CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-357

21-358

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION
Clinical Studies

NDA/Serial Number:	21-357 and 21-358 / 000
Drug Name:	Multihance (Gadobenate Dimeglumine Injection - 529 mg/mL), Multihance Multipack
Indication(s):	Intravenous use in MRI of the CNS to visualize lesions with abnormal blood brain barrier or abnormal vascularity of the brain, spine, and associated tissues.
Applicant:	Bracco Diagnostics, Inc.
Date(s):	Letter Date: July 30, 2004 PDUFA Date: February 14, 2005
Review Priority:	1S
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Key Words:	Clinical studies, NDA review

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The results of new analyses for one adult study provide additional evidence to demonstrate the efficacy of the 0.1 mmol/kg dose of Multihance for use in MRI of the CNS in adult patients.

1.2 Background

This resubmission is a response to the July 23, 2004 letter that clarified re-analyses needed to address unresolved deficiencies in the Approvable action letter dated April 14, 2004.

This statistical review represents the third review cycle for this NDA. The statistical review for the original submission is dated February 25, 2002, and a review addendum is dated May 23, 2002. Various deficiencies in the original study design, intended for a ——— claim, and inconclusive efficacy results were noted in the Approvable action letter dated May 24, 2002, and the Division recommended the Sponsor conduct new studies. Instead, the Sponsor prospectively designed and conducted a reread and reanalysis of the MR images from the three previously submitted studies with the intent of obtaining a claim for anatomical visualization only. This reread and reanalysis resulted in negative results for the adult study MH-105 based on the primary endpoint of change in lesion visualization scores between predose and postdose image sets. Statistically favorable results, however, were obtained for studies MH-106 in adults and MH-112 in children for the predefined primary efficacy analysis. These results were presented in the (second cycle) statistical review dated March 9, 2004.

Although study MH-105 failed to show the contrast agent improved lesion visualization based on the comparison of predose to the postdose MR image sets; the secondary comparison of the predose MR image set to the paired (predose + postdose) MR image sets did show statistically significant differences. However, at that time, the Division felt that improvements in anatomical visualization scores were best evaluated in unpaired image comparisons, and the use of the paired comparison is best justified when evaluating a ——————— endpoint. The inconsistencies in the results of the two methods of comparison, lack of dose-response relationship, and clinical concerns regarding the intended patient population prompted the Agency to issue the Approvable action letter of April 14, 2004.

The Sponsor met with the Division on July 9, 2004 to present information that addressed the deficiencies in the action letter. After reviewing the information, the Division reached the following decisions (cited from the July 23, 2004 letter):

- [The Division finds] that the spectrum of disease for adult CNS (brain and spine) imaging is adequately represented in the re-read studies MH-105 and MH-106.
- [The Division accepts] that the absence of the proton density sequence in MH 106 would not significantly impact results in the CNS metastatic tumor patient population.
- [The Division agrees] that when lesions do not enhance with contrast, the lack of lesion enhancement should not necessarily be considered a drug failure, when ultimately the lack of lesion enhancement may be of clinical value. We do not feel the T1 pre- vs T1 post-drug image comparisons provide the best way to evaluate what the drug's overall contribution is to anatomic delineation as a benefit to evaluate CNS patients. ... Moreover, the primary efficacy analyses in MH 106 using pre- vs. T1 post-drug image comparison as well as the pre- vs. paired reads do demonstrate efficacy for the indication of anatomic/structural delineation for patients in whom there is a suspicion of CNS metastatic malignancy. We find that reread study MH 105 is supportive in the pre- vs. paired results .

The Division provided a pathway for the sponsor to correct the outstanding issues and requested that the sponsor:

> conduct a sub-analysis of tumor-only patients (both primary and metastatic) from MH 105 using the pre- vs. post and pre- vs. paired analyses for the same three anatomic endpoints. ... [and] we request you submit a sub-analysis of MH 105 in the non-tumor brain and spine patients (patients without benign, malignant, or metastatic tumors) using the pre- vs. paired results for the three anatomic endpoints.

Multihance is indicated for intravenous use in MRI of the CNS to visualize lesions with abnormal blood brain barrier or abnormal vascularity of the brain, spine, and associated tissues.

This review presents the results of the analyses requested by the Division in the July 23, 2004 letter.

1.3 Statistical Issues and Findings

Based on a comparison of lesion visualization scores matched between pre-contrast and post-contrast images sets, subjects with tumors in study MH-105 showed statistically significant differences in mean scores for all three co-primary efficacy endpoints and for all three readers. For non-tumor subjects, statistically significant results occurred for the paired image set comparisons. These results plus the statistically significant results for study MH-106 (see the March 9, 2004 statistical review) provide evidence of efficacy for the 0.1 mmol/kg dose of Multihance for use in MR imaging of the CNS in adult patients.

2. INTRODUCTION

2.1 Overview

The Sponsor has submitted new efficacy analyses for study MH-105, in adult subjects highly suspected for CNS and spine disorders. In addition, study MH-106 is a supportive study in subjects with known metastatic disease to the brain. Both of these studies, briefly described in Table 2.1, are designed to assess efficacy for visualization of anatomic structure by comparing two doses (0.05 and 0.1 mmol/kg) of Multihance, given as first, single doses, in terms of by lesion changes in three primary endpoints. Within-dose comparisons measure the statistical significance of the mean change from pre-contrast to post-contrast image assessments, while comparison between doses is based on the statistical difference between mean change values.

This submission is a response to the Approvable action letter sent to the Sponsor on April 14, 2004.

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

This review will focus on the reanalysis of study MH-105 and will also present the results of study MH-106 (see the March 9, 2004 statistical review).

Table 2.1
Brief Summary of Clinical Studies for Multihance Re-analysis

Study Number (Country)	Subject Population	Treatment	Number Randomized	Design[1]
MH-105 (U.S.)	Men and women highly suspected for CNS and spine disorders, 18 to 88 yrs. of age	Multihance 0.05 mmol/kg Multihance 0.1 mmol/kg Omniscan 0.1 mmol/kg[2]	140 136 134	DB, R, AC, PG, MC
MH-106 (Europe)	Men and women with known metastatic disease to the brain, 23 to 81 yrs. of age	Multihance 0.05 mmol/kg Multihance 0.1 mmol/kg	74 76	DB, R, PG, MC

Source: Statistical Reviewer's listing.
[1] DB = Double-blind, R = Randomized, AC = Active Control, PG = Parallel Group, MC = Multicenter
[2] Omniscan not used as a formal comparator in the re-analysis.

2.2 Data Sources

The study reports and additional information for this submission are submitted as paper volumes with dates of submission and number of volumes as follow:

- October 10, 2003, volumes 13.1 - 13.45
- July 30, 2004 response to July 23, 2004 letter – 1 volume
- August 27, 2004 Safety Update - 4 volumes
- September 3, 2004 response to request for information of August 19, 2004 teleconference - 1 volume

The submitted SAS data sets for study MH-105 and for the tumor classification analyses are complete, well documented, and located in the Electronic Document Room at: \\CDSESUB1\N21357\N_000\2003-10-10, \\CDSESUB1\N21357\N_000\2004-09-03, and \\CDSESUB1\N21357\N_000\2004-09-14.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The Division's July 23, 2004 letter to the Sponsor requested a reanalysis of study MH-105 after classifying patients as either tumor or non-tumor patients. The Sponsor reclassified patients using the existing SAS data set DEMO for study MH-105. In this data set, patients with one of three diagnosis variables coded as 'primary malignant tumor', 'metastasis', or 'benign tumor/lesion' were classified as tumor patients. In addition, patients classified as 'differential

diagnosis' or 'post-operative changes' had their final diagnosis and/or medical history listings reviewed by a physician to determine their tumor status. Table 3.1 presents the final count of tumor and non-tumor patients for each Multihance dose.

Table 3.1
Study MH-105: Number of Subjects Classified as Either Tumor or Non-tumor and How Many Had Image Efficacy Data

	Number Classified as Tumor Subjects (Number of Subjects with Image Data)*	Number Classified as Non-tumor Subjects (Number of Subjects with Image Data)*
Multihance 0.05 mmol/kg	70 (65)	70 (59)
Multihance 0.1 mmol/kg	69 (65)	67 (61)

Source: Sponsor Attachment B, pages 14 to 24, from September 3, 2004 request for information submission and Statistical Reviewer's listing.
* Subjects excluded whose images showed no evidence of lesions at blinded read.

Analyses of the predose versus postdose image sets and predose versus paired (predose + postdose) image sets for the three co-primary efficacy endpoints (see Table 3.2) in both tumor and non-tumor patients are performed. Paired t-tests are used to evaluate the mean changes from predose to postdose or predose to paired image sets for each dose group for each of the three co-primary variables for each blinded reader in an all lesions analysis. In addition, comparison of the mean changes from predose between the two dose groups for each of the three co-primary variables is done using the pooled t-test for independent samples.

Table 3.2
Listing of the Three Co-primary Efficacy Variables Evaluated at the Blinded Reread

Three Co-primary Efficacy Variables Evaluated at the Blinded Reread		
Lesion border delineation	**Visualization of internal morphology**	**Lesion contrast enhancement**
0 = No delineation of border	0 = No visualization of internal morphology	0 = No lesion contrast enhancement
1 = Poor border delineation	1 = Poor visualization of internal morphology	1 = Poor lesion contrast enhancement
2 = Moderate border delineation	2 = Moderate visualization of internal morphology	2 = Moderate lesion contrast enhancement
3 = Good border delineation	3 = Good visualization of internal morphology	3 = Good lesion contrast enhancement
4 = Excellent border delineation	4 = Excellent visualization of internal morphology	4 = Excellent lesion contrast enhancement

Source: Statistical Reviewer's listing from Vol. 24, pages 137-138.

3.1.1 Study MH-105

The Sponsor's results for the three co-primary efficacy variables comparing the predose to postdose image sets in tumor patients are presented in Table 3.3. For the 0.10 mmol/kg dose, all three co-primary efficacy variables demonstrate a significant improvement in the postdose image set compared to the predose image set for all blinded readers (all $p<0.005$). For the 0.05 mmol/kg dose, all three co-primary efficacy variables demonstrate a significant improvement in the postdose image set compared to the predose image set only for blinded reader 1 (all $p<0.007$). Also, for the 0.05 mmol/kg dose, lesion border delineation and lesion internal morphology demonstrate a significant improvement in the postdose image set compared to the predose image for blinded reader 2 ($p<0.05$). In addition, except for blinded reader 3, no comparisons between the two doses for each of the three co-primary efficacy variables demonstrate significant differences (all $p>0.10$). For blinded reader 3, the 0.10 mmol/kg dose is significantly better than the 0.05 mmol/kg dose for all three co-primary efficacy variables.

The Sponsor's results for the three co-primary efficacy variables comparing the predose to predose + postdose (paired) image sets in tumor patients are presented in Table 3.4. For both doses, the three co-primary efficacy variables for the difference between the paired image set compared to the predose image set demonstrate significant differences (all $p<0.05$) for all efficacy variables for all blinded readers, except for lesion contrast enhancement for blinded reader 3 ($p=0.24$) for the 0.05 mmol/kg dose. In addition, except for blinded reader 3, no comparisons between the two doses for each of the three co-primary efficacy variables for each blinded reader demonstrate significant differences (all $p>0.15$). For blinded reader 3, the 0.1 mmol/kg dose for all three co-primary efficacy variables is better than the 0.05 mmol/kg dose (all $p<0.001$).

The Sponsor's results for the three co-primary efficacy variables comparing the predose to predose + postdose (paired) image sets in non-tumor patients are presented in Table 3.5. For the 0.10 mmol/kg dose, all three co-primary efficacy variables demonstrate a significant improvement in the paired image set compared to the predose image set for all blinded readers (all $p<0.02$). For the 0.05 mmol/kg dose, all three co-primary efficacy variables demonstrate a significant improvement in the paired image set compared to the predose image set for blinded reader 1 and blinded

reader 2 (all p<0.001). In addition, no comparisons between the two doses for each of the three co-primary efficacy variables for each blinded reader demonstrate significant differences (all p>0.05).

The Sponsor's results for the three co-primary efficacy variables comparing the predose to postdose image sets in non-tumor patients are presented in Table 3.6. Although this predose vs. postdose comparison was not requested in the July 23, 2004 letter it is included here for completeness. For both doses, the three co-primary efficacy variables for the difference between the postdose image set compared to the predose image set demonstrate significant differences (all p<0.05) for all efficacy variables for all blinded readers in favor of the predose image set. In addition, no comparisons between the two doses for each of the three co-primary efficacy variables for each blinded reader demonstrate significant differences (all p>0.20).

