U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science (OTS)
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-357 SE-006
Drug Name:	Multihance
Indication(s):	Intravenous use in magnetic resonance imaging (MRl) of the Central Nervous System (CNS) in pediatric patients to visualize lesions with abnormal blood brain barrier or abnormal vascularity of the brain, spine, and associated tissues
Applicant:	Bracco Groups
Date(s):	Date of Submission:
	Letter Date April 17, 20009
	Stamp Date April 20, 20009
	PDUFA Goal Date February 19, 2010
Review Priority:	Standard
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Keywords: Pediatric Patient Population, Posr-Marketing, Blinded Readers, Confidence Intervals, Open Label, Randomized, Paired t-test,

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Multihance, a gadolinium-based contrast agent from Bracco, was approved in US in 2004 for intravenous use in magnetic resonance imaging (MRl) of the CNS in adults to visualize lesions with abnormal blood brain barrier or abnormal vascularity of the brain, spine, and associated tissues. The sponsor submitted the results of additional studies as a part of Post Marketing Commitment to expand the current indication to include children over 2 years of age in the current indication. The pivotal trial (Study MH-110) demonstrates statistically significant improvement (efficacy) in quality of images with contrast compared to images without contrast. These results for the pediatric efficacy are comparable to that of adults' population approved in 2004. The frequency and the nature of the adverse reactions in the pediatric patients were similar to those seen in the adult patients.

The re-read study (MH-112) also shows supportive evidence of improvement with contrast.

This reviewer concludes that the data provided supports the proposed indication of efficacy in children > 2 years of age at the proposed dosing (0.1 mmol/kg).

1.2 Brief Overview of Clinical Studies

MULTIHANCE is a gadolinium-based contrast agent from Bracco. Original NDA 21-357 was approved in US on Nov. 23, 2004 after the re-read results were submitted in a complete response to approvable letter by the Agency. The pediatric re-read (MH-112) analysis was also submitted (Oct 2003) along with two adult re-read studies, but pediatric data were found to be insufficient. Therefore, Bracco was required to perform two additional studies in pediatric patients as a Post Marketing Commitment (PMC) -- (1) A pediatric pharmacokinetic study for the evaluation of known or suspected central nervous system (CNS) disease in pediatric patients ages 2 to 5; and (2) A pediatric safety and efficacy study for the evaluation of known or suspected CNS disease in pediatric patients ages 2 to 17.

The sponsor completed both studies and submitted current sNDA which included the following studies in support of additional indication for pediatric use.

MH-119 (PMC – Pediatric Pharmacokinetic Study): This is a single-center, open-label (n = 15) for the evaluation of known or suspected CNS disease in pediatric patients ages 2-5 undergoing MRI of CNS.

MH-110 (PMC – Confirmatory Efficacy Study): This is a phase III, multi-center, open-label, within-patient comparison of contrast-enhanced and unenhanced MRI study to evaluate safety and efficacy of Multihance at the dose of 0.10 mmol/kg IV in MRI of pediatric Central Nervous System (CNS) disorders in pediatric patients ages 2-17. The primary objective was to assess the

efficacy of MultiHance MRI of the CNS in pediatric patients in terms of border delineation of lesions, visualization of internal morphology of lesions, and contrast enhancement of lesions. There were 92 subjects.

MH-112 (Supportive Efficacy Study): The sponsor also submitted supportive efficacy MH-112. This is a newly designed blinded read of patients with brain/spine neoplastic lesions included in the original study (B19036/036). The objective of this study was 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. This was MRI detection and evaluation of CNS abnormalities in pediatric patients in a multicenter, randomized, double-blind, parallel group with 29 subjects in MultiHance 0.1 mmol/kg group and 34 subjects in Magnevist 0.1 mmol/kg group (re-read of images from patients with neoplastic lesions enrolled in study B19036/036 and does not contribute to the total number of patients.)

1.3 Statistical Issues and Findings

This reviewer evaluated the evidence in support of the efficacy of MultiHance at the dose of 0.1 mmol/kg, for MRI of the CNS including brain and spine in pediatric patients.

The protocol defined endpoints for the pivotal study MH-110 had three co-primary endpoints at the lesion level 1) border delineation of lesions; 2) visualization of internal morphology of lesions; 3) contrast enhancement of lesions. Each of the endpoints was independently evaluated by three readers using a 5-point scale (0 - 4 ordered score: 4 = excellent, 1 = poor, 0 = none (lesion not detected by the reader on that image set). The primary efficacy measure was to compare predose - contrast image set to those from predose + postdose - contrast image set on the 3 co-primary endpoints. Since the objective was to show an effect for all 3 co-primary endpoints, no adjustment was made for multiplicity

The protocol, MH -110, was originally powered based on the paired t-test for the mean change from predose images to predose + postdose images assuming (1) effect size of 0.267 based on an off-site re-read of images from a subgroup of patients with neoplastic enhancing lesions from the B19036/036 study (2) change of 0.4 (sd =1.5) from predose to predose + postdose (3) alpha = 0.05 and power = 0.80. This needed a planned enrollment of 150 evaluable patients.

