Category	**All Adverse Events**	**Related Adverse Events**
No. of Adverse Events	31	18
No. (%) of Subjects With at Least 1 AE	24 (11.1)	14 (6.5)
Mild	19 (8.8)	13 (6.0)
Moderate	3 (1.4)	0
Severe	1 (0.5)	0
Not recorded/not collected	1 (0.5)	1 (0.5)
No. (%) of Subjects With at Least 1 Serious AE	2 (0.9)	1 (0.5)
Number (%) of Deaths	0	0
Number (%) of Subjects Discontinued Due to AE	0	0

Related AEs include definite, probable, possible, doubtful, unknown, remote, and missing relationship.

The most commonly reported adverse events for the 217 subjects dosed in the pediatric population were vomiting (1.8%, 4 subjects), pyrexia (1.4%, 3 subjects), abdominal pain (0.9%, 2 subjects), headache (0.9%, 2 subjects), and hyperhidrosis (0.9%, 2 subjects). All other adverse events occurred in only 1 subject. The most commonly reported related adverse events were vomiting (1.4%, 3 subjects), pyrexia (0.9%, 2 subjects), and hyperhidrosis (0.9%, 2 subjects).

7.3.1 Deaths

No subject died during study participation.

7.3.2 Nonfatal Serious Adverse Events

Serious adverse events were reported for 2 (0.9%) subjects. One patient with a brain tumor (glioma) experienced worsening of vomiting that was considered by the Investigator to be possibly related to the study contrast agent. The patient has a posterior fossa tumor with hydrocephalus experienced oxygen saturation abnormal that was considered to be not related to the study contrast agent.

Narratives for reported serious adverse events are provided below:

- Patient 03R00 (Study 19036/036, MultiHance 3.9 mL): a 5-year-old black male patient with a history of rhinitis, thick cough, left muscular weakness, left strabismus, headache, vomiting, and aplasia (secondary to chemotherapy), taking sulfamethoxazole trimethoprim, 5% glucose, 30% sodium chloride, potassium chloride and mesna as concomitant medication, experienced 1 episode of worsening of vomiting 4½ hours after completion of contrast agent administration. The patient had also received chemotherapy 2½ hours following MultiHance administration for a mesencephalic glioma. This vomiting was treated 26 hours after injection of study contrast agent with intravenous alizapride and lasted for 24 hours. The Investigator considered the adverse event to be possibly related to MultiHance. The patient recovered from the episode without any sequelae.
- Patient 02R00 (Study 19036/036; MultiHance 2 mL): an 11-month-old white male patient with a history of ventriculoperitoneal shunt for hydrocephalus (posterior fossa tumor) and laryngeal edema with dyspnea (pre-intubation), taking methylprednisolone as concomitant medication, experienced a 3 hour long episode of oxygen desaturation (hypoxia), commencing within 30 minutes of completion of the contrast agent administration. There was a pre-existing condition (dyspnea before MR examination) due to laryngeal edema associated with the premedication (barbiturates and chloral hydrate). This event was considered by the Investigator to be not related to the study contrast agent and was treated with glucocorticoids. The patient was then hospitalized for 2 days in intensive care. The patient recovered from the episode without any sequelae.

7.3.3 Dropouts and/or Discontinuations

No subject discontinued as a result of adverse events.

7.3.4 Submission Specific Primary Safety Concerns

MultiHance is predominantly eliminated by the kidney. Because of young children's immature renal function, one submission specific safety concern is the safety profile within different age

groups of the pediatric population. Table 21 compares the incidence of adverse events in four pediatric age subgroups: 0-2 years, 2-5 years, 6-10 years, and 11-17 years. The related adverse events are essentially evenly distributed in the four age groups. The laboratory data, vital signs, and ECG profiles of the pediatric population were all similar to those observed in adult patients.

