similar to the mean cumulative urinary excretion that is observed in patients with moderate or severe renal impairment (see Table #6 below).

Table #6 Patients with Renal Impairment or on Dialysis

	Renal Function (CrCL mL/min)			
	Normal >60 volunteers[1]	Moderate 30 to ≤ 60 n=9	Severe 10 to ≤ 30 n=11	Dialysis <10 n=11
Elimination Half-Life (hrs)	2.0	6.1	9.5	1.2[2]
Renal Clearance (L/hr/kg)	0.143	0.039	0.015	NA
Total Body Clearance (L/hr/kg)	0.158	0.041	0.021	NA
Mean Cumulative Urinary Excretion	87%	74%	69%	72%[2,3]
Mean Cumulative Fecal Excretion	1.9%	5.6%	7.7%	NA

[1]historical controls
[2]value with dialysis
[3]mean % of administered dose of Gd found in the dialysate fluid.
NA=not available or applicable

The sponsor concludes that: "as MultiHance is given as a single IV bolus dose only, accumulation is not of concern in patients with renal impairment. Thus, dosage adjustment is not considered necessary in patients with impaired renal function". [pg 222 volume 1 of the NDA submission]

MO Comment: The sponsor's conclusion states that MultiHance is given as a bolus only and as a single dose.

In study 43,779-4, the urinary excretion of zinc and iron was evaluated. The concentration of iron in urine was below the limit of quantification for the assay. An increase in zinc urinary excretion was observed. There was an approximately five-fold increase in the quanitity of zinc excreted in the urine in the 24 hours period following administration of MultiHance for both moderate and severe renally impaired patients when compared to patients who received placebo. The sponsor compares the mean zinc excretion value for another gadolinium MRI agent in normal subjects at 3 hours post-dose (27.4 µmmol) to a calculated (adjusted for renal impairment) mean value of 25.4 µmmol for MultiHance. The sponsor, therefore, concludes that zinc excretion is comparable to other gadolinium MRI agents.

MO Comment: The sponsor should have evaluated zinc excretion in normal healthy volunteers following MultiHance administration at 3 hours or should have included a comparison gadolinium MRI agent into their renal impairment study, in order to make their claim of equivalence less dependent upon the assumptions that are used for the adjustment calculation.

The sponsor performed statistical analyses of the effect of gender on weight normalized creatinine clearance and found no significant difference (both were approximately 0.20 L/hr/kg).

B. Hepatic Impairment

Study 43,779-8

In study 43,779-8, 11 US patients with hepatic impairment (Class B or C) were given 0.1 mmol/kg of 0.5M formulation of MultiHance over approximately 1 minute and 5 were given placebo. Values were compared to that found for normal healthy volunteers.

From the resulting values (summarized in Table #7), the sponsor concluded that the distribution characteristics of MultiHance do not appear to be influenced by hepatic failure and that hepatic impairment has little effect on the pharmacokinetics of MultiHance.

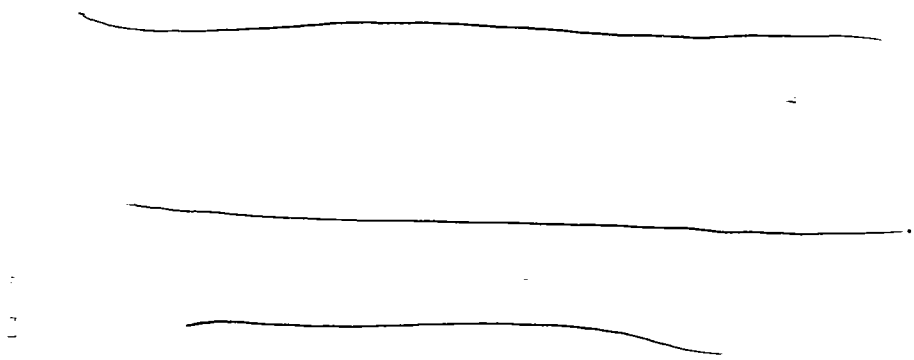
MO Comment: The sponsor did not provide a sub-analysis by degree of hepatic impairment (type B versus C).