In a meeting between Bracco and the Agency in July 2008, an agreement was reached to terminate the pivotal study (MH-110) prior to the planned enrollment of 150 evaluable patients. The reasons were based on the new sample size calculations based on new knowledge about the effectiveness of MultiHance-enhanced MRI over plain MRI, the distribution of CNS pathology in the enrolled patient population being similar to that seen in routine clinical practice, and the distribution of enrolled patients by age classes being also similar to that seen in routine practice.

The sponsor carried out the protocol defined analyses with agreed upon changes from the Agency. This reviewer did not find any statistical issues related to the analysis.

Based on all lesion analysis comparing pre contrast vs. pre+post contrast images, the pivotal trial (Study MH-110) demonstrates statistically significant improvement (efficacy) with contrast for all 3 co-primary endpoints for all 3 readers who independently evaluated images using a 5-point scale (0-4) ordered score. Sponsor's primary efficacy objective based on comparison of pre-contrast vs. pre + post-contrast images was met. The primary results of the pivotal efficacy trial MH-110 for the pre-specified 3 co-primary endpoints for 3 readers are summarized in the Table 1 below:

Table 1: Primary Efficacy - All Lesions Analysis
Mean change from predose to predose+postdose - MULTIHANCE

Readers	Reader 1	Reader 2	Reader 3
Lesion Borders Delineation			
Number of Lesions	148	135	131
Pre-dose ± SD	1.7 ± 1.16	1.9 ± 1.15	1.7 ± 1.19
Pre+Post dose ± 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
95% CI on Change	(1.1, 1.5)	(0.9, 1.4)	(0.4, 0.9)
p-value (t-test)	< 0.0001	< 0.0001	< 0.0001
Visualization of Lesion Internal Morphology			
Number of Lesions	148	135	131
Pre-dose ± SD	1.9 ± 1.18	2.1 ± 1.17	1.4 ± 1.06
Pre+Post dose ± 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
95% CI on Change	(1.1, 1.6)	(0.8, 1.4)	(0.4, 0.8)
p-value (t-test)	< 0.0001	< 0.0001	< 0.0001
Lesion Contrast Enhancement			
Number of Lesions	148	135	131
Pre dose ± SD	1.8 ± 1.16	2.0 ± 1.20	1.4 ± 0.96
Pre+Post dose ± 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
95% CI on Change	(1.0, 1.5)	(0.9, 1.4)	(0.6, 1.1)
p-value (t-test)	< 0.0001	< 0.0001	< 0.0001

Most secondary analyses in the pivotal trial (MH-110) also show improvement with contrast for common lesion-level pre vs. pre+post and pre vs. post analyses, as well as patient level pre vs. pre+post and pre vs. post analyses. These results for the pediatric (MH-110) primary efficacy are comparable to that of adults' population approved in 2004. The frequency and the nature of the adverse reactions in the pediatric patients were similar to those seen in the adult patients.

The re-read study (MH-112) also shows supportive evidence of improvement with contrast in both Pre- vs. Pre+Post and Pre- vs. Post analyses. The data provided supports the proposed indication of efficacy in children > 2 years of age at the proposed dosing (0.1 mmol/kg).

2. INTRODUCTION

2.1 Overview

MULTIHANCE is a gadolinium-based contrast agent from Bracco. Original NDA 21-357 was approved in US on Nov. 23, 2004 after the re-read results were submitted in a complete response to approvable letter by the Agency. The pediatric re-read (MH-112) were submitted (Oct 2003) along with two adult re-read studies, but pediatric data were found insufficient. Therefore, Bracco was required to perform two additional studies in pediatric patients as a Post Marketing Commitment (PMC) -- (1) A pediatric pharmacokinetic study for the evaluation of known or suspected central nervous system (CNS) disease in pediatric patients ages 2 to 5; and (2) A pediatric safety and efficacy study for the evaluation of known or suspected CNS disease in pediatric patients ages 2 to 17.

The current indication (revised 9/07) is - MULTIHANCE is indicated for intravenous use in magnetic resonance imaging (MRl) of the CNS in adults to visualize lesions with abnormal blood brain barrier or abnormal vascularity of the brain, spine, and associated tissues.