Table 21: Summary of Adverse Events by Subject Age in the Pediatric Population

			No. (%) of patients with at least 1 AE	
Subgroup	**Category**	**N**	**All AE**	**Related AE[a]**
All subjects		217	24 (11.1)	14 (6.5)
Gender:	Male	112	14 (12.5)	8 (7.1)
	Female	105	10 (9.5)	6 (5.7)
Age:	< 2yrs	15	2 (13.3)	1 (6.7)
	2 to 5 yrs	55	8 (14.5)	4 (7.3)
	6 to 10 yrs	71	5 (7.0)	4 (5.6)
	11 to 17 yrs	76	9 (11.8)	5 (6.6)

[a] Includes definite, probable, possible, doubtful, unknown, remote, and missing relationship.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

A summary of adverse events by SOC and preferred term is provided in Table 22. The most commonly reported adverse events for the 217 subjects dosed in the Pediatric Population were vomiting (1.8%, 4 subjects), pyrexia (1.4%, 3 subjects), abdominal pain (0.9%, 2 subjects), headache (0.9%, 2 subjects), and hyperhidrosis (0.9%, 2 subjects). All other adverse events occurred in only 1 subject. The most commonly reported related adverse events were vomiting (1.4%, 3 subjects), pyrexia (0.9%, 2 subjects), and hyperhidrosis (0.9%, 2 subjects). All other related adverse events occurred in only 1 subject.

Table 22: MultiHance Adverse Events by System Organ Class and Preferred Term in the Pediatric Population

MedDRA System Organ Class / Preferred Term	Number (%) of Subjects (N = 217)	
	All Adverse Events	Related Adverse Events
Number (%) of Subjects With Adverse Events	24 (11.1)	14 (6.5)
Eye Disorders	**2 (0.9)**	**2 (0.9)**
Eye pain	1 (0.5)	1 (0.5)
Eyelid oedema	1 (0.5)	1 (0.5)
Gastrointestinal Disorders	**8 (3.7)**	**5 (2.3)**
Abdominal pain	2 (0.9)	1 (0.5)
Constipation	1 (0.5)	0
Retching	1 (0.5)	1 (0.5)
Vomiting	4 (1.8)	3 (1.4)
General Disorders/Administration Site Conditions	**6 (2.8)**	**5 (2.3)**
Chest pain	1 (0.5)	1 (0.5)
Injection site discomfort	1 (0.5)	1 (0.5)
Pyrexia	3 (1.4)	2 (0.9)
Thirst	1 (0.5)	1 (0.5)
Infections and Infestations	**1 (0.5)**	**0**
Otitis media	1 (0.5)	0
Investigations	**2 (0.9)**	**0**
Blood test abnormal	1 (0.5)	0
Oxygen saturation decreased	1 (0.5)	0
Nervous System Disorders	**5 (2.3)**	**1 (0.5)**
Complex partial seizures	1 (0.5)	0
Dizziness	1 (0.5)	1 (0.5)
Headache	2 (0.9)	0
Somnolence	1 (0.5)	0
Respiratory, Thoracic, and Mediastinal Disorders	**1 (0.5)**	**0**
Epistaxis	1 (0.5)	0
Skin and Subcutaneous Tissue Disorders	**4 (1.8)**	**4 (1.8)**
Hyperhidrosis	2 (0.9)	2 (0.9)
Rash	1 (0.5)	1 (0.5)
Rash papular	1 (0.5)	1 (0.5)
Vascular Disorders	**1 (0.5)**	**1 (0.5)**
Flushing	1 (0.5)	1 (0.5)

a Subjects with more than one event within a MedDRA system organ class were counted once.
b Subjects with more than one event assigned to the same MedDRA preferred term were counted once.
c Subjects with more than one event were counted once.
Related AEs include definite, probable, possible, doubtful, unknown, remote, and missing relationship.

7.4.2 Laboratory Findings

No clinically significant changes were noted in laboratory parameters.