Table #7 Impaired Hepatic Function and Pediatrics

	Hepatic Function		Pediatrics	
	Normal Volunteers	Impaired N=11	Normal Adults Volunteers	2 to < 16 yrs n=25
Volume of Distribution (L.kg)*	0.35	0.28	0.12	0.17
Elimination Half-Life (hrs)	1.81	2.06	1.21	1.51
Renal Clearance (L/hr/kg)	0.143	0.106	NR	NP
Total Body Clearance (L/hr/kg)	0.158	0.128	0.16	0.20
Mean Cumulative Urinary Excretion	86%	80%	86%	91%
Mean Cumulative Fecal Excretion	1.9%	NP	1.9%	NP

*For the hepatic study (for the steady state), for the pediatric study (of the central compartment)
NR=not reported
NP=not performed

C.



D. Dissociation

Study B19036/034

In study B19036/034, the chelating agent BOPTA, was assayed in plasma, urine, and feces. The results of the assays showed that the cumulative percentage of the injected dose eliminated in the urine and in the feces as BOPTA, was between 1.5% to 2.3% and less than 0.71% for urine and feces, respectively. The sponsor concludes that the gadobenate ion dose not dissociate from the complex in vivo.

IV. Description of Clinical Data and Sources

A. Overall Data

The sources for this NDA review consist of 83 (9 US, 63 European and 11 Japanese) clinical trials that were conducted by the sponsor from the original NDA submission and the 4 month safety update submitted on September 13, 2001. Also used were pertinent letters or faxes to and from the sponsor during this review.

B. Clinical Trials

The following Table #8 is a list of all the 83 Clinical Trials submitted for review.

Table #8 List of all Clinical Trials

83 Clinical Studies	Location (# of studies)	ITT (enrolled) N=4087	Safety (completed) N=3960	Efficacy (off-site)*
21 CNS Studies		n=1041	n=1034	
43,779-9A	US (1)	136	136	44[af] 51[bf]
43,779-9B	US (1)	141	140	48[af] 50[bf]
B19036/020	Europe (1)	154	150	74[c] 69[d]
B19036/036 (Pediatric)	Europe (1)	85	85	
Supplementary	Europe (14) Japan (3)	144 381	144 379	- -
31 Liver Studies		n=1739	n=1734	
			179	
			214	
			97	
			113	
			11	
			30	
			608	
			482	
31 Other Studies		n=1307	n=1192	
			25	
			31	
			43	
			22	
				-
				-
				-
				-
Ongoing				
				-
				-

[a]reader #1 [b]reader #2 *With proposed dose and formulation
[c]number of lesions

[g]subset of patients with histopathology

C. Postmarketing Experience

The sponsor provided a 4 month safety update which included the safety database for all completed studies as of February 28, 2001.

Also the safety update included ongoing postmarket data from countries where MultiHance is approved. (See page 18, foreign market experience).

D. Literature Review

None was performed.

V. Clinical Review Methods

A. Conduct of Review

For the safety review, the enrolled subjects in all 83 clinical trials or synposes were evaluated for the safety of the proposed doses. Safety monitoring included: adverse events, vital signs, ECG, laboratory tests, and physical examination.

For the efficacy review out of the 78 completed studies, the two pivotal US studies (43,779-9A and 43,779-9B) and one European study (B19036/020) for the CNS indication [redacted] for the [redacted] Also reviewed were four pharmacokinetic US studies for selected population [renal function (43,779-4; 43,779-5), hepatic function (43,779-8), [redacted], and one European pediatric clinical CNS study (B19036/036). The selection of these studies is based on them being Phase II/III, Phase III, or selected population PK studies.