The proposed indication seeks to add pediatric population and reads as "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."

The recommended dose of MULTIHANCE Injection is 0.1 mmol/kg (0.2 mL/kg) administered as a rapid bolus intravenous injection.

The sponsor completed both PMC studies and submitted current sNDA for pediatric use.

An overview of all submitted studies by the sponsor is given in the following Table 2.

Table 2: Overview of Submitted Studies (Sponsor's Table)

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*.

The focus of this review is pivotal trial MH-110 and supportive efficacy trial MH-112.

2.2 Data Sources

The applicant submitted this NDA in 4 volumes of paper submission. The data were submitted to the FDA CDER Electronic Document Room (EDR). The data sets were documented and included definition files. The analysis dataset was not adequate and required data management, programming and information request. The clinical study reports and datasets are located at the following location:
\\Fdswa150\NONECTD\N21357\S_006\2009-04-17 and at
\\Fdswa150\NONECTD\N21357\S_006\2009-11-05

3. STATISTICAL EVALUATION

The focus of this review is pivotal efficacy study (MH-110) and supportive efficacy study MH-112 in this sNDA.

3.1 Evaluation of Efficacy – Pivotal Study MH-110

This was a Phase III, prospective, multi-national, multicenter, within-patient controlled trial aimed at comparing unenhanced MRI and contrast-enhanced MRI using MultiHance at the dose of 0.1 mmol/kg, in terms of efficacy in MRI of the CNS including brain and spine in pediatric patients. MR images for pediatric patients included in the study were evaluated on-site by the Investigator. An off-site assessment of all MR image sets, i.e., predose, postdose, and predose + postdose was conducted by 3 independent neuroradiologists, who had no involvement with the patients, investigators, centers, or any other individuals involved in the study. These readers were blinded to all patients' information. The lesion tracking portion of the blinded read was performed by a third party adjudicator.

3.1.1 Subject disposition

Patient Disposition is given in the following table 3:

Table 3: MH-110: Patient Disposition

	MULTIHANCE Number of Patients
Number of Patients Enrolled	94
Number of Patients Discontinued Prior to Dosing (Screening Failures)	2
Number of Patients Dosed	92
Completed	89 (96.7%)
Discontinued	3 (3.3%)
Withdrawal of consent	1 (1.1%)
One or more blood and/or urine samples not obtained (a parent refused blood draws)	1 (1.1%)
Other (did not complete the 24-hour follow-up visit)	1 (1.1%)
Included in Evaluation of Safety	92 (100%)
Included in Evaluation of on-site Efficacy	92 (100%)
Included in off-site Efficacy Read	92 (100%)

3.1.2 Baseline Demographic Characteristics

A total of 94 patients were enrolled (parent or guardian signed informed consent form), and 92 patients were dosed with MULTIHANCE. Two patients were discontinued prior to receiving MULTIHANCE (screening ECG could not be obtained due to machine malfunction for 1 patient and unenhanced MRI was canceled for 1 patient due to vomiting). The Baseline Demographic Characteristics for Study MH-110 are given in table 4.

Table 4: Baseline Demographic Characteristics for Study MH-110 MultiHance (N=92)

Sex, n (%)	
Male	45 (48.9)
Female	47 (51.1)
Age (years)	
Mean (SD)	10.6 (4.02)
Range	2 years to 17.8 years
Race, n (%)	
White	71 (77.2)
Black	5 (5.4)
Other	5 (5.4)
Asian	12 (13.0)
Not recorded	0
Weight (Kg)	
Mean (SD)	42.3 (22.47)
Range	10.5 to 114
Height (cm)	N=90
Mean (SD)	139.8 (27.24)
Range	67 to 188
CNS Tumor Patients	60 (65.2)
Non-tumor patients	32 (34.8)

3.1.3 Analysis population

The analysis population included all lesions – Pre-vs. Pre+post (compare pre-contrast image set to those from pre + post-contrast image set on the 3 co-primary endpoints) and all 92 dosed patients. Imputation of 0 scores for the lesions not detected in an image set was used. All images (predose, postdose, and predose + postdose) were assessed as technically adequate.

3.1.4 Primary efficacy analysis

Three were three co-primary measures of efficacy (endpoints):

- Lesion border delineation
- Visualization of internal lesion morphology
- Contrast enhancement of lesions

There were 3 blinded readers. Each reader scored images on a scale of 0-4: 4 = excellent, 1 = poor, 0 = none (lesion not detected by the reader on that image set). Up to 10 largest lesions were to be assessed per subject. However, most patients in study MH-110 had 1 or 2 lesions, One subject had 6 lesions, two subjects have 5 lesions. Scores from pre contrast image set are compared to those from pre+post contrast image set on the 3 co-primaries for all lesions. A score of 0 was imputed for lesions not detected. P-values are based on paired t-test for change from pre-dose to pre-dose + post-dose (sponsor's primary efficacy analysis). The results of the primary analysis are given in Table 5.