This reviewer has no additional issues with the way the data have been analyzed by the Sponsor and concludes that no further analysis is necessary.

Table 3.3
Study MH-105: Lesion Border Delineation, Visualization of Lesion Internal Morphology, Lesion Contrast Enhancement Comparison of Predose to Postdose Image Sets in Tumor Patients for the 0.05 mmol/kg dose (N=65) and 0.1 mmol/kg dose (N=65) of Multihance

	Border Delineation		Internal Morphology		Contrast Enhancement	
	Multihance 0.05 mmol/kg	Multihance 0.1 mmol/kg	Multihance 0.05 mmol/kg	Multihance 0.1 mmol/kg	Multihance 0.05 mmol/kg	Multihance 0.1 mmol/kg
Reader 1						
Number of Lesions[1]	119	132	119	132	119	132
Number of Patients[2]	61	64	61	64	61	64
Predose Mean (s.d.)	1.6 (1.2)	1.5 (1.1)	1.7 (1.2)	1.7 (1.1)	1.9 (1.3)	1.9 (1.2)
Postdose Mean (s.d.)	2.3 (1.3)	2.2 (1.5)	2.2 (1.3)	2.2 (1.4)	2.4 (1.4)	2.4 (1.5)
Mean Change (s.d.)	0.6 (1.9)	0.7 (1.9)	0.5 (1.8)	0.5 (1.8)	0.5 (2.0)	0.5 (2.0)
p-value[3]	<0.001	<0.001	0.003	<0.001	0.006	0.003
Dose comparison p-value[4]	0.64		0.98		0.89	
Reader 2						
Number of Lesions[1]	153	136	153	136	153	136
Number of Patients[2]	58	56	58	56	58	56
Predose Mean (s.d.)	1.6 (1.2)	1.5 (1.1)	1.7 (1.2)	1.7 (1.2)	1.7 (1.2)	1.7 (1.3)
Postdose Mean (s.d.)	2.0 (1.5)	2.3 (1.5)	2.1 (1.6)	2.4 (1.6)	2.0 (1.6)	2.4 (1.6)
Mean Change (s.d.)	0.4 (2.2)	0.7 (2.1)	0.5 (2.3)	0.7 (2.1)	0.3 (2.2)	0.7 (2.2)
p-value[3]	0.039	<0.001	0.014	<0.001	0.092	<0.001
Dose comparison p-value[4]	0.14		0.37		0.18	
Reader 3						
Number of Lesions[1]	115	100	115	100	115	100
Number of Patients[2]	59	56	59	56	59	56
Predose Mean (s.d.)	1.8 (1.1)	1.6 (1.2)	1.9 (1.2)	1.7 (1.2)	2.2 (1.3)	1.9(1.3)
Postdose Mean (s.d.)	2.0 (1.6)	2.8 (1.4)	2.1 (1.6)	2.9 (1.4)	2.1 (1.6)	2.9 (1.4)
Mean Change (s.d.)	0.2 (2.1)	1.2 (2.0)	0.2 (2.1)	1.2 (2.1)	-0.1 (2.3)	1.0 (2.1)
p-value[3]	0.213	<0.001	0.352	<0.001	0.716	<0.001
Dose comparison p-value[4]	0.001		<0.001		<0.001	

Source: Sponsor Tables A and B, pages 008 and 009 from the July 30, 2004 response to July 23, 2004 letter and Statistical Reviewer's analyses.
1 Number of lesions used in the "All Lesions" analysis.
2 Number of patients from the Statistical Reviewer's analyses.
3 p-value based on paired t-test for the change from predose to postdose.
4 p-value for the dose comparison based Statistical Reviewer's analysis using pooled t-test for independent samples.

Table 3.4
Study MH-105: Lesion Border Delineation, Visualization of Lesion Internal Morphology, Lesion Contrast Enhancement Comparison of Predose to Predose + Postdose Image Sets in Tumor Patients for the 0.05 mmol/kg dose (N=65) and 0.1 mmol/kg dose (N=65) of Multihance

	Border Delineation		Internal Morphology		Contrast Enhancement	
	Multihance 0.05 mmol/kg	Multihance 0.1 mmol/kg	Multihance 0.05 mmol/kg	Multihance 0.1 mmol/kg	Multihance 0.05 mmol/kg	Multihance 0.1 mmol/kg
Reader 1						
Number of Lesions[1]	122	127	122	127	122	127
Number of Patients[2]	61	60	61	60	61	60
Predose Mean (s.d.)	1.6 (1.2)	1.6 (1.0)	1.7 (1.2)	1.8 (1.1)	1.9 (1.3)	2.0 (1.2)
Predose + Postdose Mean (s.d.)	2.6 (0.9)	2.6 (1.1)	2.7 (1.0)	2.7 (1.1)	2.8 (1.0)	2.8 (1.1)
Mean Change (s.d.)	1.0 (1.3)	1.1 (1.5)	1.0 (1.4)	1.0 (1.4)	0.9 (1.4)	0.8 (1.6)
p-value[3]	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Dose comparison p-value[4]	0.76		0.86		0.64	
Reader 2						
Number of Lesions[1]	154	127	154	127	154	127
Number of Patients[2]	57	56	57	56	56	56
Predose Mean (s.d.)	1.6 (1.2)	1.6 (1.1)	1.7 (1.2)	1.8 (1.2)	1.7 (1.2)	1.8 (1.2)
Predose + Postdose Mean (s.d.)	2.3 (1.3)	2.7 (1.3)	2.5 (1.3)	2.8 (1.3)	2.4 (1.3)	2.7 (1.3)
Mean Change (s.d.)	0.8 (1.8)	1.0 (1.7)	0.8 (1.8)	1.1 (1.8)	0.7 (1.8)	0.9 (1.8)
p-value[3]	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Dose comparison p-value[4]	0.19		0.23		0.22	
Reader 3						
Number of Lesions[1]	115	109	115	109	115	109
Number of Patients[2]	58	59	58	59	58	59
Predose Mean (s.d.)	1.8 (1.1)	1.5 (1.2)	1.9 (1.2)	1.6 (1.3)	2.2 (1.3)	1.7 (1.4)
Predose + Postdose Mean (s.d.)	2.2 (1.4)	3.0 (1.1)	2.3 (1.4)	3.0 (1.1)	2.4 (1.4)	3.2 (1.0)
Mean Change (s.d.)	0.4 (1.8)	1.5 (1.6)	0.4 (1.8)	1.5 (1.7)	0.2 (2.1)	1.5 (1.7)
p-value[3]	0.025	<0.001	0.046	<0.001	0.241	<0.001
Dose comparison p-value[4]	<0.001		<0.001		<0.001	

Source: Sponsor Tables E and F, pages 011 and 012 from the July 30, 2004 response to July 23, 2004 letter and Statistical Reviewer's analyses.
1 Number of lesions used in the "All Lesions" analysis.
2 Number of patients from the Statistical Reviewer's analyses.
3 p-value based on paired t-test for the change from predose to postdose.
4 p-value for the dose comparison based Statistical Reviewer's analysis using pooled t-test for independent samples.

Table 3.5
Study MH-105: Lesion Border Delineation, Visualization of Lesion Internal Morphology, Lesion Contrast Enhancement Comparison of Predose to Predose + Postdose Image Sets in Non-Tumor Patients for the 0.05 mmol/kg dose (N=59) and 0.1 mmol/kg dose (N=61) of Multihance

	Border Delineation		Internal Morphology		Contrast Enhancement	
	Multihance 0.05 mmol/kg	Multihance 0.1 mmol/kg	Multihance 0.05 mmol/kg	Multihance 0.1 mmol/kg	Multihance 0.05 mmol/kg	Multihance 0.1 mmol/kg
Reader 1						
Number of Lesions[1]	196	268	196	268	196	268
Number of Patients[2]	51	58	51	58	51	58
Predose Mean (s.d.)	1.5 (1.0)	1.5 (1.1)	1.7 (1.1)	1.6 (1.1)	2.0 (1.2)	1.9 (1.3)
Predose + Postdose Mean (s.d.)	2.1 (0.8)	2.2 (0.7)	2.2 (0.8)	2.3 (0.7)	2.4 (0.9)	2.5 (0.7)
Mean Change (s.d.)	0.6 (1.8)	0.7 (1.2)	0.6 (1.3)	0.7 (1.2)	0.5 (1.4)	0.6 (1.5)
p-value[3]	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Dose comparison p-value[4]	0.64		0.11		0.36	
Reader 2						
Number of Lesions[1]	222	257	222	257	222	257
Number of Patients[2]	50	54	50	54	50	54
Predose Mean (s.d.)	1.5 (1.0)	1.7 (1.0)	1.6 (1.0)	1.7 (1.0)	1.6 (1.0)	1.8 (1.0)
Predose + Postdose Mean (s.d.)	2.1 (0.9)	2.0 (0.9)	2.1 (1.0)	2.1 (1.0)	2.1 (0.9)	2.1 (1.0)
Mean Change (s.d.)	0.5 (1.2)	0.3 (1.2)	0.6 (1.3)	0.4 (1.3)	0.5 (1.3)	0.3 (1.3)
p-value[3]	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Dose comparison p-value[4]	0.08		0.24		0.16	
Reader 3						
Number of Lesions[1]	139	190	139	190	139	190
Number of Patients[2]	48	50	48	50	48	50
Predose Mean (s.d.)	1.9 (1.1)	1.8 (1.2)	2.0 (1.1)	1.8 (1.3)	2.3 (1.2)	2.2 (1.4)
Predose + Postdose Mean (s.d.)	2.1 (1.1)	2.1 (1.0)	2.1 (1.1)	2.1 (1.0)	2.5 (1.2)	2.6 (1.1)
Mean Change (s.d.)	0.2 (1.5)	0.4 (1.6)	0.1 (1.5)	0.3 (1.7)	0.1 (1.8)	0.4 (2.0)
p-value[3]	0.203	0.003	0.412	0.012	0.343	0.003
Dose comparison p-value[4]	0.26		0.27		0.17	

Source: Sponsor Tables I and J, pages 014 and 015 from the July 30, 2004 response to July 23, 2004 letter and Statistical Reviewer's analyses.
1 Number of lesions used in the "All Lesions" analysis.
2 Number of patients from the Statistical Reviewer's analyses.
3 p-value based on paired t-test for the change from predose to postdose.
4 p-value for the dose comparison based Statistical Reviewer's analysis using pooled t-test for independent samples.

Table 3.6
Study MH-105: Lesion Border Delineation, Visualization of Lesion Internal Morphology, Lesion Contrast Enhancement Comparison of Predose to Postdose Image Sets in Non-Tumor Patients for the 0.05 mmol/kg dose (N=59) and 0.1 mmol/kg dose (N=61) of Multihance

	Border Delineation		Internal Morphology		Contrast Enhancement	
	Multihance 0.05 mmol/kg	Multihance 0.1 mmol/kg	Multihance 0.05 mmol/kg	Multihance 0.1 mmol/kg	Multihance 0.05 mmol/kg	Multihance 0.1 mmol/kg
Reader 1						
Number of Lesions[1]	178	231	178	231	178	231
Number of Patients[2]	55	58	55	58	55	58
Predose Mean (s.d.)	1.7 (1.0)	1.8 (1.0)	1.8 (1.0)	1.8 (1.0)	2.1 (1.1)	2.2 (1.1)
Postdose Mean (s.d.)	1.4 (1.2)	1.5 (1.3)	1.5 (1.3)	1.6 (1.3)	1.7 (1.4)	1.8 (1.4)
Mean Change (s.d.)	-0.3 (1.5)	-0.3 (1.7)	-0.3 (1.6)	-0.2 (1.7)	-0.4 (1.9)	-0.4 (2.0)
p-value[3]	0.022	0.021	0.006	0.036	0.003	0.001
Dose comparison p-value[4]	0.95		0.51		0.96	
Reader 2						
Number of Lesions[1]	202	245	202	245	202	245
Number of Patients[2]	53	56	53	56	53	56
Predose Mean (s.d.)	1.7 (0.9)	1.8 (0.9)	1.8 (1.0)	1.8 (0.9)	1.8 (0.9)	1.9 (1.0)
Postdose Mean (s.d.)	1.4 (1.3)	1.3 (1.3)	1.4 (1.4)	1.3 (1.3)	1.4 (1.4)	1.4 (1.4)
Mean Change (s.d.)	-0.3 (1.7)	-0.5 (1.7)	-0.3 (1.8)	-0.5 (1.8)	-0.3 (1.8)	-0.5 (1.8)
p-value[3]	0.005	<0.001	0.009	<0.001	0.017	<0.001
Dose comparison p-value[4]	0.44		0.42		0.23	
Reader 3						
Number of Lesions[1]	130	171	130	171	130	171
Number of Patients[2]	45	51	45	51	45	51
Predose Mean (s.d.)	2.0 (1.0)	2.0 (1.2)	2.2 (1.0)	2.0 (1.2)	2.5 (1.1)	2.4 (1.3)
Postdose Mean (s.d.)	1.2 (1.4)	1.2 (1.4)	1.2 (1.4)	1.3 (1.4)	1.4 (1.5)	1.4 (1.5)
Mean Change (s.d.)	-0.8 (1.8)	-0.7 (2.1)	-0.9 (1.8)	-0.7 (2.1)	-1.1 (2.1)	-1.0 (2.4)
p-value[3]	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Dose comparison p-value[4]	0.52		0.40		0.65	

Source: Sponsor Attachment D, Tables 22.1.2 22.2.2 and 22.3.2, pages 54 to 62, from the September 3, 2004 request for information submission and Statistical Reviewer's analyses.
1 Number of lesions used in the "All Lesions" analysis.
2 Number of patients from the Statistical Reviewer's analyses.
3 p-value based on paired t-test for the change from predose to postdose.
4 p-value for the dose comparison based Statistical Reviewer's analysis using pooled t-test for independent samples.