B. Additional Materials Consulted for Review

The division files including faxes, letters, and minutes for IND 43,779.

C. Methods Used to Evaluate Data Quality and Integrity

DSI audited three representative US sites. These were the following:

[redacted]

D. Ethics

Ethical standard issues or concerns were not identified by the individual hospital review boards.

E. Financial Disclosure

A representative (Melanie Benson) of the sponsor (Bracco Diagnostics) certified on April 23, 2001 that the sponsor has not entered into any financial arrangements with the listed investigators using Form FDA 3454 for the following "considered" studies:

US		European	
43,779-9A	CNS		
43,779-9B	CNS	B19036-020	CNS
43,779-10	Pediatric PK	B19036-036	Pediatric CNS

The list included both off-site readers and on-site investigators. The list does not include core laboratory support personnel/technicians or EKG readers.

The sponsor also stated that "all covered studies and those having a large patient population were completed prior to February 02, 1999, the effective date of the Final Rule of Financial Disclosure, with the exception of study B19036-036. Study B19036-36 was completed in February 1999."

VI. Integrated Review of Efficacy

A. Proposed Label Claim

GENERAL *"MultiHance is indicated for intravenous use in adults magnetic resonance imaging (MRI) of the Central Nervous System*

B. General Approach to Efficacy Review

The efficacy review

First, all of the key studies (pivotal and supportive) and pilot studies (as defined by the sponsor) will be identified.
Second, the studies not performed with the proposed dose and formulation are identified and are eliminated.
Third, of the remaining studies, those that have critical protocol design flaws will be eliminated.
Finally, the core studies will be evaluated for the proposed primary endpoints and if necessary for any secondary endpoints that the sponsor used for support of their indication in the package insert or those that might show an important trend or may have been approved for other FDA approved gadolinium MRI agents.

All on-site efficacy assessments and results are not discussed due to the strong potential for bias.

C. Detailed Review

1. CNS

a. Proposed CNS Indication

The following Tables #9 and 10, provides a comparison of MultiHance's proposed CNS indication, efficacy endpoints, and pediatric use to that of the other four FDA approved MRI gadolinium agents.

Table # 9 CNS Indications

MRI AGENT	CNS INDICATION
MultiHance	[redacted]
Magnevist (1989)	*"Magnevist Injection is indicated for use with magnetic resonance imaging (MRI) in adults and pediatric patients (2 years of age and older) to visualize lesions with abnormal vascularity in the brain (intracranial lesions), spine, and associated tissues. Magnevist Injection has been shown to facilitate visualization of intracranial lesions including but not limited to tumors."*
ProHance (1992)	*"ProHance (Gadoteridol Injection) is indicated for use in MRI in adults and children over 2 years of age to visualize lesions with abnormal vascularity in the brain (intracranial lesions), spine and associated tissues."*
Omniscan (1993)	*"OMNISCAN is indicated for intravenous use in MRI to visualize lesions with abnormal vascularity (or those thought to cause abnormalities in the blood brain barrier) in the brain (intracranial lesions), spine, and associated tissues."*
Optimark (1999)	*"OptiMARK Injection is indicated for use with magnetic resonance imaging (MRI) in patients with abnormal blood brain barrier or abnormal vascularity of the brain, spine, and associated tissues."*

Table #10 CNS Efficacy Endpoints and Pediatric Use

MRI AGENT	EFFICACY ENDPOINTS	PEDIATRIC USE
MultiHance (2002)	[redacted] changes in number of lesions", [redacted]	[redacted]
Magnevist (1989)	"Film quality, film contrast, lesion configuration (border, size, and location), and the number of lesions"	≥ 2 years old
Prohance (1992)	Enhancement and "provided additional diagnostic information"	≥ 2 years old
Omniscan (1993)	"Provided more diagnostic value", "increased number of brain and spine lesions", "added diagnositic information, diagnostic confidence, and new patient management information"	≥ 2 years old
Optimark (1999)	"Level of conspicuity of all lesions, the ability to delineate lesion borders from parenchyma/structures, the number of lesions, and the confidence in the number of lesions"	Not Studied