Table 5: Primary Efficacy - All Lesions Analysis
Mean change from predose to predose+postdose - MULTIHANCE

Readers	Reader 1	Reader 2	Reader 3
Lesion Borders Delineation			
Number of Lesions	148	135	131
Pre-dose ± SD	1.7 ± 1.16	1.9 ± 1.15	1.7 ± 1.19
Pre+Post dose ± 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
95% CI on Change	(1.1, 1.5)	(0.9, 1.4)	(0.4, 0.9)
p-value (t-test)	< 0.0001	< 0.0001	< 0.0001
Visualization of Lesion Internal Morphology			
Number of Lesions	148	135	131
Pre-dose ± SD	1.9 ± 1.18	2.1 ± 1.17	1.4 ± 1.06
Pre+Post dose ± 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
95% CI on Change	(1.1, 1.6)	(0.8, 1.4)	(0.4, 0.8)
p-value (t-test)	< 0.0001	< 0.0001	< 0.0001
Lesion Contrast Enhancement			
Number of Lesions	148	135	131
Pre dose ± SD	1.8 ± 1.16	2.0 ± 1.20	1.4 ± 0.96
Pre+Post dose ± 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
95% CI on Change	(1.0, 1.5)	(0.9, 1.4)	(0.6, 1.1)
p-value (t-test)	< 0.0001	< 0.0001	< 0.0001

3.1.5 Secondary efficacy analysis

The secondary efficacy analysis was performed on;

(1) Analysis of Pre-dose vs. Pre-dose + Post-dose

- Patient Level Analysis - For this analysis, the score of each of the three endpoints, was calculated as an average of the lesion scores for each image set of the patients. Patients with no lesions detected at both image sets were excluded from this analysis.

- Common lesions - Pre-vs. Pre + Post (lesion seen both on predose and on predose + postdose)

(2) Analysis of Pre-dose vs. Post-dose alone

- All lesions – Pre-vs. Post (compare pre-contrast image set to those from post-contrast image set on the 3 co-primary endpoints).

- Common lesions - Pre-vs. Post (lesion seen both on predose and on postdose)

- Patient Level Analysis - Pre-vs. Post (patients with lesion seen on both image sets of interest, i.e., predose and postdose)

The results are given in the following Tables 6, 7, 8, 9 and 10. All the p-values given here are nominal and are for information only.

Table 6: Secondary Efficacy - Patient Level Analysis
Mean change from predose to predose+postdose - MULTIHANCE

Readers	Reader 1	Reader 2	Reader 3
Lesion Borders Delineation			
Number of Patients	77	74	74
Pre-dose ± SD	2.3 ± 0.68	2.5 ± 0.66	2.2 ± 0.85
Pre+Post dose ± 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
Nominal p-value (t-test)	< 0.0001	< 0.0001	< 0.0001
Visualization of Lesion Internal Morphology			
Number of Patients	77	74	74
Pre-dose ± SD	2.5 ± 0.60	2.7 ± 0.53	1.9 ± 0.92
Pre+Post dose ± 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
Nominal p-value (t-test)	< 0.0001	< 0.0001	< 0.0001
Lesion Contrast Enhancement			
Number of Patients	77	74	74
Pre-dose ± SD	2.4 ± 0.65	2.6 ± 0.68	1.7 ± 0.75
Pre+Post dose ± 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
Nominal p-value (t-test)	< 0.0001	< 0.0001	< 0.0001

Table 7: Secondary Efficacy – Common Lesion Analysis
(lesion seen both on predose and on predose + postdose)
Mean change from predose to predose+postdose - MULTIHANCE

Readers	Reader 1	Reader 2	Reader 3
Lesion Borders Delineation			
Number of Lesions	100	98	91
Pre-dose ± SD	2.3 ± 0.75	2.5 ± 0.69	2.2 ± 0.93
Pre+Post dose ± SD	3.5 ± 0.66	3.4 ± 0.61	2.7 ± 0.78
Change ± SD	1.1 ± 0.75	1.0 ± 0.69	0.5 ± 0.91
Nominal p-value (t-test)	< 0.0001	< 0.0001	< 0.0001
Visualization of Lesion Internal Morphology			
Number of Lesions	100	98	91
Pre-dose ± SD	2.5 ± 0.75	2.7 ± 0.58	1.8 ± 0.91
Pre+Post dose ± SD	3.7 ± 0.50	3.5 ± 0.60	2.3 ± 1.06
Change ± SD	1.1 ± 0.68	0.8 ± 0.66	0.5 ± 0.82
Nominal p-value (t-test)	< 0.0001	< 0.0001	< 0.0001
Lesion Contrast Enhancement			
Number of Lesions	100	98	91
Pre-dose ± SD	2.4 ± 0.64	2.5 ± 0.74	1.7 ±0.80
Pre+Post dose ± SD	3.4 ± 0.67	3.5 ± 0.58	2.4 ± 1.25
Change ± SD	1.0 ± 0.80	1.0 ± 0.76	0.7 ± 1.03
Nominal p-value (t-test)	< 0.0001	< 0.0001	< 0.0001