3.1.2 Study MH-106

The Sponsor's results for the three co-primary efficacy variables for each dose demonstrate a significant improvement in the postdose image set compared to the predose image set for each blinded reader. (See the statistical review dated March 9, 2004.) No comparisons between the two doses for each of the three co-primary efficacy variables demonstrate significant differences (all $p>0.10$).

Similar secondary efficacy analyses of the three co-primary efficacy variables for the difference between the paired (predose + postdose) image set compared to the predose image set demonstrate significant differences (all $p<0.001$) for all efficacy variables for all blinded readers. In addition, no comparisons between the two doses for each of the three co-primary efficacy variables for blinded readers 1 and 2 demonstrate significant differences (all $p>0.13$). For blinded reader 3, the 0.1 mmol/kg dose for all three co-primary variables is better than the 0.05 mmol/kg dose (all $p<0.03$).

3.2 Evaluation of Safety

There is no statistical evaluation of safety necessary for this review. For information, reference the clinical review evaluation of safety section.

4. FINDINGS IN SUBGROUP POPULATIONS

The subgroup populations of interest are tumor and non-tumor patients. The findings are described in Section 3.

5. CONCLUSIONS AND RECOMMENDATIONS

Study MH-105 in adults shows statistically significant results for the three co-primary efficacy endpoints in tumor and non-tumor patients. These results plus the statistically significant results for study MH-106 provide evidence of efficacy for the 0.1 mmol/kg dose of Multihance for use in MR imaging of the CNS in adult patients.

Tables 5.1 and 5.2 are recommended for inclusion to the clinical trials section of the label.

TABLE 5.1: Lesion Level Results of MRI Central Nervous System Studies with 0.1 mmol/kg MULTIHANCE

	Study A			Study B		
	Reader 1	Reader 2	Reader 3	Reader 1	Reader 2	Reader 3
Endpoints	N=395	N=384	N=299	N=245	N=275	N=254
Border Delineation: Difference of Means (a)	0.8*	0.6*	0.8*	1.8*	1.5*	1.9*
Worse (b)	44 (11%)	61 (16%)	57 (19%)	13 (5%)	24 (9%)	15 (6%)
Same	146 (37%)	168 (44%)	89 (30%)	11 (5%)	19 (7%)	18 (7%)
Better	205 (52%)	155 (40%)	153 (51%)	221 (90%)	232 (84%)	221 (87%)
Internal Morphology: Difference of Means	0.8*	0.6*	0.7*	1.7*	1.4*	2.1*
Worse	37 (10%)	63 (17%)	62 (21%)	13 (5%)	26 (10%)	14 (5%)
Same	147 (37%)	151 (39%)	84 (28%)	16 (7%)	22 (8%)	22 (9%)
Better	211 (53%)	170 (44%)	153 (51%)	216 (88%)	227 (82%)	218 (86%)
Contrast Enhancement: Difference of Means	0.7*	0.5*	0.8*	1.9*	1.3*	1.9*
Worse	75 (19%)	74 (19%)	50 (17%)	13 (5%)	32 (12%)	17 (7%)
Same	148 (37%)	152 (40%)	109 (36%)	11 (5%)	21 (7%)	14 (5%)
Better	172 (44%)	158 (41%)	140 (47%)	221 (90%)	222 (81%)	223 (88%)

(a) Difference of means = (paired[c] mean) - (pre mean)
(b) Worse = paired score is less than the pre score
Same = paired score is the same as the pre score
Better = paired score is greater than the pre score
(c) Paired = side-by-side pre and post MULTIHANCE
* Statistically significant for the mean (paired t test)

Source: Sponsor End-of-Text tables - Tables 3.1 – 3.3, pp. 013 – 021, Tables 6.1 – 6.3, pp. 034 – 036, Table 15, p. 067, and Table 17, pp. 071 – 073 from Vol. 27 and Tables 3.1 – 3.3, pp. 013 – 021, Tables 6.1 – 6.3, pp. 034 – 036, Table 15, p. 066, and Table 17, pp. 070 – 072 from Vol. 34.

TABLE 5.2: Patient Level Results of MRI Central Nervous System Studies with 0.1 mmol/kg MULTIHANCE

	Study A			Study B		
	Reader 1	Reader 2	Reader 3	Reader 1	Reader 2	Reader 3
Endpoints†	N=78	N=73	N=70	N=65	N=71	N=69
Border Delineation: Difference of Means (a)	0.5*	0.6*	0.5*	1.4*	1.1*	1.2*
Internal Morphology: Difference of Means	0.5*	0.7*	0.5*	1.2*	0.8*	1.0*
Contrast Enhancement: Difference of Means	0.3*	0.5*	0.4*	1.5*	0.9*	1.2*

(a) Difference of means = (post MULTIHANCE mean) - (pre mean)
† Endpoints are on a patient level, with each endpoint being the mean score across all lesions within a patient
* Statistically significant for the mean (paired t test)

Source: Sponsor End-of-Text tables – Tables 28.1 – 28.3, pp. 137 – 145 from Vol. 27 and Tables 28.1 – 28.3, pp. 136 – 144 from Vol. 34.

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/s/

Sonia Castillo
11/22/04 03:46:28 PM
BIOMETRICS

Mike Welch
11/23/04 12:55:38 PM
BIOMETRICS
Concur with review.

Safety Update Reviews: * See Clinical Review

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION
Clinical Studies

NDA/Serial Number:	21-357 and 21-358 / 000
Drug Name:	Multihance (Gadobenate Dimeglumine Injection - 529 mg/mL), Multihance Multipack
Indication(s):	Intravenous use in MRI of the CNS to visualize lesions with abnormal blood brain barrier or abnormal vascularity of the brain, spine, and associated tissues.
Applicant:	Bracco Diagnostics, Inc.
Date(s):	Letter Date: October 10, 2003 PDUFA Date: April 14, 2004
Review Priority:	1S
Biometrics Division:	Division of Biometrics 2, HFD-715
Statistical Reviewer:	Sonia Castillo, Ph.D.
Biometrics Team Leader:	Michael Welch, Ph.D.
Medical Division:	Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160
Clinical Team:	Robert Yaes, M.D., Medical Reviewer Ramesh Raman, M.D., Team Leader
Project Manager:	Diane Smith
Key Words:	Clinical studies, NDA review

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The resubmitted data and new analyses for two adult studies and one pediatric study do not provide clear evidence to demonstrate the efficacy of either the 0.05 mmol/kg dose or the 0.1 mmol/kg dose of Multihance for use in MRI of the CNS in — adult —

1.2 Background

This resubmission is a complete response to the Approvable action letter sent to the Sponsor on May 24, 2002 for the following indication:

MultiHance is indicated for intravenous use in adults — as an adjunct to magnetic resonance imaging (MRI) of the Central Nervous System (brain, spine, and surrounding structures). —

The statistical reviews for the first submission are dated February 25, 2002 and May 23, 2002 (an addendum to the February review). Various deficiencies in the original study design (including image reading methodology, endpoints, and dosing regimens) prompted the Agency to deny approval and to request one new study in adults — Instead of conducting new studies to address the various deficiencies, the Sponsor has decided to conduct a reread and reanalysis of the three previously submitted studies. The Sponsor's rationale for not conducting a new study is to "not expose new patients unnecessarily to administration of study agents" because:

- the majority of CNS disorders that are routinely investigated with contrast-enhanced MRI were well covered in the two studies
- the imaging conditions employed in those two studies are the ones that are used in current clinical practice in the United States (Vol. 24, page 145, Section 1.4.1 g)

Multihance is indicated for intravenous use in MRI of the CNS to visualize lesions with abnormal blood brain barrier or abnormal vascularity of the brain, spine, and associated tissues.

The Division agreed that a reread of the existing studies along with newly defined visualization endpoints would be reviewable.

1.3 Statistical Issues and Findings

The major statistical issue is the Sponsor's presentation of secondary analyses of the three co-primary efficacy variables (lesion border delineation, visualization of lesion internal morphology, and lesion contrast enhancement) instead of the primary analyses as evidence of efficacy for principal study MH-105 in adults. The primary efficacy analysis is based on the comparison of the pre-dose to the post-dose MR image sets, while the secondary analysis is based on the comparison of the pre-dose MR image set to the paired (pre-dose + post-dose) MR image set. The protocol specified primary analysis for adult study MH-105 of the three co-primary efficacy variables does not reach statistical significance but the secondary analysis does.

In addition, since the Sponsor did not conduct new clinical studies, there remain study design deficiencies for each of the three studies which include: no utilization of a standard of truth, number of blinded readers per study, small number of subjects with spinal disorders, lack of standard pre-dose MRI sequences (T1, T2, PD) for all subjects, small number of pediatric subjects, lack of variety of CNS conditions in pediatric subjects.

Principal study MH-105 in adults is not statistically significant for the primary efficacy analysis while studies MH-106 in adults and MH-112 in children are statistically significant for the primary efficacy analysis. These results plus original design deficiencies do not show consistent evidence of efficacy for either the 0.05 mmol/kg or 0.1 mmol/kg dose of Multihance for use in MR imaging of the CNS in — adult —

2. INTRODUCTION

2.1 Overview

The Sponsor has resubmitted three clinical studies in subjects with CNS disorders and/or lesions. Principal study MH-105, which is the combination of key studies 43,779-9A and 43,779-9B, is in adult subjects highly suspected for CNS and spine disorders; study MH-106, which is supportive study B19036/020, is in subjects with known metastatic disease to the brain; and study MH-112, which is study B19036/036 (a pediatric CNS lesion study), is in children with neoplastic brain tumors. These studies are designed to assess efficacy for visualization of anatomic structure by comparing two doses (0.05 and 0.1 mmol/kg) of Multihance, given as first, single doses, in terms of by lesion changes (change from pre-dose to post-dose) in three primary endpoints. Table 2.1 presents a brief summary of each of the three studies addressed in this review.