b. CNS studies

Out of a total of 21 CNS studies, 4 Phase II/III efficacy studies are identified by the sponsor as pivotal (key). This section will review the 4 key studies: B19036/020 (European), 43,779-9A (US), 43,779-9B (US) [redacted]. The remaining 17 studies (the 14 Pilot Phase II European studies and the 3 Japanese Phase IIb/III studies) are considered supportive and will only be briefly summarized.

Table #11 CNS studies

	Number of subjects/patients with off-site evaluations for efficacy with each cumulative dose (mmol/kg)						
	0.05	0.1[a]	0.15	0.2	0.3	Other	Total
43,779-9A	0	0	71	65	0	69[b]	205
43,779-9B	0	0	67	71	0	65[b]	203
B19036/020	0	0	0	74	74	0	148
Supplementary Trials -14	0	85	0	59	0	27[c]	171
Japanese Trials - 3	66	241	0	66	0	179[c]	552
Totals	66	406	138	335	74	395	1441

[a] proposed for market dose
[b] Omniscan
[c] Magnevist

Table #12 Demographics of the 3 Key Adult CNS studies

	43,779-9A and 9B			B19036/020		Total
Demographic	0.05 + 0.1 M	0.1 + 0.1 M	0.1+ 0.2 O	0.05 + 0.05 + 0.1 M	0.1 + 0.1 +0.1 M	
Sex, n (%)						
Male	63 (45)	66 (49)	71 (53)	44 (60)	44 (58)	288 (51)
Female	77 (55)	70 (51)	63 (47)	30 (40)	32 (42)	272 (49)
Age (yrs), n (%)						
18-40	47 (34)	42 (31)	42 (31)	4 (5)	5 (7)	140 (25)
41-64	76 (54)	69 (51)	68 (51)	42 (57)	52 (68)	307 (55)
≥65	17 (12)	25 (18)	24 (18)	28 (38)	19 (25)	113 (20)
Mean	47.4	48.9	48.5	58.5	57.0	
Range	18-79	19-88	20-86	34-82	23-81	
Race, n (%)						
White	111 (79)	112 (82)	108 (81)	74 (100)	76 (100)	481 (86)
Black	15 (11)	10 (7)	12 (9)	0	0	37 (7)
Hispanic	8 (6)	12 (9)	10 (8)	0	0	30 (5)
Asian	4 (3)	2 (2)	2 (1)	0	0	8 (1)
Other	2 (1)	0	2 (1)	0	0	4 (1)
Weight (kg), n (%)						

< 60	23 (16)	26 (19)	19 (14)	9 (12)	11 (15)	88 (16)
60-90	86 (61)	77 (57)	81 (60)	59 (80)	55 (72)	358 (64)
>90	31 (22)	33 (24)	34 (26)	6 (8)	10 (13)	114 (20)
Mean	76.7	77.3	80.0	72.9	73.1	
Range	41-136	42-127	39-132	47-100	47-130	
Anatomical Area of Evaluation, n (%)						
Brain	120 (86)	114 (84)	114 (85)	74 (100)	76 (100)	348 (85)
Spine	20 (14)	21 (15)	20 (15)	0	0	61 (15)
No Images Acquired	0	1 (1)	0	0	0	1 (0)

M=MultiHance
O=Omniscan
n=number
yrs=years

(i) PHASE 2

The 13 pilot US/European and 3 Japanese Phase II studies were not designed to provide substantial data. At best, they could suggest that MultiHance enhanced MRI may subjectively improve the observer's ability to see a contrast improvement over that of the non-enhanced MRI. For additional details regarding these 16 supplementary studies, please refer to the appendix.

c. Proposed CNS dose (0.1 mmol/kg of the 0.5 M formulation)

Adults: "The recommended dose of MultiHance is 0.1 mmol/kg (0.2 mL/kg) administered as a rapid intarvenous infusion or bolus injection.