Table 8: Secondary Efficacy – All Lesions Analysis

(compare pre-contrast image set to those from post-contrast image set on the 3 co-primary endpoints).

Mean change from predose to postdose - MULTIHANCE

Readers	Reader 1	Reader 2	Reader 3
Lesion Borders Delineation			
Number of Lesions	131	132	132
Pre-dose ± SD	2.0 ± 1.04	2.0 ± 1.13	1.7 ± 1.20
Post dose ± 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
Nominal p-value (t-test)	0.0108	0.8457	0.1592
Visualization of Lesion Internal Morphology			
Number of Lesions	131	132	132
Pre-dose ± SD	2.1 ± 1.02	2.1 ± 1.14	1.4 ± 1.06
Post dose ± SD	2.4 ± 1.57	1.9 ± 1.38	1.6 ± 1.32
Change ± SD	0.2 ± 1.78	-0.2 ± 1.77	0.2 ± 1.27
Nominal p-value (t-test)	0.1314	0.2408	0.0398
Lesion Contrast Enhancement			
Number of Lesions	131	132	132
Pre-dose ± SD	2.1 ± 1.02	2.0 ± 1.17	1.3 ± 0.96
Post dose ± 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
Nominal p-value (t-test)	0.0166	0.5990	0.0001

Results are mixed for some Pre vs. Post comparison. For all lesions – Pre vs. Post statistical comparison did not achieve 5% nominal significance level for 1> lesion border delineation for readers 2 & 3; 2>visualization of internal lesion morphology for readers 1 & 2, and 3> contrast enhancement of lesions for reader 2.

Table 9: Secondary Efficacy – Common Lesions Analysis
(lesion seen both on predose and on postdose)
Mean change from predose to postdose - MULTIHANCE

Readers	Reader 1	Reader 2	Reader 3
Lesion Borders Delineation			
Number of Lesions	79	71	72
Pre-dose ± SD	2.4 ± 0.69	2.6 ± 0.67	2.4 ± 0.86
Post dose ± SD	3.3 ± 0.76	2.9 ± 0.85	2.5 ± 0.93
Change ± SD	0.8 ± 0.92	0.3 ± 0.87	0.2 ± 1.07
Nominal p-value (t-test)	< 0.0001	0.0026	0.1550
Visualization of Lesion Internal Morphology			
Number of Lesions	79	71	72
Pre-dose ± SD	2.6 ± 0.56	2.7 ± 0.55	2.0 ± 0.95
Post dose ± SD	3.3 ± 0.67	2.8 ± 0.72	2.4 ± 1.07
Change ± SD	0.6 ± 0.74	0.0 ± 0.74	0.4 ± 0.83
Nominal p-value (t-test)	< 0.0001	0.7418	0.0001
Lesion Contrast Enhancement			
Number of Lesions	79	71	72
Pre-dose ± SD	2.5 ± 0.62	2.7 ± 0.69	1.8 ± 0.84
Post dose ± SD	3.3 ± 0.81	3.0 ± 0.88	2.6 ± 1.35
Change ± SD	0.9 ± 0.96	0.3 ± 0.92	0.9 ± 1.20
Nominal p-value (t-test)	< 0.0001	0.0030	< 0.0001

Results are again mixed for some Pre vs. Post comparison for Common lesions. For lesion border delineation for reader 3 and for visualization of internal lesion morphology for readers 2, the Pre vs. Post comparison did not achieve nominal significance level of 5%.