Table 2.1
Brief Summary of Clinical Studies for Multihance Resubmission

Study Number (Original Study Number)	Subject Population	Treatment	Number Treated with Pre- and Post-images	Design[1]
MH-105 (Combined U.S. Studies 43,779-9A and 43,779-9B)	Men and women highly suspected for CNS and spine disorders, 18 to 88 yrs. of age	Multihance 0.05 mmol/kg Multihance 0.1 mmol/kg Omnihance 0.1 mmol/kg	140 136 134	DB, R, AC, PG, MC
MH-106 (European Study B19036/020)	Men and women with known metastatic disease to the brain, 23 to 81 yrs. of age	Multihance 0.05 mmol/kg Multihance 0.1 mmol/kg	74 75	DB, R, AC, PG, MC
MH-112 (Subgroup of European Study B19036/036)	Subgroup of children with neoplastic brain tumors from study of 174 children with CNS lesions, 2 to 16 yrs. of age	Multihance 0.1 mmol/kg Magnevist 0.1 mmol/kg	29 34	DB, R, AC, PG, MC

Source: Statistical Reviewer's listing.
[1] DB = Double-blind, R = Randomized, AC = Active Control, PG = Parallel Group, MC = Multicenter

This submission is a response to the Approvable action letter sent to the Sponsor on May 24, 2002 for the following indication:

MultiHance is indicated for intravenous use [redacted] *as an adjunct to magnetic resonance imaging (MRI) of the Central Nervous System (brain, spine, and surrounding structures).* [redacted]

Various deficiencies in the original study design (including image reading methodology, endpoints, and dosing regimens) prompted the Agency to deny approval and to request one new study in adults [redacted] Instead of conducting new studies to address the various deficiencies, the Sponsor has decided to conduct a reread and reanalysis of the three previously submitted studies. The Sponsor's rationale for not conducting a new study is to "not expose new patients unnecessarily to administration of study agents" because:

- the majority of CNS disorders that are routinely investigated with contrast-enhanced MRI were well covered in the two studies
- the imaging conditions employed in those two studies are the ones that are used in current clinical practice in the United States (Vol. 24, page 145, Section 1.4.1 g)

[redacted]

Multihance is indicated for intravenous use in MRI of the CNS to visualize lesions with abnormal blood brain barrier or abnormal vascularity of the brain, spine, and associated tissues.

This new indication is an anatomical visualization claim that the Sponsor needs to at least demonstrate a benefit of Multihance in the post-dose image compared to the baseline (pre-dose) image alone. This benefit is based on improvement in three co-primary endpoints over the baseline image: lesion border delineation, visualization of lesion internal morphology, and lesion contrast enhancement. The Agency has reviewed the blinded reread protocol for studies MH-105 and MH-106 but not the protocol for study MH-112. This review presents the Sponsor's protocol specified primary efficacy analyses in detail and briefly presents the secondary efficacy analyses and one important secondary efficacy analysis on the number of lesions.

Since the Sponsor is seeking approval for the efficacy of Multihance (as compared to pre-contrast), this review will focus on Multihance and not address either Omniscan or Magnevist. These active control groups were part of the original study designs and are not relevant to the resubmission.

2.2 Data Sources

The study reports and additional information for these three studies are submitted as paper volumes. Their dates of submission and number of volumes are as follow:

- October 10, 2003, volumes 13.1 - 13.45
- December 9, 2003 response to request for additional information - 2 volumes
- December 9, 2003 response to request for additional information of November 19, 2003 - 2 volumes

The submitted SAS data sets for studies MH-105 and MH-106 are complete and well documented. They are located in the Electronic Document Room at \\CDSESUB1\N21357\N_000\2003-10-10. No SAS data sets are submitted for study MH-112.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The protocol specified primary objective for studies MH-105 and MH-106 is:

To compare the two doses (0.05 and 0.1 mmol/kg) of Multihance, given as first, single doses, in terms of by lesion changes (changes from pre-dose to post-dose) in all three primary endpoints:

- Border delineation of lesions
- Visualization of internal morphology of lesions
- Contrast enhancement of lesions

The protocol for pediatric study MH-112 was not reviewed by the Agency and is not included in the submission. The Sponsor states that the endpoints and efficacy analyses are the same as those for studies MH-105 and MH-106. Since study MH-106 evaluates only the 0.1 kg/mmol Multihance dose, the primary comparison of interest is the change from baseline.

Table 3.1 presents the three new co-primary efficacy variables, all on 5-point scales, used for the blinded reread in all three studies.

Table 3.1
Listing of the Three Co-primary Efficacy Variables Evaluated at the Blinded Reread for Studies MH-105, MH-106, and MH-112

Three Co-primary Efficacy Variables Evaluated at the Blinded Reread		
Lesion border delineation	**Visualization of internal morphology**	**Lesion contrast enhancement**
0 = No delineation of border	0 = No visualization of internal morphology	0 = No lesion contrast enhancement
1 = Poor border delineation	1 = Poor visualization of internal morphology	1 = Poor lesion contrast enhancement
2 = Moderate border delineation	2 = Moderate visualization of internal morphology	2 = Moderate lesion contrast enhancement
3 = Good border delineation	3 = Good visualization of internal morphology	3 = Good lesion contrast enhancement
4 = Excellent border delineation	4 = Excellent visualization of internal morphology	4 = Excellent lesion contrast enhancement

Source: Statistical Reviewer's listing from Vol. 24, pages 137-138.

The MR image sets for studies MH-105, MH-106, and MH-112 were blindly reread with the following key features listed in Table 3.2. The pre-dose image set consists of the T_1, T_2, and, possibly, PD (proton density) sequences and the post-dose image set consists of the T_1 sequence.

Table 3.2
Key Features of the Blinded Reread for Studies MH-105, MH-106, and MH-112

	Study MH-105	Study MH-106	Study MH-112
Number of independent blinded readers	3	3	1
Lesion tracking (pre- to post-dose image sets)	Yes	Yes	Yes
Separate randomized blinded read of both pre- and post-dose image sets for all treatment groups	Yes	Yes	Yes
Separate randomized blinded read of paired images (pre- and post-dose image sets in a side-by-side fashion) for all treatment groups	Yes	Yes	Yes
Quantification of number of lesions seen	Yes	Yes	Yes
No discarding of technically inadequate images	Yes	Yes	Yes
Blinded reader qualitative and quantitative (technical, secondary) evaluations	Yes	Yes	Yes
Standard pre-dose MRI sequences of T_1, T_2, and PD acquired for all subjects	Yes	No	No
Evaluation of three co-primary efficacy endpoints: lesion border delineation, visualization of internal morphology, and contrast enhancement	Yes	Yes	Yes

Source: Statistical Reviewer's listing.

For all three studies, paired t-tests are used to evaluate the mean changes from pre-dose to post-dose image sets for each dose group for each of the three co-primary variables for each blinded reader in an all lesions analysis. For studies MH-105 and MH-106, comparison of the mean changes from pre-dose between the two dose groups for each of the three co-primary variables is done using an analysis of covariance (ANCOVA) model with treatment group as a fixed effect and pre-dose score as the covariate.

The major statistical issue in this submission is the Sponsor's presentation of secondary analyses of the three co-primary efficacy variables (which reached statistical significance) instead of the primary analyses (which did not reach statistical significance) as evidence of efficacy for study MH-105. The protocol specified primary efficacy analysis is based on the comparison of the pre-dose to the post-dose MR image sets, while the secondary analysis is based on the comparison of the pre-dose MR image set to the paired (pre-dose + post-dose) MR image set. The Division typically uses this pre-dose versus paired analysis for a [redacted] indication. Thus, this review presents the protocol specified primary efficacy analyses in detail and briefly presents the secondary efficacy analyses and one important secondary efficacy analysis on the number of lesions.

For studies MH-105 and MH-106, an important secondary efficacy analysis is the change in the number of lesions seen at pre-dose compared to post-dose in those subjects who had two or fewer lesions identified on the pre-dose images. According to the medical team leader, this analysis gives important clinical information for those subjects who show an increase in the number of lesions seen with contrast compared to the few (2 or less) seen at baseline. This data is analyzed using the Wilcoxon Rank Sum (which ignores zero changes cases) test between the two doses for each blinded reader. The aspect of tracking is applied to this analysis in the sense that at least one of the lesions seen on the pre-dose image set is seen on the post-dose image set. For example, if two lesions are seen on the pre-dose image set, then there should be none or at least one of those lesions seen on the post-dose image is the same pre-dose image lesion. A special case is if there is one lesion seen at pre-dose. The subject is kept in the analysis if this lesion is not seen on the post-dose image and no other lesion is seen or if this lesion is seen on post-dose along with no other lesions or more.

3.1.1 Study MH-105

The Sponsor's results for the three co-primary efficacy variables for principal study MH-105 in adults are presented in Table 3.3. None of the three co-primary efficacy variables for each dose demonstrate a significant improvement in the post-image set compared to the baseline image set for all blinded readers. Although the results for blinded reader 3 for the 0.05 mmol/kg dose are significant, the direction of the improvement is with the pre-dose image set instead of the post-dose image set. In addition, no comparisons between the two doses for each of the three co-primary efficacy variables for each blinded reader demonstrate significant differences (all $p>0.20$).

Similar secondary efficacy analyses of the three co-primary efficacy variables for the difference between the paired (pre-dose + post-dose) image sets compared to the pre-image set demonstrate significant differences (all $p<0.05$) for all efficacy variables for all blinded readers, except for blinded reader 3. For blinded reader 3, the 0.05 mmol/kg dose for lesion contrast enhancement is not different ($p=0.13$). In addition, except for blinded reader 3, no comparisons between the two doses for each of the three co-primary efficacy variables for each blinded reader demonstrate significant differences (all $p>0.20$). For blinded reader 3, the 0.1 mmol/kg dose for lesion border delineation and lesion contrast enhancement is better than the 0.05 mmol/kg dose (both $p<0.03$).

Table 3.3
Study MH-105: Lesion Border Delineation, Visualization of Lesion Internal Morphology, Lesion Contrast Enhancement
All Lesions Analyses, Comparison of Pre-dose to Post-dose Image Sets
for the 0.05 mmol/kg dose (N=140) and 0.1 mmol/kg dose (N=136) of Multihance

	Border Delineation		Internal Morphology		Contrast Enhancement	
	Multihance 0.05 mmol/kg	Multihance 0.1 mmol/kg	Multihance 0.05 mmol/kg	Multihance 0.1 mmol/kg	Multihance 0.05 mmol/kg	Multihance 0.1 mmol/kg
Reader 1						
Number of Lesions*	297	363	297	363	297	363
Number of Pre-dose Lesions	233	286	233	286	233	286
Number of Post-dose Lesions	206	250	206	250	206	250
Pre-dose Mean (s.d.)	1.7 (1.0)	1.7 (1.0)	1.8 (1.1)	1.8 (1.0)	2.1 (1.2)	2.1 (1.2)
Post-dose Mean (s.d.)	1.7 (1.3)	1.8 (1.4)	1.8 (1.4)	1.8 (1.4)	2.0 (1.4)	2.0 (1.5)
Mean Change (s.d.)	0.1 (1.8)	0.1 (1.8)	0.0 (1.8)	0.0 (1.8)	-0.1 (2.0)	-0.1 (2.1)
p-value**	0.39	0.29	1.0	0.70	0.64	0.45
Dose comparison p-value***	0.92		0.86		0.84	
Reader 2						
Number of Lesions*	355	381	355	381	355	381
Number of Pre-dose Lesions	273	299	273	299	273	299
Number of Post-dose Lesions	217	232	217	232	217	232
Pre-dose Mean (s.d.)	1.6 (1.0)	1.7 (0.99)	1.7 (1.1)	1.8 (1.1)	1.7 (1.1)	1.8 (1.1)
Post-dose Mean (s.d.)	1.6 (1.4)	1.6 (1.4)	1.7 (1.5)	1.7 (1.5)	1.7 (1.5)	1.7 (1.5)
Mean Change (s.d.)	0.0 (1.9)	0.0 (1.9)	0.0 (2.0)	0.0 (2.0)	0.0 (2.0)	-0.1 (2.0)
p-value**	0.74	0.73	0.90	0.64	0.71	0.37
Dose comparison p-value***	0.99		0.86		0.96	
Reader 3						
Number of Lesions*	245	271	245	271	245	271
Number of Pre-dose Lesions	203	206	203	206	203	206
Number of Post-dose Lesions	138	166	138	166	138	166
Pre-dose Mean (s.d.)	1.9 (1.1)	1.8 (1.2)	2.0 (1.1)	1.9 (1.2)	2.4 (1.2)	2.2 (1.3)
Post-dose Mean (s.d.)	1.6 (1.5)	1.8 (1.6)	1.6 (1.6)	1.9 (1.6)	1.7 (1.6)	2.0 (1.6)
Mean Change (s.d.)	-0.3 (2.0)	0.0 (2.3)	-0.4 (2.0)	0.0 (2.3)	-0.6 (2.3)	-0.2 (2.5)
p-value**	0.009	0.94	0.002	0.98	<0.001	0.11
Dose comparison p-value***	0.21		0.20		0.23	

Source: Sponsor Tables 3-4, 3-5, and 3-6, pages 149 to 151, Vol.24 and Table A, page 4, Vol. 1 of Dec. 9, 2003: Response to Request of Nov.19, 2003.
* Number of lesions used in the "All Lesions" analysis.
** p-value based on paired t-test for the change from pre-dose to post-dose.
*** p-value for the pre-dose to post-dose changes based on ANCOVA with treatment group as a fixed effect and pre-dose score as a covariate.