7.4.3 Vital Signs

No clinically significant changes were noted for vital signs. For subjects who received MultiHance in the pediatric population, differences were small between mean predose and postdose changes for all vital sign parameters. Changes in vital signs are commonly reported in patients undergoing magnetic resonance examinations and are mostly related to anxiety as well as claustrophobic reactions.

7.4.4 Electrocardiograms (ECGs)

Summary statistics for mean changes from baseline for ECG parameters are provided in Table 23. The differences between predose and postdose values varied between small increases and small decreases with no observable pattern or trend. No clinically meaningful differences at any timepoint were observed between mean predose and postdose changes for any ECG parameter in subjects who received MultiHance in the Pediatric Population.

Table 23: Mean Change (SD) From Baseline in ECG Parameters, MultiHance, Pediatric Population, ECG Data

	Postdose Timepoint			
Baseline*	**1 hr**	**2 hr**	**4 hr**	**24 hr**
Ventricular Rate (bpm)				
N=127 83.8 (17.34)	N=122 -0.2 (13.34)	N=123 2.4 (10.72)	N=25 2.0 (7.86)	N=121 1.0 (11.22)
PR Interval (msec)				
N=127 134.3 (20.22)	N=122 -2.1 (10.92)	N=123 -2.6 (11.87)	N=25 -2.0 (9.34)	N=121 -1.4 (12.85)
QRS Interval (msec)				
N=127 75.6 (10.69)	N=122 1.0 (7.66)	N=123 1.6 (7.73)	N=25 0.2 (3.25)	N=121 0.4 (7.81)
QT Interval (msec)				
N=127 351.8 (31.88)	N=122 -0.3 (23.02)	N=123 -6.6 (16.54)	N=25 -4.2 (13.27)	N=121 -8.4 (22.34)
QTc Value (msec) (Bazett)				
N=127 410.6 (25.04)	N=122 -2.2 (22.78)	N=123 -2.2 (20.75)	N=25 -1.1 (16.19)	N=121 -7.7 (20.95)
QTc Value (msec) (Fridericia)				
N=127 389.5 (21.49)	N=122 -1.5 (19.10)	N=123 -3.7 (15.86)	N=25 -2.3 (11.71)	N=121 -8.0 (18.21)

7.4.5 Special Safety Studies/Clinical Trials

Nephrogenic systemic fibrosis (NSF) Observational Study in Adult At-Risk Populations
At the request of FDA, Bracco is conducting a prospective, multicenter, multinational, large scale, observational clinical study with MultiHance to better understand the risk of NSF

following the administration of MultiHance in adult patients with moderate to severe acute or chronic kidney disease. This request was made to all the Sponsors who hold approvals for gadolinium-containing contrast agents in the United States (i.e., GE Healthcare, Bayer Schering Pharma, Tyco Healthcare, and Bracco Imaging).

The study will enroll at least 1000 adult patients with GFR <60 mL/min/1.73m2, including 400 patients with estimated GFR <30 mL/min/1.73m2. The following specific information be collected:

- The date and dose of the gadolinium-containing contrast agent administration will be recorded;
- The patient GFR (or estimated GFR from serum creatinine) will be recorded;
- A card (or similar contact mechanism) will be provided to each patient to describe contact information in the event NSF symptoms develop over the following 2 years;
- At the end of each year of follow-up for each patient, all registered patients will be contacted to assess whether symptoms or signs of NSF developed and additional details obtained for patients with NSF (e.g., co-morbid conditions and any other gadolinium-containing contrast agent exposure).

Pediatric Research Equity Act (PREA) of 2003 Expectations
Incorporating inputs from the FDA Pediatric Review Committee (PeRC), a pediatric clinical study for children under 2 years of age was not conducted due to concerns on increased risk of developing NSF given immature renal function in this patient population.

7.5 Other Safety Explorations

7.5.1 Drug-Demographic Interactions

No specific age-, gender-, or race-related trends were noted.

7.5.2 Drug-Drug Interactions

Interaction studies with other medicinal products were not carried out during the clinical development of MultiHance. No clinical events attributable to potential drug interactions were reported during the clinical development program for MultiHance.