(i) "SUPPORTIVE" PHASE 2/3

Study B19036/020
First patient enrolled 1996
Last patient enrolled 1997

(a) Design of Study B19036/020

This was a double-blind, parallel group, dose-controlled, randomized, multicenter Phase II/III European study. Eligible patients were adults with a known malignancy outside the CNS (with a known or unknown diagnosis) and with intra-axial metastatic disease to the CNS already identified with CEMRI or CECT. Overall, 150 patients were randomized to receive one of two cumulative doses (0.2 and 0.3 mmol/kg) of the 0.5 M formulation. The two cumulative dosing regimens consisted of three consecutive injections of 0.05 +0.05 + 0.1 mmol/kg or 0.1 + 0.1 + 0.1 mmol/kg. The injections were administered at 10

minute intervals. Because the elimination half-life of MultiHance is 1.2 to 2 hours the doses given are effectively equivalent to doses of 0.2 and 0.3 mmol/kg. A post-contrast MRI T1 weighted scan was performed after each of the three injections.

The two off-site blinded readers were appropriately blinded to all patient data and imaging data, including whether the MRI scan was after the first, second, or third injection. All pre-contrast (T1wSE and T2wSE) and post-contrast (T1wSE) scans were initially read unpaired (for a total of 5 randomized individual readings per patient) and then paired (a single combination reading per patient, which included all three injection T1wSE scans as well as the T1wSE and T2wSE pre-contrast scans).

MO Comment: The sponsor did not note whether these readers were also blinded to the protocol, patient entry criteria, dosing scheme, or drug type. A blinded reader protocol and training manual was not provided for this study.

The secondary efficacy endpoints that were evaluated by the off-site blinded reader case report forms (CRF) included: number of lesions detected, lesion detection, technical adequacy, confidence in lesion detection/exclusion, size of smallest lesion detected, lesion conspicuity, and lesion location.

The following six paired comparisons were evaluated by the sponsor, for diagnostic confidence of lesion detectability (worse, equal, better):

#1 first post-contrast to pre-contrast
#2 second post-contrast to pre-contrast
#3 second post-contrast to first post-contrast
#4 third post-contrast to pre-contrast
#5 third post-contrast to first post-contrast
#6 third post-contrast to second post-contrast

Lesion conspicuity was evaluated for the first, second, and third injection T1 post-contrast scans as worse, equal, or better than the pre-contrast scans.
Location was identified as:

- Intracerebral/Intraspinal
  Lobar, Basal ganglia, Ventricular, Brain stem, Cerebellar, Pituitary area, Spinal cord, Other
- Extracerebral/Extraspinal
  Extradural, Intradural, Other

MO Comment: Since the proposed dose is for a single injection of 0.1 mmol/kg, the relevant efficacy evaluations for the post-contrast MRI scans, would be obtained from the reading of the

(b) Critical Design Flaws of Study B19036/020:

The trial design contains several flaws in the patient enrollment, blinded read methods

Specifically,:

- All the patients have either a proven or unproven malignancy and intraaxial metastatic disease to the CNS determined by either a Gd enhanced MRI or contrast enhanced CT (CECT).