Table 3.4 presents the distribution of changes from pre-dose in the number of lesions detected for subjects with two or fewer lesions seen at pre-dose. For all readers and doses, the majority of subjects (>50%) had no change. For each dose, there are more subjects with additional lesions seen post-dose for all blinded readers, except for blinded reader 3 for the 0.05 mmol/kg dose, where more subjects had less lesions seen at pre-dose compared to post-dose. Also, there is no statistical difference between the two doses (all $p>0.05$) for each blinded reader.

Table 3.4
Study MH-105: Distribution of Changes from Pre-dose in the Number of Lesions Detected for Subjects with Two or Fewer Lesions Detected at Pre-dose.

Change in number of lesions from pre-dose to post-dose	Reader 1		Reader 2		Reader 3	
	Multihance 0.05 mmol/kg	Multihance 0.1 mmol/kg	Multihance 0.05 mmol/kg	Multihance 0.1 mmol/kg	Multihance 0.05 mmol/kg	Multihance 0.1 mmol/kg
No. of Subjects (%)	**113**	**98**	**104**	**98**	**114**	**111**
-2	3 (2.7)	5 (5.1)	1 (1.0)	4 (4.1)	5 (4.4)	2 (1.8)
-1	13 (11.5)	15 (15.3)	11 (10.6)	17 (17.3)	15 (13.2)	12 (10.8)
0	72 (63.7)	51 (52.0)	67 (64.4)	53 (54.1)	80 (70.2)	76 (68.5)
1	16 (14.2)	21 (21.4)	19 (18.3)	17 (17.3)	11 (9.6)	14 (12.6)
2	6 (5.3)	5 (5.1)	3 (2.9)	5 (5.1)	1 (0.9)	6 (5.4)
3	1 (0.9)	1 (1.0)	2 (1.9)	1 (1.0)	1 (0.9)	0
4	2 (1.8)	0	1 (1.0)	1 (1.0)	0	0
≥ 5	0	0	0	0	1 (0.9)	1 (0.9)
No. of subjects with more lesions seen post-dose (%)	25 (22.1)	27 (27.6)	25 (24.0)	24 (24.5)	14 (12.3)	21 (18.9)
Dose comparison p-value*	0.85		0.32		0.10	

Source: Based on Sponsor Table 17a, pp. 074-076, Vol. 27.
* p-value based on Wilcoxon Rank Sum test, which ignores zero change cases.

Study design deficiencies are other important information that needs to be taken into account when interpreting the overall results. These deficiencies and reasons for their importance are listed below:

- There is no standard of truth utilized, so one is not sure if lesions seen are real or artifacts.
- According to the medical team leader, there are only 8 subjects with spinal disorders, 4 in each Multihance group (Table 3-1, page 117, Vol. 24). This is a problem for the proposed CNS indication that includes the brain, spine, and associated tissues.

This reviewer has no additional issues with the way the data have been analyzed by the Sponsor and concludes that no further analysis is necessary.

3.1.2 Study MH-106

The Sponsor's results for the three co-primary efficacy variables for adult study MH-106 are presented in Table 3.5. All of the three co-primary efficacy variables for each dose demonstrate a significant improvement in the post-image set compared to the baseline image set for each blinded reader. No comparisons between the two doses for each of the three co-primary efficacy variables demonstrate significant differences (all $p>0.10$).

Similar secondary efficacy analyses of the three co-primary efficacy variables for the difference between the paired (pre-dose + post-dose) image set compared to the pre-dose image set demonstrate significant differences (all $p<0.001$) for all efficacy variables for all blinded readers. In addition, no comparisons between the two doses for each of the three co-primary efficacy variables for blinded readers 1 and 2 demonstrate significant differences (all $p>0.13$). For blinded reader 3, the 0.1 mmol/kg dose for all three co-primary variables is better than the 0.05 mmol/kg dose (all $p<0.03$).

Table 3.5
Study MH-106: Lesion Border Delineation, Visualization of Lesion Internal Morphology, Lesion Contrast Enhancement
All Lesions Analyses, Comparison of Pre-dose to Post-dose Image Sets
for the 0.05 mmol/kg dose (N=74) and 0.1 mmol/kg dose (N=75) of Multihance

	Border Delineation		Internal Morphology		Contrast Enhancement	
	Multihance 0.05 mmol/kg	Multihance 0.1 mmol/kg	Multihance 0.05 mmol/kg	Multihance 0.1 mmol/kg	Multihance 0.05 mmol/kg	Multihance 0.1 mmol/kg
Reader 1						
Number of Lesions*	142	250	142	250	142	250
Number of Pre-dose Lesions	91	120	91	120	91	120
Number of Post-dose Lesions	132	237	132	237	132	237
Pre-dose Mean (s.d.)	1.0 (0.8)	0.7 (0.8)	1.1 (0.98)	0.8 (0.98)	1.0 (0.9)	0.7 (0.8)
Post-dose Mean (s.d.)	2.3 (1.1)	2.4 (1.1)	2.5 (1.1)	2.5 (1.1)	2.5 (1.1)	2.6 (1.1)
Mean Change (s.d.)	1.4 (1.2)	1.8 (1.2)	1.4 (1.2)	1.6 (1.2)	1.5 (1.2)	1.9 (1.2)
p-value**	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Dose comparison p-value***	0.13		0.22		0.14	
Reader 2						
Number of Lesions*	180	274	180	274	180	274
Number of Pre-dose Lesions	106	145	106	145	106	145
Number of Post-dose Lesions	170	256	170	256	170	256
Pre-dose Mean (s.d.)	1.2 (1.2)	1.0 (1.1)	1.3 (1.2)	1.2 (1.2)	1.4 (1.3)	1.2 (1.2)
Post-dose Mean (s.d.)	2.5 (1.2)	2.6 (1.2)	2.5 (1.2)	2.6 (1.1)	2.6 (1.1)	2.7 (1.1)
Mean Change (s.d.)	1.3 (1.3)	1.5 (1.4)	1.2 (1.3)	1.5 (1.4)	1.2 (1.4)	1.5 (1.4)
p-value**	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Dose comparison p-value***	0.56		0.38		0.30	
Reader 3						
Number of Lesions*	171	259	171	259	171	259
Number of Pre-dose Lesions	112	127	112	127	112	127
Number of Post-dose Lesions	152	248	152	248	152	248
Pre-dose Mean (s.d.)	1.3 (1.1)	1.0 (1.2)	1.6 (1.4)	1.2 (1.4)	1.4 (1.2)	1.1 (1.2)
Post-dose Mean (s.d.)	2.5 (1.3)	2.9 (1.1)	2.9 (1.3)	3.2 (1.0)	2.7 (1.3)	3.1 (1.0)
Mean Change (s.d.)	1.2 (1.5)	1.9 (1.4)	1.3 (1.7)	2.0 (1.6)	1.3 (1.5)	2.0 (1.5)
p-value**	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Dose comparison p-value***	0.21		0.21		0.16	

Source: Sponsor Tables 3-36, 3-37, and 3-38, pages 200 to 201, Vol.24 and Table B, page 5, Vol. 1 of Dec. 9, 2003: Response to Request of Nov.19, 2003
* Number of lesions used in the "All Lesions" analysis.
** p-value based on paired t-test for the change from pre-dose to post-dose.
*** p-value for the pre-dose to post-dose changes based on ANCOVA with treatment group as a fixed effect and pre-dose score as a covariate.

Table 3.6 presents the distribution of changes from pre-dose in the number of lesions detected for subjects with two or fewer lesions seen at pre-dose. For all readers and doses, the majority of subjects (>50%) had no change. For each dose, there are more subjects with additional lesions seen post-dose for all blinded readers. Also, there is no difference between the two doses (all $p \geq 0.10$) for each blinded reader.

Table 3.6
Study MH-106: Distribution of Changes from Pre-dose in the Number of Lesions Detected for Subjects with Two or Fewer Lesions Detected at Pre-dose.

Change in number of lesions from pre-dose to post-dose	Reader 1		Reader 2		Reader 3	
	Multihance 0.05 mmol/kg	Multihance 0.1 mmol/kg	Multihance 0.05 mmol/kg	Multihance 0.1 mmol/kg	Multihance 0.05 mmol/kg	Multihance 0.1 mmol/kg
No. of Subjects (%)	**71**	**66**	**68**	**59**	**66**	**62**
-1	4 (5.6)	1 (1.5)	1 (1.5)	1 (1.7)	2 (3.0)	1 (1.6)
0	39 (54.9)	34 (51.5)	37 (54.4)	27 (45.8)	40 (60.6)	31 (50.0)
1	20 (28.2)	14 (21.2)	15 (22.1)	14 (23.7)	12 (18.2)	14 (22.6)
2	5 (7.0)	10 (15.2)	11 (16.2)	10 (16.9)	7 (10.6)	10 (16.1)
3	2 (2.8)	1 (1.5)	2 (2.9)	3 (5.1)	4 (6.1)	1 (1.6)
4	0	3 (4.5)	1 (1.5)	0	0	1 (1.6)
≥ 5	1 (1.4)	3 (4.5)	1 (1.5)	4 (6.8)	1 (1.5)	4 (6.5)
No. of subjects with more lesions seen post-dose (%)	28 (39.4)	31 (47.0)	30 (44.1)	31 (52.5)	24 (36.4)	30 (48.4)
Dose comparison p-value*	0.10		0.28		0.15	

Source: Based on Sponsor Table 17a, pp. 073-075, Vol. 34.
* p-value based on Wilcoxon Rank Sum test, which ignores zero change cases.

Study design deficiencies are other important information that needs to be taken into account when interpreting the overall results. These deficiencies and reasons for their importance are listed below:

- There is no standard of truth utilized, so one is not sure if lesions seen are real or artifacts.
- Investigators did not acquire all standard pre-dose MRI sequences (T_1, T_2, PD) for all subjects. The PD sequence was not acquired based on investigator discretion. This was an issue in the previous submission and listed as a deficiency in the Action letter of May 24, 2002.

This reviewer has no additional issues with the way the data have been analyzed by the Sponsor and concludes that no further analysis is necessary.

3.1.3 Study MH-112

This reviewer has no additional issues with the way the data have been analyzed by the Sponsor and concludes that no further analysis is necessary.

3.2 Evaluation of Safety

There is no statistical evaluation of safety necessary for this review. For information, reference the clinical review evaluation of safety section.

4. FINDINGS IN SUBGROUP POPULATIONS

5. CONCLUSIONS

Principal study MH-105 in adults is not statistically significant for the primary efficacy analysis while studies MH-106 in adults and ——— are statistically significant for the primary efficacy analysis. These results plus original design deficiencies do not show consistent evidence of efficacy for either the 0.05 mmol/kg or 0.1 mmol/kg dose of Multihance for use in MR imaging of the CNS in —— adult ———

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

/s/

Sonia Castillo
3/3/04 04:05:32 PM
BIOMETRICS

Mike Welch
3/9/04 10:36:14 AM
BIOMETRICS
Concur with review.

04/30/02

Addendum to The Statistical Review and Evaluation - NDA Review

NDA#:	21-357
SPONSOR:	Bracco Diagnostics Inc.
DRUG:	MultiHance (gadobenate dimeglumine injection)
INDICATION:	Intravenous MRI Contrast Agent for CNS [redacted]
DOCUMENTS REVIEWED:	
DATE:	New submission received by Medical Division (Stamp Date): March 18, 2002
PDUFA DATE:	February 27, 2002
STATISTICAL REVIEWER:	Shahla S. Farr, M.S., HFD 715
MEDICAL REVIEWERS:	Roger Li, M.D., HFD 160
PROJECT MANAGER/CSO:	James Moore, HFD 160

STATISTICAL REVIEW AND EVALUATION

Introduction

This is an addendum to the statistical review for NDA 21-357, dated April 30, 2001, MultiHanc (gadobenate dimeglumine injection) Intravenous MRI Contrast Agent for CNS ———

The purpose of this addendum is to address the sponsor's concern regarding the agency's unacceptability of the clinical trials' results submitted in the original NDA.