7.6 Additional Safety Evaluations

7.6.1 Human Reproduction and Pregnancy Data

No formal studies have been conducted in humans to assess the effect of MultiHance on pregnancy and lactation.

7.6.2 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There have been no cases of overdose reported in clinical trials. Therefore, the signs and symptoms of overdosage have not been characterized. Doses up to 0.4 mmol/kg were administered to adult healthy volunteers, without any serious adverse events.

Since MultiHance is administered intravenously in conjunction with MRI procedures, the potential for drug abuse does not exist.

No signs of withdrawal or rebound have been observed in the clinical development program for MultiHance as the product is indicated for single administration and diagnostic use.

7.7 Additional Submissions

At the request of FDA, Bracco submitted the proposed labeling in PLR format on 06/12/2009 and 12/16/2009. See Section 9.2 below on labeling recommendations.

8 Postmarket Experience

The submission contains a summary of serious adverse reactions reported for pediatric patients from postmarketing surveillance (Table 24) and provides narrative summaries for each case.

Table 24: Serious Adverse Drug Reactions Reported in Pediatric Patients During Postmarketing Surveillance

Number of Reports (Case ID)	MedDRA Preferred Term
1 (BCM-000852)	Eyelid edema
1 (DE-000208)	Pyrexia, extravasation, feeling hot, injection site swelling, injection site irritation, injection site erythema, fatigue, pain in extremity, growing pains, nightmare, dyspnea, hyperhidrosis, swelling face, erythema
2 (BDI-010485, US-002071)	Hypersensitivity
2 (BDI-010536, BRO-011824)	Anaphylactoid shock
5 (BRO-011564, BDI-010384, DE-000256, US-001881, US-002269)	Anaphylactoid reaction
1 (BRO-005451)	Bronchospasm
1 (DE-000061)	Dyspnea
1 (IT-000238)	Rash, bronchospasm, dyspnea, urticaria

Review of patients' records shows that each case above is related to hypersensitivity reactions, with some cases progressing to anaphylactic shock. In each case, the patient was treated promptly and all patients recovered. Although acute allergic-like reactions are known to be reported in pediatric patients administered gadolinium-containing contrast media, a recent review of FDA AERS database (mostly adults) by Dr. Kate Gelperin in the Office of Surveillance and Epidemiology (OSE) raised specific concerns for MultiHance among other gadolinium-based contrast agents with higher fatality rates associated with MultiHance related anaphylaxis. There is ongoing joint effort between the Division and OSE on continued safety updates and development of risk mitigation strategies.

9 Appendices

9.1 Literature Review/References

Gelperin, K. Risk of Anaphylaxis with Gadolinium-based Contrast Agents (GBCAs). FDA internal communication.

9.2 Labeling Recommendations

1) Update the MultiHance labeling to the new Physician Labeling Rule (PLR) format
2) Update the pediatric pharmacokinetic section with data from the two submitted PK studies
3) Recommend approval of the proposed indication for MultiHance to be used in MRI of the CNS in children over 2 years of age
4) Recommend approval of proposed dosing of 0.1 mmol/kg for children over 2 years of age
5) Update the Clinical Studies section to incorporate results from the pediatric confirmatory trial MH-110
6) Reorganize the Adverse Reactions section under MedDRA System Organ Class (SOC) and Preferred Term (PT) for both adult and pediatric populations; update with new adverse reaction terms from clinical trials and postmarketing surveillance safety data for both adult and children
7) Update the Warnings and Precautions section on acute renal failure risk and extravasation and injection site reactions

9.3 Advisory Committee Meeting

No advisory committee meeting was held for this pediatric supplement.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21357	SUPPL-6	BRACCO DIAGNOSTICS INC	MULTIHANCE(GADOBENATE DIMEGLUMINE INJ)

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

/s/

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02/24/2010

LIBERO L MARZELLA
02/24/2010