MO Comment: This poses two main conflicts. First, there is no expected benefit added of performing a MultiHance enhanced MRI after a Gd enhanced Mri, CECT, or biopsy had already identified 1-3 lesions. Second, the Gd enhanced MRI cannot be used as the gold standard for the study

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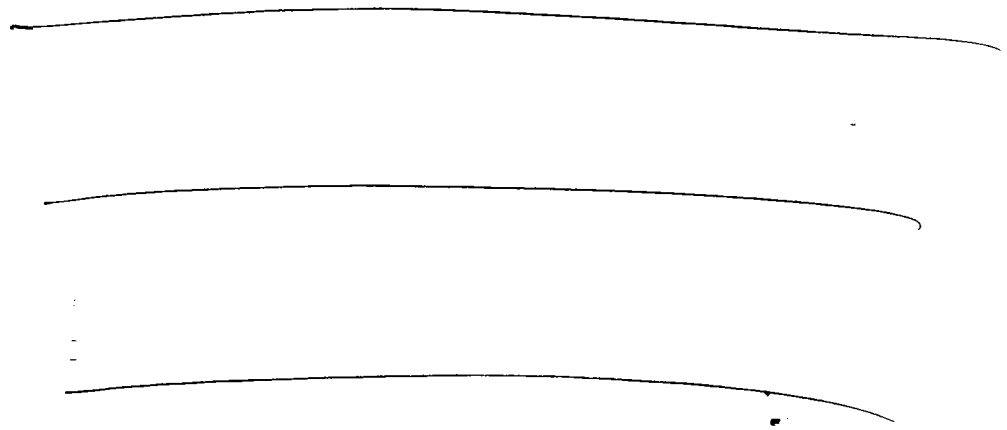
M-6

1 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling



(2) Lesion Detection (change in number of lesions detected) [secondary endpoint]

The following tables (# 14A & B) are adapted from the sponsor's data for the change in the reader's count of the "number of lesions detected".

Table # 14A Change in Number of CNS Lesions Detected (cumulative 0.1 mmol/kg versus pre-dose)

Frequency of Patients Reporting a Change in the Number of Lesions Detected				
Cumulative 0.1 mmol/kg vs predose	*0.05+0.05*+0.1 Regimen post 2nd dose[a] compared to predose[b] (read #2)		*0.1*+0.1+0.1 Regimen post 1st dose[c] compared to predose[b] (read #1)	
	Review 1	Reviewer 2	Reviewer 1	Reviewer 2
Increase	18 (24.7)	24 (32.4)	22 (31.0)	24 (32.9)
No change	38 (52.1)	39 (52.7)	33 (46.5)	39 (53.4)
Decrease	17 (23.3)	11 (14.9)	16 (22.5)	10 (13.7)
Not recorded	1	0	3	1

[a]pre-dose T1wSE+T2wSE + post-2nd dose T1wSE
[b]pre-dose T1wSE+T2wSE
[c]pre-dose T1wSE+T2wSE + post-1st dose T1wSE

Table # 14B Change in Number of Lesions Detected (cumulative 0.2 mmol/kg versus 0.1 mmol/kg)

Frequency of Patients Reporting a Change in the Number of Lesions Detected				
Cumulative 0.2 mmol/kg vs 0.1 mmol/kg	*0.05+0.05+0.1* Regimen post-3rd dose compared to post 2nd dose (read #6)		*0.1+0.1+*0.1 Regimen post 2nd dose compared to post 1st dose (read #3)	
	Review 1	Reviewer 2	Reviewer 1	Reviewer 2
Increase	17 (23.0)	10 (13.5)	24 (32.4)	19 (25.7)
No change	52 (70.3)	56 (75.7)	45 (60.8)	48 (64.9)
Decrease	3 (4.1)	8 (10.8)	2 (2.7)	6 (8.1)
Not recorded	2 (2.7)	0 (0)	3 (4.1)	1 (1.4)

[a]pre-dose T1wSE+T2wSE + post-2nd dose T1wSE
[b]pre-dose T1wSE+T2wSE
[c]pre-dose T1wSE+T2wSE + post-1st dose T1wSE

"Lesion tracking was not performed across the incremental doses received by each patient in this study to ascertain which lesions were visualized following each dose."

"When comparing the third dose with the second dose there was no statistically significant difference in the number of lesions detected for either reviewer, indicating no added benefit for the 0.3 mmol/kg dose over the 0.2 mmol/kg dose in terms of lesion detection for Regimen 2" (0.1+0.1+0.1 mmol/kg).