The sponsor has submitted the results of one more study for the indication of CNS (Study BBG/701, in conjunction with additional analyses on the original data.

CNS Indication

Study BBG/701 (the new submission):

The title of this study was "Comparison of the Contrasting Behavior of Gd-BOPTA and Gd-DTPA in CNS Indication. This was a two-center, double-blind, randomized, intra-individual crossover comparison between Gd-BOPTA, 0.5 M and Gd-DTPA, 0.5 M.

A total of 24 patients were planned for the study. However 27 were entered and randomized into the trial. Out of which only 15 subjects were evaluable for efficacy analyses. Two independent, blinded readers assessed the efficacy.

The primary endpoints was "The Global Assessment of Contrast Enhancement, Summarizing the Contrasting Behavior of All post-CM Sequences". The readers compared the contrast enhancement in summary of all MR sequences on a continuous scale from –9 (MR session 1 better than session 2) over 0 (both equal) to 9 (MR session 2 better than session 1).

The investigators judged that Gd-BOPTA led to a better contrast enhancement in 11 patients, whereas, Gd-DTPA was better in only 1 subject.

Reviewer's Comment:
The primary endpoint is a technical endpoint and a subjective variable. The method of the analyses is unverified and inappropriate.

In addition, the study sample size is too small to draw any conclusions.

Studies 43,779-9A and 43,779-9B (the previously submitted studies):

Table 1 provides a brief description of these two studies.

Table 1: Pivotal, Phase 3 Studies for the CNS Indication

Study # (Location/# of Centers)	N (M/F) (W/B/O)	Study Design (Study start date)	Treatment Arm (n)	Endpoint
43,779-9A (USA/ 16 Centers)	206 (98/108) (177/17/12)	Double-blind, randomized, parallel-group (February 1997)	MultiHance 0.05 + 0.1(71) MultiHance 0.1 + 0.1(66) Omniscan (70)	% of patients whose "Level Of ——— Information" increased from pre-dose to paired post-first dose
43,779-9B (USA/ 12 Centers)	207 (105/102) (157/20/30)	Double-blind, randomized, parallel-group (April 1997)	MultiHance 0.05 + 0.1 (70) MultiHance 0.1 + 0.1(71) Omniscan (66)	% of patients whose "Level Of ——— Information" increased from pre-dose to paired post-first dose

For more details on these studies, please refer to the original Statistical and Medical reviews.

The sponsor has submitted the results of a retrospective Meta Analysis based on these two studies. In order to combine the two studies, the sponsor had to make some modification on the primary endpoint variable. For this reason, they combined the results from the two readers within each study. This was accomplished for each patient by counting the number of readers showing an increase in the "Level of ——— Information" (the primary endpoint in the two studies), namely, "Neither", "One" or "Both" readers. Then the results were combined across studies. The sponsor is claiming non-inferiority between MultiHance 0.1 and Omniscan 0.1 based on these results.

Sponsors' results of the combined studies based on the new endpoint was as follows (Page 25, of March 12, 2002 submission):

	MultiHance (0.1 mmol/kg) (N=131)	Omniscan (0.1 mmol/kg) (N=130)
Both Readers	32 (24%)	35 (27%)
One Reader	63 (48%)	59 (45%)
Neither Reader	36 (27%)	36 (28%)

Reviewer's Comment:
These results are not acceptable by this reviewer because:
1. The analyses are "Retrospective".
2. The sponsor is using the same subjective endpoint "Level of ——— Information" that was not acceptable by the agency in the original submission.
3. As it can be observed in the table above, although, 24% of subjects showed an increase in the level of ——— information according to both of the readers, but, 27% showed a decrease.

<u>Study B19036/020</u> (the metastatic study):

At the request of the medical division, a subset of the subjects in this study, namely, subjects with 0 or 1 lesions before CM and compared these numbers to their number of lesions observed after the first post CM.

This was a Phase 2 study with 144 subjects. The objective of this study was to evaluate the safety and efficacy of two different regiments of 3 incremental doses of Gd-BOPTA (0.05 + 0.05 + 0.1 mmol/kg and 0.1 + 0.1 + 0.1 mmol/kg) in MRI detection and evaluation of metastatic lesion in the CNS.

Increase in the number of lesions after the first post dose:
Reader # 1:
A total of 11 out of 73 (11/73=15%) subjects with number of lesions 0 or 1 at pre-dose had more lesions counted after the first post **0.05 mmol/kg** dose.

A total of 24 out of 71 (24/71=34%) subjects, in the **0.1 mmol/kg** arm, whose number of lesions was 0 or 1 at pre-dose, had more lesions observed after the first dose.

Reader # 2:
A total of 18 out of 73 (18/73=25%) subjects with number of lesions 0 or 1 at pre-dose had more lesions counted after the first post **0.05 mmol/kg** dose.

A total of 18 out of 73 (18/73=25%) subjects, in the **0.1 mmol/kg** arm, whose number of lesions was 0 or 1 at pre-dose, had more lesions observed after the first dose.

Decrease in the number of lesions after the first post dose:
Reader # 1:
A total of 6 out of 73 (6/73=8%) subjects with number of lesions 0 or 1 at pre-dose had less lesions counted after the first post **0.05 mmol/kg** dose.

A total of 4 out of 71 (4/71=6%) subjects, in the **0.1 mmol/kg** arm, whose number of lesions was 0 or 1 at pre-dose, had less lesions observed after the first dose.

Reader # 2:
A total of 7 out of 73 (7/73=10%) subjects with number of lesions 0 or 1 at pre-dose had less lesions counted after the first post **0.05 mmol/kg** dose.

A total of 6 out of 73 (6/73=8%) subjects, in the **0.1 mmol/kg** arm, whose number of lesions was 0 or 1 at pre-dose, had less lesions observed after the first dose.

Reviewer's Comments:
As it can be noted in the preceding results, more lesions were observed by both readers after the first dose as opposed to the pre-dose.

Conclusions for the CNS Studies:
The following issues summarize the concerns of this reviewer for the efficacy of MultiHance for the indication of CNS. It should also be noted that the definitions of the primary endpoint variables used in each of these studies are different from each other. Therefore, it is not possible to make a conclusion for all the studies as a whole.

Study BBG/701 (the new submission):
The study sample size is too small, therefore, not enough power to conduct any statistical analyses or draw any conclusions. In addition, the primary endpoint is a subjective variable.

Studies 43,779-9A and 43,779-9B (the previously submitted studies):
1. The analyses are "Retrospective".
2. The sponsor is using the same subjective endpoint "Level of ——— Information" that was not acceptable by the agency in the original submission.
3. As it can be observed in the table above, although, 24% of subjects showed an increase in the level of ——— information according to both of the readers, but, 27% showed a decrease.

Study B19036/020 (the metastatic study):
As it can be noted in the preceding results, more lesions were observed by both readers after the first dose as opposed to the pre-dose.

[redacted]

Shahla S. Farr
Mathematical Statistician, HFD-715

Concur:

Michael Welch, Ph.D.
Team Leader

Statistical Review and Evaluation - NDA Review

NDA#:	21-357
SPONSOR:	Bracco Diagnostics Inc.
DRUG:	MultiHance (gadobenate dimeglumine injection)
INDICATION:	Intravenous MRI Contrast Agent for CNS ———
DOCUMENTS REVIEWED:	NDA Volumes 1 and 1.241 through 1.336 and Electronic Database
DATE:	Date received by Medical Division (Stamp Date): April 30, 2001
PDUFA DATE:	February 27, 2002
STATISTICAL REVIEWER:	Shahla S. Farr, M.S., HFD 715
MEDICAL REVIEWERS:	Roger Li, M.D., HFD 160
PROJECT MANAGER/CSO:	James Moore, HFD 160

Key words: NDA Review, Clinical Studies, Equivalence (Clinical), ——— Accuracy

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1. EXECUTIVE SUMMARY OF STATISTICAL FINDINGS[1]

This NDA is intended to support claims that MultiHance (gadolinium dimeglumine) is a safe and effective contrast agent for Magnetic Resonance Imaging (MRI) of the Central Nervous System (CNS). The sponsor submitted 21 CNS studies. However, only four CNS studies are identified as "key" or principal studies by the sponsor and by the reviewers. The reader is referred to the medical officer's review for discussion of the complete efficacy and safety data base.

For the CNS indication, the sponsor proposes that MultiHance provides "additional information" over that observed with unenhanced MRI images and that the enhanced images contribute to detection of CNS lesions in adult suspected of having CNS lesions. Primary endpoints focused on the reader's (subjective) confidence in making; secondary endpoints included numbers of lesions observed.

1.1 Overview of CNS Imaging Trials

The sponsor submitted four, key studies in support of a proposed dose of 0.1 mmol/kg for intravenous use in adults as an adjunct to (unenhanced) Magnetic Resonance Imaging (MRI) of the Central Nervous System (CNS) (brain, spine and surrounding structures).

Studies 43,779-9A and -9B

Two trials in adults suspected of having CNS lesions were identically designed as double-blind, randomized, parallel-group, multicenter studies with three arms: MultiHance at sequential doses of 0.05 and 0.1 mmol/kg; MultiHance at sequential doses of 0.1 and 0.1 mmol/kg; and Omniscan at sequential doses of 0.1 and 0.2 mmol/kg, respectively. Each study consisted of 205 evaluable subjects. The primary study objectives were to compare efficacy and safety of first dose effects as well as cumulative dose effects. The primary patient outcome, which was modified for the blinded read, was defined as "level of Information" rated on a three-point, categorical scale 'responders' were defined as patients whose rating increased from baseline (unenhanced) image sets to pre-dose plus post-first dose image sets, as evaluated by two, independent blinded readers. Thus a possible "multiple image" bias may exist from combining pre and post-dose images when evaluating the treatment effect. No assessment was made from post-dose images alone.

The sponsor proposed a non-inferiority hypotheses intending to show that the responder rate for the MultiHance groups was not inferior to the Omniscan responder rate. However, the analysis, based on a confidence interval approach, failed to consistently support this non-inferiority hypothesis across readers and doses. The reviewer's analysis did show, however, that MultiHance images indicate a statistically significant positive shift in the endpoint "level of Information" from pre-dose to 1st post-dose for both readers and doses. This shift may be indicative of a "contrast effect" in terms of a image quality. However, it is not clear how such as result can be interpreted for labeling purposes.

The primary outcome (level of information) is a subjective endpoint that was not externally verified. For example, an rating indicates that the reader was able to make a with high confidence. However, any diagnoses were not based on prospectively criteria nor were they compared to any truth standard result. Thus the image rating (hence magnitude of change between treatment groups) is only relative and lacks validity as well as reproducibility. Potential bias introduced by subjective assessments are a major concern in any kind of study; in a non-inferiority study, the problem is confounded as such endpoints lack assay sensitivity. Thus, on the basis of the primary endpoint alone, these studies are fundamentally flawed as confirmatory trials.

1 The executive summary was written by the primary and secondary reviewers.

The sponsor's proposed indication also claimed benefit regarding lesion detection
As a secondary analysis, the means for the total number of the lesions for pre and post-dose images were compared; however, no statistically significant differences between the means were indicated.

Study B19036/020

In this double-blind, parallel group, European study, 150 adult subjects with known malignancies and metastatic disease were randomized to receive one of two dose sequences: 0.05 + 0.05 + 0.1 or 0.1 + 0.1 + 0.1 mmol/kg administered at 10 minute intervals. Two off-site readers, blinded to patient histories and image dose and injection number rated pre-contrast images, post-contrast images (separately by injection) and all images combined. The primary endpoint was a lesion
of interest selected by on-site investigators. The blinded readers looked at secondary endpoints including number of lesions detected, technical adequacy, confidence in detection, and lesion conspicuity. The signal to noise measurements showed an increasing dose response with accumulation of dose, although dose timing appeared to be a critical factor regarding enhancement (see the medical officer's discussion). Such an endpoint is purely a technical one, however, and insufficient for identifying specific clinical benefit. The sponsor's analysis of change in the number of lesions detected was basically flawed since lesion tracking was not performed across the incremental doses; moreover, simple numbers of lesions is not a clinically meaningful endpoint according to the medical officer; a more meaningful indication of efficacy would include showing increases from zero or one lesion to more than one. Such an analysis should also provide appropriate validation of number through an independent truth standard result. Overall, this study provides observational data on contrast effect, and any prospective intent to support a specific dose and timing sequence is unclear.