Table 10: Secondary Efficacy – Patient Level Analysis
(patients with lesion seen on both image sets of interest, i.e., predose and postdose)
Mean change from predose to postdose - MULTIHANCE 0.10

Readers	Reader 1	Reader 2	Reader 3
Lesion Borders Delineation			
Number of Lesions	70	66	68
Pre-dose ± SD	2.3 ± 0.66	2.5 ± 0.64	2.2 ± 0.83
Post dose ± 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
Nominal p-value (t-test)	< 0.0001	0.0004	0.0078
Visualization of Lesion Internal Morphology			
Number of Lesions	70	66	68
Pre-dose ± SD	2.6 ± 0.54	2.7 ± 0.53	1.9 ± 0.93
Post dose ± SD	3.3 ± 0.70	2.8 ± 0.69	2.3 ± 1.05
Change ± SD	0.7 ± 0.68	0.1 ± 0.76	0.4 ± 0.85
Nominal p-value (t-test)	< 0.0001	0.3074	0.0001
Lesion Contrast Enhancement			
Number of Lesions	70	66	68
Pre-dose ± SD	2.4 ± 0.61	2.6 ± 0.64	1.7 ± 0.76
Post dose ± 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
Nominal p-value (t-test)	< 0.0001	0.0002	< 0.0001

For visualization of internal lesion morphology for readers 2, the Pre vs. Post comparison did not achieve nominal significance level of 5%.

3.2 Evaluation of Efficacy – Supportive Re-read Study MH-112

3.2.1 Study MH-112 Design

Protocol MH-112 was a newly designed blinded re-read of all the pediatric patients with brain/spine neoplastic enhancing lesions included in the original patient population of study BI9036/036 aimed at comparing MultiHance and Magnevist at the dose of 0.1 mmol/kg in terms of qualitative and quantitative assessment of unenhanced and contrast-enhanced MR for visualization of brain and spine in pediatric disease.

3.2.2 Study MH-112 Objectives

The primary objective was to compare MultiHance and Magnevist in terms of changes (changes from predose to predose + postdose) in quality of visualization of CNS lesions for all three primary endpoints: Border delineation of lesions; Visualization of internal morphology of lesions; and Contrast enhancement of lesions (the 3 co-primary endpoints in MH-110).

A total of 63 children from studyBI9036/036 (29 in the MultiHance group and 34 in the Magnevist group) with a diagnosis of CNS neoplastic enhancing lesions were included in this re-read study. The Baseline Demographic Characteristics for Study MH-112 are provided in Table 11.

Table 11: Baseline Demographic Characteristics for Supportive Re-read Study MH-112

MultiHance 0.1 mmol/kg (N=29)	MultiHance 0.1 mmol/kg (N=29)	Magnevist at the dose of 0.1 mmol/kg (N = 34)
Sex, n (%)		
Male	18 (62.1)	13 (38.2)
Female	11 (37.9)	21 (61.8)
Age (years)		
Mean (SD)	7.5 (4.8)	7.9 (4.7)
Range	4 days to 16 years	7 months to 15 years
Weight (Kg)		
Mean (SD)	32.2 (21.1)	32.2 (19.6)
Range	9 to 87	8 to 95
CNS Tumor Patients	29 (100%)	34 (100%)
Non-tumor patients	0	0

Three co-primary variables (described above as qualitative parameters) were analyzed: Lesion border delineation, visualization of lesion internal morphology, and degree of lesion contrast enhancement. Analyses were performed at the lesion level. There was 1 blinded reader.

3.2.3 Study MH-112 Efficacy Results

The results of the changes from predose to predose + postdose image sets based on the "Lesion-Level, All Lesions" analyses (with imputation of zero scores for the lesions not detected in an image set) are summarized below and in Table 12:

- A statistically significant improvement from the predose to the predose + postdose image sets for all the three co-primary variables and for both study groups;

- The changes from predose in the scores were consistently and significantly greater with MultiHance 0.1 mmol/kg than with Magnevist 0.1 mmol/kg..

Table 12: Summary Statistics of the 3 Co-Primary Variables, Al Lesions Analysis Re-read Study MH-112