Study B19036/036

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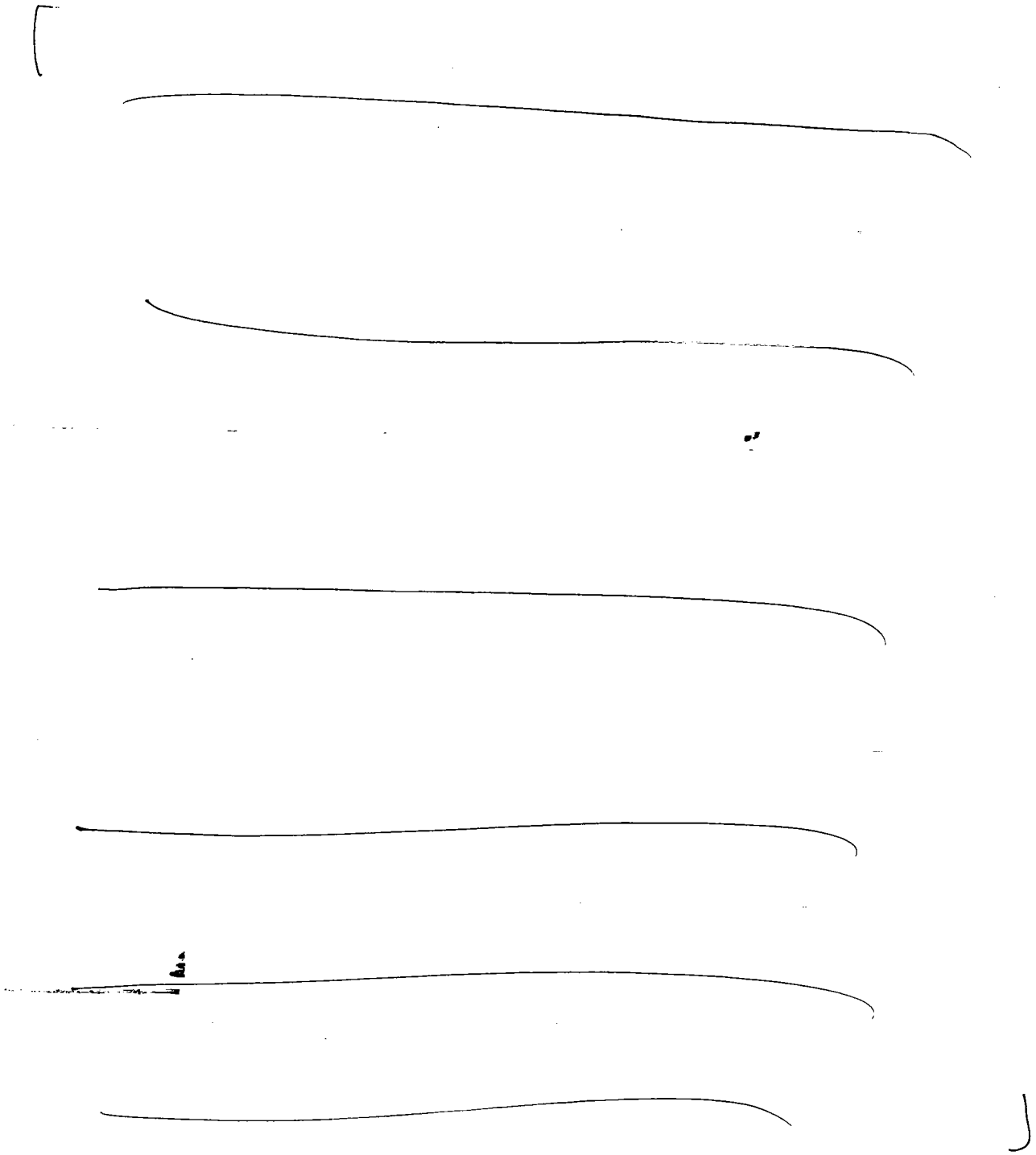
_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling



1.3 Summary and Recommendations

CNS. From a statistical perspective, the sponsor's principal studies have critical design flaws that undermine any confirmatory conclusion supporting efficacy of the drug product. The major shortcoming centers on the lack of objective and clinically relevant primary endpoints. The latter, based primarily on

the image reader's [redacted]. In particular, the sponsor's noninferiority approach, comparing MultiHance and Omniscan percentages of patients whose images showed increased [redacted] from pre-contrast to post-contrast images sets, lacks assay [redacted]
Even at face value, the results fail to be statistically significant across readers and test doses. The reviewer's exploratory analysis, however, does show a consistent trend or shift in the information score between non-contrast and post-dose images alone which may be indicative of an image enhancement effect.

Secondary benefits claimed regarding CNS lesion detection [redacted] are also unsupportable as the sponsor's analyses, largely based on simple numbers of lesions visualized, are uninformative and fail to show specific added value of the post-contrast images. This is especially relevant as the studies did not employ prospective and clearly defined methods to identify and track lesions across the various image sets.

[redacted]

2. STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 Introduction

The sponsor has submitted the results of six principal trials in support of the efficacy of MultiHance for the indication of:

1. Intravenous use in adults [redacted], as an adjunct to Magnetic Resonance Imaging (MRI) of the Central Nervous System (CNS) (brain, spine and surrounding structures) [redacted]

Reviewer's Comment:
In the review of this submission, the emphasis has been on efficacy results. The safety review can be found in the clinical reviewer's report.

2.2 CNS Indication

The two adult studies (Studies 43,779-9A and 43,770B) for the indication of CNS had identical study design, study objectives, patient population, primary and secondary efficacy endpoints and statistical methodology. Table A provides a brief description of these two studies.

Table A: Pivotal, Phase 3 Studies for the CNS Indication

Study # (Location/# of Centers)	N (M/F) (W/B/O)	Study Design (Study start date)	Treatment Arm (n)	Endpoint
43,779-9A (USA/ 16 Centers)	206 (98/108) (177/17/12)	Double-blind, randomized, parallel-group (February 1997)	MultiHance 0.05 + 0.1(71) MultiHance 0.1 + 0.1(66) Omniscan (70)	% of patients whose "Level Of [redacted] Information" increased from pre-dose to paired post-first dose
43,779-9B (USA/ 12 Centers)	207 (105/102) (157/20/30)	Double-blind, randomized, parallel-group (April 1997)	MultiHance 0.05 + 0.1 (70) MultiHance 0.1 + 0.1(71) Omniscan (66)	% of patients whose "Level O[redacted] Information" increased from pre-dose to paired post-first dose

Objectives

The primary objectives of these studies were:

- To compare the safety of two cumulative doses of MultiHance (0.15 and 0.2 mmol/kg, respectively) and one cumulative dose of gadodiamide (Omniscan) (0.3 mmol/kg) for magnetic resonance imaging of CNS lesions.

- To compare the [redacted] information obtained from pre and post first dose MultiHance (0.05 and 0.1 mmol/kg, respectively) images with that obtained from pre and post first dose Omniscan (0.1 mmol/kg) images in parallel patient groups.

Design

Both studies were Phase III, double-blind, multicenter, randomized, parallel-group comparative studies in patients highly suspected of having a lesion (or lesions) of the CNS as indicted by a comparative procedure conducted prior to the studies.

Patients were randomized to receive one of the three incremental dosing regimens:
0.05 mmol/kg followed by 0.1mmol/kg of MultiHance

0.1 mmo1/kg followed by 0.1 mmol/kg of MultiHance
0.1 mmol/kg followed by 0.2 mmol/kg of Omniscan

These studies were designed to test the hypotheses that Multihance was not inferior to a currently available extracellular MRI contrast agent, Omniscan.

Patient Population & Randomization

Approximately 200 patients were to be enrolled at approximately 16 sites. Each site was to enroll a minimum of 9 and maximum of 36 patients. Each patient who met the inclusion criteria and none of the exclusion criteria was assigned a screening number and was randomized to receive one of three incremental dose regimens:

0.05 and mmol/kg followed by 0.1 mmol/kg of MultiHance
0.1 mmol/kg followed by 0.1 mmol/kg of MultiHance
0.1 mmol/kg followed by 0.2 mmol/kg of Omniscan

The randomization schedule was stratified according to the patient's suspected pathology (metastatic vs. non-metastatic lesions) based on all available clinical information.
A patient number was assigned as follows:

- For patients suspected of having metastases, the lowest number available from the randomization schedule was assigned
- For patients suspect of having lesions of the CNS other than metastases, the highest number available from the randomization schedule was assigned.

A block size of three was used to generate the randomization schedule.

Reviewer's Comment:
The sponsor had not provided the specific method of randomization in advance, in the protocol. This method of randomization may be subject to treatment bias.

Image Viewing Strategy

Two independent readers that were unfamiliar with the history and prior MR images of the patients were to review the images (Vol. 242, Page 10 43). The off-site assessments contained both unmatched (i.e., pre-dose images) and matched pair (i.e., pre-dose and post-dose images) review sessions. For each block of images the unmatched review session was completed prior to executing the matched session. The pre-dose T1wSE, proton density and T2wSE or T2wFSE images were randomized by patient numbers for the unmatched assessments. Each patient had two randomization numbers for the matched assessment, one for the pre-dose plus post-first dose image set, and another for the pre-dose plus post-second dose image set. The matched pairs assessments were randomized by patient number and dose.

Primary & Secondary Efficacy Endpoints

In the protocol (Vol. 1.243, Page 10 163), the primary efficacy endpoint has been defined as:

[redacted]

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_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Secondary Efficacy Results:

Table I: Change From Un-Enhanced To Contrast-Enhanced MRI In The Total Number Of Lesions Detected Per Patient (Sponsor's Analyses, Vol.328, Page 10 43) (T1 pre vs. T1 post)

	No. (%) of Patients					
	MultiHance N=80			Magnevist N=90		
	Decrease	No Change	Increase	Decrease	No Change	Increase
Reader # 1	19 (24%)	45 (56%)	16 (20%)	12 (15%)	46 (56%)	24 (29%)
Reader # 2	17 (21%)	41 (51%)	22 (28%)	13 (16%)	49 (60%)	20 (24%)

Reviewer's Comment:
As it is seen in the sponsor's Table, the majority of patients did not have any change from pre-contrast to post-contrast for both treatment arms and Readers (between 51% to 60%). Reader # 1 showed a higher decrease (24%) than increase (20%) for MultiHance treatment arm. Also, Reader # 1 showed a larger increase (29%) and smaller decrease (15%) for Magnevist treatment group.

[ ]

2.2.1.4 Study B19036/20

Objective:

The objectives of this study were: to evaluate the safety and efficacy of Gd-BOPTA in MRI detection of metastatic lesions in the CNS. Efficacy was assessed in terms of:

1. Change from un-enhanced to Gd-BOPTA enhanced MRI [ ] Percent enhancement,
2. Number and size of metastatic lesions detected,
3. Confidence in lesion detection and
4. Lesion Conspicuity

Dose:

Gd-BOPTA administered as 3 intravenous bolus injections, 10 minutes intervals over a total period of 20 minutes, to each patient:
Regimen 1: 0.05 mmol/kg + 0.05 mmol/kg + 0.1 mmol/kg for a cumulative dose of 0.2 mmol/kg or
Regimen 2: 0.1 mmol/kg + 0.1 mmol/kg + 0.1 mmol/kg for a cumulative dose of 0.3 mmol/kg

Study Design:

This was a Phase 2 study consisting of a:

- Randomized, double-blind, parallel-group comparison of two different incremental dose regimens of the test compound,
- Prospective, double-blind, within patient comparison of different dose level of the test compound,
- Prospective, open-label, within patient comparison of un-enhanced and contrast-enhanced MRI.

Off-site quantitative efficacy assessment was performed by one experienced radiologist not affiliated with the study centers and blinded to patients' identities, clinical profile and dose of Gd-BOPTA administrated. Off-site qualitative efficacy assessment was performed by two neuroradiologists not affiliated with the study centers and blinded to patients' identities, clinical profile and dose of Gd-BOPTA administered.

Patient Population:

A total of 154, 76 for regimen 1 and 78 for regimen 2 enrolled into the study. Out of which 150, 74 for regimen 1 and 76 from regimen 2 were dosed and 148, 74 in each regimen were analyzed qualitatively and 137, 68 from regimen 1 and 69 in regimen 2 quantitatively.

Main Inclusion Criteria:

Proven malignancy outside the CNS and intraaxial metastatic disease to the CNS, i.e., 1 to 8 lesions already diagnosed by means of either an MRI examination with a marketed gadolinium compound at the approved dose routinely used by the center for this indication, or by contrast-enhanced CT performed within 30 to 2 days before Gd-BOPTA administration, or
unknown malignancy and intraaxial metastatic disease to the CNS, i.e., 1 to 8 lesions proved by biopsy performed after either GD-REF MRI or contrast-enhanced CT.

Methods:

Each patient underwent MR scanning before Gd-BOPTA administration and after each Gd-BOPTA injection. The complete MR examination consisted of 5 sets of images: pre-contrast T1 and T2 weighted SE images and first, second and third post-contrast T1 weighted SE images. Post-contrast images were acquired immediately after each Gd-BOPTA injection.

Primary Efficacy Endpoint:

Secondary Efficacy Endpoints:

1. Quantitative evaluation based on the percent enhancement,
2. Qualitative assessment based on:
   - Lesion count,
   - Average confidence in lesion detection/exclusion per patient,
   - Size of the smallest lesion detected,
   - Matched pairs assessment (un-enhanced vs. Gd-BOPTA enhanced) of confidence in lesion detection/exclusion,
   - Lesion conspicuity

Statistical Methods:

Quantitative variables (lesion percent enhancement) were analyzed within each regimen using ANOVA to compare doses and to test for a dose response in cumulative dose. Within each regimen a post hoc analysis of changes from baseline in lesion counts, as well as changes with successive doses were tested using the Sign Test.

Sponsor's Results:

Reviewer's Comments:

Lesion Count: The two off-site readers reported an in crease form baseline in lesion counts in 22% and 29% of patients following the first dose of Gd-BOPTA in regimen 1 (0.05 mmol/kg) and in 31% and 33% of patients following the first dose in regimen 2 (0.1 mmol/kg). For both regimens, there was an addition increase in lesion count after the second dose compared to the first dose.

Reviewer's Comments:

The sponsor's analysis of "change in the number of lesions" was basically flawed since lesion tracking was not performed across the incremental doses; moreover, simple numbers of lesions is not a clinically meaningful endpoint according to the medical officer; a more meaningful indication of efficacy would include showing increases from zero or one lesion to more than one.

Overall, this study provides observational data on contrast effect

2.2.2 **Conclusions for the CNS Studies:**

The following issues summarize the concerns of this reviewer for the efficacy of MultiHance for the indication of CNS:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- In regards to the number of lesions (the secondary endpoint), the pre-dose was compared to the post 1st dose. The means for the total number of the lesions for pre and post-dose were examined. No statistically significant results between the means were found when the post-dose images were compared with pre-dose.
- The randomization schedule may be subject to treatment bias.
- [redacted]
- Regarding the secondary endpoint variable (change from un-enhanced to contrast-enhanced MRI in the total number of lesions detected per patient), the majority of patients did not have any change from pre-contrast to post-contrast for both treatment arms and Readers (between 51% to 60%). Reader #1 showed a higher decrease (24%) than increase (20%) for MultiHance treatment arm. Also, Reader #1 showed a larger increase (29%) and smaller decrease (15%) for Magnevist group.
- [redacted]

ST-3

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Appendix I:
Results of the Analyses of the Efficacy Data for Study 43,779-9A

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ST-4

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The Secondary Efficacy Endpoint, The Number of Lesions:
The purpose of this section of the review is to determine if the number of lesions detected by each reader was significantly more after the first and second dose as compare to the pre-dose for each treatment arm individually.

It should be noted that there was no matching of the lesions in the reporting of these numbers. In other words, the lesions reported by each reader at post doses had not been matched with the exact lesions at the pre-dose. Therefore, one might have missed a lesion that was seen in the first MRI, in the 2nd scan.

The following results were estimated based on one way ANOVA. However, the analyses were repeated using Wilcoxon Rank Sum test. The results were similar.

MultiHance 0.15:

Table 8: Number of the Lesions: Mean±Std for Pre and Post & Related P-Values

Reviewer # 1 N=71						Reviewer # 2 N=71					
Pre-Dose (138)*	Post 1st Dose (148)	Post 2nd Dose (159)	P-Value** Pre Vs. Post1st	Pre Vs. Post2nd	Post1st Vs. Post2nd	Pre-Dose (153)	Post 1st Dose (198)	Post 2nd Dose (188)	P-Value Pre Vs. Post1st	Pre Vs. Post2nd	Post1st Vs. Post2nd
1.9±2.7	2.08±2.8	2.2±2.9	0.8	0.5	0.7	2.2±2.8	2.8±3.4	2.7±3.2	0.2	0.3	0.8

*Total number of the lesions
**Based on one way ANOVA test, with contrast

As it can be observed from Table 8, although the number of lesions observed by reader #1 increased from pre to post 1st and post 2nd doses, but, these increases were not statistically different ($p \geq 0.5$).

As a whole, Reader #2 observed more lesions than the Reader #1. In this case, the total number of lesions seen by Reader #2 at 2nd post dose was more than the pre-dose. However, after the 2nd dose, Reader #2 saw less lesions than the post 1st dose. These differences were not statistically significant ($p \geq 0.2$).

MultiHance 0.2:

Table 9: Number of the Lesions: Mean±Std for Pre and Post & Related P-Values

Reviewer # 1 N=65						Reviewer # 2 N=65					
Pre-Dose (168)*	Post 1st Dose (183)	Post 2nd Dose (174)	P-Value: Pre Vs. Post1st	P-Value: Pre Vs. Post2nd	P-Value: Post1st Vs. Post2nd	Pre-Dose (187)	Post 1st Dose (227)	Post 2nd Dose (226)	P-Value: Pre Vs. Post1st	P-Value: Pre Vs. Post2nd	P-Value: Post1st Vs. Post2nd
2.6±3.2	2.8±3.1	2.7±3.0	0.7	0.9	0.8	2.9±3.4	3.5±3.8	3.5±3.7	0.3	0.3	0.9

*Total number of the lesions

As it is shown in Table 9, again, as a whole, Reader #2 observed more lesions than the Reader #1. But, in this case, the total number of lesions seen by both Reviewers at 2nd post dose was more than the pre-dose. However, after the 2nd dose, both Readers saw less lesions than the post 1st dose. These differences, however, were not statistically significant ($p \geq 0.3$).

Omniscan 0.3:

Table 10: Number of the Lesions: Mean±Std for Pre and Post & Related P-Values

Reviewer # 1 N=66						Reviewer # 2 N=68					
Pre-Dose (144)*	Post 1st Dose (139)	Post 2nd Dose (153)	P-Value: Pre Vs. Post1st	P-Value: Pre Vs. Post2nd	P-Value: Post1st Vs. Post2nd	Pre-Dose (181)	Post 1st Dose (190)	Post 2nd Dose (205)	P-Value: Pre Vs. Post1st	P-Value: Pre Vs. Post2nd	P-Value: Post1st Vs. Post2nd
2.2±2.8	2.1±2.8	2.3±2.9	0.9	0.8	0.7	2.7±3.3	2.8±3.4	3.0±3.4	0.8	0.5	0.7

*Total number of the lesions

No statistically significant differences were found when the mean total number of lesions were compared among the different time points for either of the reviewers ($p \geq 0.5$).

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Appendix II:
Results of the Analyses of the Efficacy Data for Study 43,779-9B

ST-5

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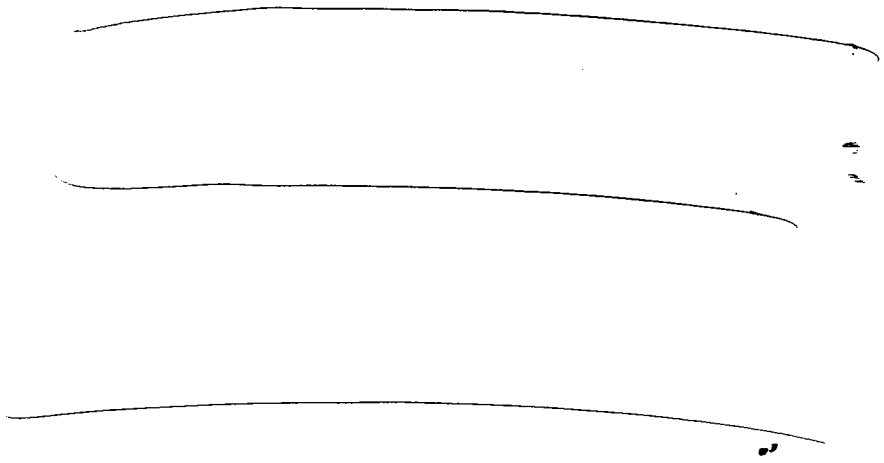

The Secondary Efficacy Endpoint, The Number of Lesions:

The purpose of this section of the review is to determine whether or not the number of lesions detected by each reader was significantly more after the first and second dose as compare to the pre-dose for each treatment arm individually.

It should be noted that there was no matching of the lesions in the reporting of these numbers. In other words, the lesions reported by each reader at post doses had not been matched with the exact lesions at the pre-dose. Therefore, one might have missed a lesion that was seen in the first MRI, in the 2nd scan.

MultiHance 0.15:

Table 18: Number of the Lesions: Mean±Std for Pre and Post and Related P-Values Study 43,779-9B

Reviewer # 1 N=67						Reviewer # 2 N=66					
Pre-Dose (105)*	Post 1st Dose (122)	Post 2nd Dose (122)	P-Value Pre Vs. Post1st	P-Value Pre Vs. Post2nd	P-Value Post1st Vs. Post2nd	Pre-Dose (97)	Post 1st Dose (139)	Post 2nd Dose (125)	P-Value Pre Vs. Post1st	P-Value Pre Vs. Post2nd	P-Value Post1st Vs. Post2nd
1.6±2.2	1.8±2.3	1.9±2.4	0.5	0.4	0.9	1.5±1.9	2.1±2.4	1.9±2.3	0.1	0.2	0.7

*Total number of the lesions

As it can be observed from Table 18, although the number of lesions observed by reader #1 increased from pre to post 1st and post 2nd doses, but, these increases were not statistically different ($p \geq 0.5$).

As a whole, Reader #2 observed more lesions than the Reader #1. In this case, the total number of lesions seen by Reader #2 at 2nd post dose was more than the pre-dose. However, after the 2nd dose, Reader #2 saw less lesions than the post 1st dose. These differences were not statistically significant ($p \geq 0.2$).

MultiHance 0.2:

Table 19: Number of the Lesions: Mean±Std for Pre and Post and Related P-Values Study 43,779-9B

Reviewer # 1 N=67						Reviewer # 2 N=68					
Pre-Dose (110)*	Post 1st Dose (131)	Post 2nd Dose (136)	P-Value Pre Vs. Post1st	Pre Vs. Post2nd	Post1st Vs. Post2nd	Pre-Dose (131)	Post 1st Dose (149)	Post 2nd Dose (159)	P-Value Pre Vs. Post1st	Pre Vs. Post2nd	Post1st Vs. Post2nd
1.6±2.2	2±2.4	2±2.4	0.4	0.3	0.9	1.9±2.2	2.2±2.4	2.3±2.4	0.5	0.3	0.7

*Total number of the lesions

As it is shown in Table 19, again, as a whole, Reader #2 observed more lesions than the Reader #1. But, in this case, the total number of lesions seen by both Reviewers at 2nd post dose was more than the pre-dose. However, after the 2nd dose, both Readers saw less lesions than the post 1st dose. These differences, however, were not statistically significant (p≥0.3).

Omniscan 0.3:

Table 20: Number of the Lesions: Mean±Std for Pre and Post and Related P-Values Study 43,779-9B

Reviewer # 1 N=65						Reviewer # 2 N=65					
Pre-Dose (100)*	Post 1st Dose (135)	Post 2nd Dose (136)	P-Value Pre Vs. Post1st	Pre Vs. Post2nd	Post1st Vs. Post2nd	Pre-Dose (177)	Post 1st Dose (189)	Post 2nd Dose (211)	P-Value Pre Vs. Post1st	Pre Vs. Post2nd	Post1st Vs. Post2nd
1.5±2.4	2.1±2.6	2.1±2.6	0.2	0.2	0.9	2.7±3.3	2.9±3.2	3.2±3.4	0.8	0.4	0.6

*Total number of the lesions

No statistically significant differences were found when the mean total number of lesions were compared among the different time points for both of the reviewers (p≥0.1).