	Lesion Border Delineation		Visualization of Lesion Internal Morphology		Lesion Contrast Enhancement	
	MH 0.1	MG 0.1	MH 0.1	MG 0.1	MH 0.1	MG 0.1
Predose vs. Predose + Postdose						
No. of lesions	N=33	N=42	N=33	N=42	N=33	N=42
Predose ± SD	2.0 ± 1.1	2.6 ± 0.7	2.1 ± 1.1	2.7 ± 0.6	2.1 ± 1.1	2.7 ± 0.6
Pre+Postdose ± SD	3.3 ± 0.7	3.1 ± 0.9	3.2 ± 0.8	3.3 ± 0.8	3.4 ± 0.6	3.2 ± 0.8
Change ± SD	1.2 ± 1.2	0.5 ± 0.9	1.2 ± 1.0	0.6 ± 0.8	1.4 ± 1.2	0.5 ± 0.9
p-value [a]	p < 0.001	p < 0.001	p < 0.001	p < 0.001	p < 0.001	p < 0.001
Difference MH-MG [b]	0.74		0.53		0.86	
p-value (95% C.I.)[c]	p = 0.002 (0.274, 1.211)		p = 0.012 (0.119, 0.946)		p <0.001 (0.390, 1.337)	
Predose vs. Predose + Postdose						
No. of lesions	N=33	N=44	N=33	N=44	N=33	N=44
Predose ± SD	2.0 ± 1.1	2.5 ± 0.9	2.1 ± 1.1	2.6 ± 0.8	2.1 ± 1.1	2.6 ± 0.8
Pre+Postdose ± SD	3.2 ± 1.0	2.8 ± 0.9	3.1 ± 1.1	3.1 ± 1.0	3.2 ± 1.0	2.9 ± 1.0
Change ± SD	1.1 ± 1.6	0.4 ± 1.1	1.0 ± 1.4	0.6 ± 1.0	1.2 ± 1.5	0.3 ± 1.1
p-value [a]	p < 0.001	p = 0.031	p < 0.001	p < 0.001	p < 0.001	p =0.097
Difference MH-MG [b]	0.76		0.42		0.88	
p-value (95% C.I.)[c]	p = 0.002 (0.159, 1.356)		p = 0.145 (-0.121, 0.969)		p = 0.005 (0.301, 1.457)	

MH 0.1 -- MultiHance 0.1 mmol/kg MG 0.1 - Magnevist 0.1 mmol/kg

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

[b] Difference between the predose to postdose changes (MH 0.1 -MG 0.1). '

[c] P-value based on t test, and 95% confidence interval of the difference between MultiHance and Magnevist.

3.3 Evaluation of Safety from Clinical Studies

There were 217 pediatric patients who received MultiHance in clinical studies. This included 25 healthy subjects and 192 patients undergoing MRI. A total number of 31 adverse events were reported for 24 (11.1%) of the 217 subjects. Related adverse events were reported for 14 (6.5%) of the subjects. No subject died during study participation, and no subject discontinued as a result of adverse events. Serious adverse events were reported for 2 (0.9%) subjects, both in prior study B19036/036: One patient with a brain tumor (glioma) experienced worsening of vomiting that was considered by the Investigator to be possibly related to the study agent, and one patient with a posterior fossa tumor with hydrocephalus experienced oxygen saturation abnormality that was considered to be not related to the study agent. Adverse events are summarized in the Tables 13 and 14.

Table 13: Summary of Adverse Events in MH-110 (N = 92)

Category	MultiHance 0.1 mmol/kg	
	All Adverse Events	Related AEs
No. of Adverse Events	9	3
No. of Local Adverse Events	0	0
No. of Adverse Events Related to Sedation	0	N/A
No. (%) of Patients with at least 1 AE	8 (8.7)	2 (2.2)
Mild	6 (6.5)	2 (2.2)
Moderate	2 (2.2)	0
Severe	0	0
No. (%) of Patients with at least 1 Local AE	0	0
No. (%) of Patients with at least 1 AE Related to Sedation	0	N/A
No. of Patients with at least 1 Serious AE	0	0
Number (%) of Deaths	0	0
No. of Patients Discontinued Due to AE	0	0

Table 14: Summary of Adverse Events in all Pediatric Studies (N=217)

Category	MultiHance 0.1 mmol/kg	
	All Adverse Events	Related AEs
No. of Adverse Events	31	18
No. (%) of Patients 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 Patients with at least 1 Serious AE	2 (0.9)	1 (0.5)
Number (%) of Deaths	0	0
No. of Patients Discontinued Due to AE	0	0

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Data were analyzed by gender (male, female) and age groups (Children (2 to <12 years, Adolescents (12 to <18 years) for change from predose to predose+postdose for each of the primary endpoints and for each reader. The results are given in Tables 15 and 16. As seen from these tables, results are consistent across various subgroups for each reader. The majority of subjects (77 .2%) were white with 13% Asian, 5.4% Black and 5.4% other races.

Table 15: Primary Efficacy by Gender- All Lesions Analysis
Mean change from predose to predose+postdose - MULTIHANCE

Readers	Reader 1		Reader 2		Reader 3	
Gender	Male	Female	Male	Female	Male	Female
Lesion Borders Delineation						
Number of Lesions	85	63	76	59	69	62
Change ± SD	1.4± 1.70	1.2 ± 1.06	1.3±1.7	1.0±1.11	0.8±1.45	0.6±1.39
95% CI on Change	(1.0 , 1.7)	(0.9 , 1.5)	(0.9,1.7)	(0.7, 1.3)	(0.4,1.1)	(0.3,1.0)
Visualization of Lesion Internal Morphology						
Number of Lesions	85	63	76	59	69	62
Change ± SD	1.4± 1.77	1.3 ± 1.20	1.3±1.7	0.9±1.12	0.7±1.24	0.4±1.14
95% CI on Change	(1.0 , 1.7)	(0.9 , 1.6)	(0.9,1.7)	(0.6, 1.2)	(0.4,1.0)	(0.1,0.7)
Lesion Contrast Enhancement						
Number of Lesions	85	63	76	59	69	62
Change ± SD	1.2± 1.84	1.2 ± 1.11	1.4±1.7	0.9±1.18	1.0±1.75	0.6±1.24
95% CI on Change	(0.8 , 1.6)	(0.9 , 1.5)	(1.0,1.8)	(0.6, 1.2)	(0.6,1.5)	(0.3,0.9)

Table 16: Primary Efficacy by Age Categories- All Lesions Analysis
Mean change from predose to predose+postdose - MULTIHANCE

Readers	Reader 1		Reader 2		Reader 3	
Age Category	Children (2 to <12 years)	Adolescents (12 to <18 years)	Children (2 to <12 years)	Adolescents (12 to <18 years)	Children (2 to <12 years)	Adolescents (12 to <18 years)
Lesion Borders Delineation						
Number of Lesions	88	60	86	49	82	49
Change ± SD	1.5± 1.28	1.1 ± 1.67	1.3±1.36	0.9±1.57	0.7±1.40	0.7±1.53
95% CI on Change	(1.2 , 1.7)	(0.6 , 1.5)	(1.0,1.6)	(0.5, 1.4)	(0.4,1.0)	(0.3,1.1)
Visualization of Lesion Internal Morphology						
Number of Lesions	88	60	86	49	82	49
Change ± SD	1.4± 1.40	1.7 ± 1.76	1.2±1.41	1.0±1.63	0.5±1.31	0.6±1.00
95% CI on Change	(1.1 , 1.7)	(0.7 , 1.6)	(0.9,1.5)	(0.5, 1.4)	(0.2,0.8)	(0.3,0.9)
Lesion Contrast Enhancement						
Number of Lesions	88	60	86	49	82	49
Change ± SD	1.4± 1.34	0.9 ± 1.80	1.3±1.4	1.0±1.58	0.9±1.64	0.8±1.37
95% CI on Change	(1.1 , 1.7)	(0.4 , 1.3)	(0.9,1.6)	(0.6, 1.5)	(0.5,1.2)	(0.4,1.2)

4.2 Other Special/Subgroup Populations

Final Diagnosis (tumor, non-tumor) was one special factor of clinical relevance identified by the clinical team. Subgroup analyses were carried out for change from predose to predose+postdose for each of the primary endpoints and for each reader for each category of 'Final Diagnosis'. The results are given in Tables 17. As seen from this table, results are consistent for each reader.

Table 17: Primary Efficacy by Final Diagnosis - All Lesions Analysis
Mean change from predose to predose+postdose - MULTIHANCE

Readers	Reader 1		Reader 2		Reader 3	
Final Diagnosis	Tumor	Non-Tumor	Tumor	Non-Tumor	Tumor	Non-Tumor
Lesion Borders Delineation						
Number 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						
Number 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						
Number 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)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The sponsor followed the pre-defined statistical analysis plan for the pivotal study (MH-110) as well as for the supportive studies.

Results are mixed for some secondary endpoints.

- All lesions analysis comparing pre contrast vs. post contrast fail to show statistically significant improvement (efficacy) with contrast for some readers at 5% nominal significance level.

- Common lesions analysis comparing pre vs. post fail to show statistically significant improvement (efficacy) with contrast for some readers at 5% nominal significance level.

5.2 Conclusions and Recommendations

Multihance, a gadolinium-based contrast agent from Bracco, was approved in US in 2004 for intravenous use in magnetic resonance imaging (MRl) of the CNS in adults to visualize lesions with abnormal blood brain barrier or abnormal vascularity of the brain, spine, and associated tissues. The sponsor submitted the results of additional studies as a part of Post Marketing Commitment to expand the current indication to include children over 2 years of age in the current indication. The pivotal trial (Study MH-110) demonstrates statistically significant improvement (efficacy) in quality of images with contrast compared to images without contrast. These results for the pediatric efficacy are comparable to that of adults' population approved in 2004. The frequency and the nature of the adverse reactions in the pediatric patients were similar to those seen in the adult patients.

The re-read study (MH-112) also shows supportive evidence of improvement with contrast.

This reviewer concludes that the data provided supports the proposed indication of efficacy in children > 2 years of age at the proposed dosing (0.1 mmol/kg).

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

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