MO Comment:

Table #15 comparing the 0.2 mmol/kg and 0.1 mmol/kg doses should have been sub-analyzed for those that improved from the no change group to increase or the decrease group to either the no change or increase group from the point of the initial comparison of the 0.1 mmol/kg and precontrast groups. For example, the second table should be revised for reader 1 and the cumulative 0.2 dose, to reflect the analysis for the remaining unimproved 55 patients (the 38 no change and 17 decreased patients). A shift table for each category (increase, no change, and decrease) could provide similar type information. The sponsor did not provide the data in this form for analysis.

The sponsor must be able to track for each individual patient the lesions that are being counted in the images obtained after each sequential cumulative dose in order to be able to identify the number of new lesions found for each additional injection. The evaluation of an increase in mean total number of lesions (all patients combined) from the 1st 0.1 (or 0.5+0.5) to the second 0.1 mmol/kg dose is not appropriate since the number of new lesions are combined with the number of old lesions previously identified. The analysis should be based upon a comparison of the true number of new lesions identified for an individual patient, by reader and dose, between the 1st 0.1 mmol/kg dose and the 2nd 0.1 mmol/kg dose.

Without further statistical analysis, no definite meaningful trend regarding the improvement gained with the second 0.1 mmol/kg MultiHance injection for the ability to count lesions can be determined from this study. In addition, there is no gold standard in this study to verify the true number of lesions present.

A significant number of lesions disappeared (Table #14A row 5 "decrease") with MultiHance administration. This would suggest that MultiHance can obscure lesions as well as enhance them.

An increase in number of lesions detected is more important when the increase is from 0 to 1 or from 1 to more than 1. For example, an increase from 7 to 10 is not as clinically relevant. The sponsor did not sub-analyze the results in this manner; therefore this reviewer did perform the analysis and the results are presented in Tables 15A & B.

Table # 15A Patients (%) with an increase in number of lesions (Pre-dose is the higher of the number of lesions detected on either the T1wSE or the T2wSE)

	Reader #1 N=71			Reader #2 N=73		
	0 to 1+	1 to 2+	others	0 to 1+	1 to 2+	others
1st post-dose to 2nd post-dose	0/1 (0)	6/21 (29)	49	1/ 2 (50)	4/26 (15)	45
Pre-dose to 1st post-dose	1/ 2 (50)	6/22 (27)	47	1/ 2 (50)	8/31 (26)	40

Adapted from data from volume 75, pg 8-296 and pg 8-301.
It is not clear that the post-dose readings paired the post-dose T1wSE with the pre-dose T1wSE and the pre-dose T2wSE.

Table # 15B Patients (%) with an increase in number of lesions (Pre-dose is the number of lesions detected on T1wSE)

	Reader #1 N=71			Reader #2 N=73		
	0 to 1+	1 to 2+	others	0 to 1+	1 to 2+	others
1st post-dose to 2nd post-dose	0/1 (0)	6/21 (29)	49	1/ 2 (50)	4/26 (15)	45
Pre-dose to 1st post-dose	7/8 (88)	17/35 (49)	28	1/ 2 (50)	17/42 (40)	29

Adapted from data from volume 75, pg 8-310 and pg 8-315.
It is not clear that the post-dose readings paired the post-dose T1wSE with the pre-dose T1wSE and the pre-dose T2wSE.

MO Comment: The reading of the pre-dose T2wSE with the pre-dose T1wSE (Table 15A) results in fewer patients with no lesions at baseline than when the pre-dose T1wSE is read alone (2 versus 8 for reader #1) and fewer single lesions at baseline (22 versus 35 for reader #1). This would indicate the importance of the inclusion the T2wSE images in both the pre-dose and post-dose readings. MultiHance enhancement is not the driving

force for the improvement in the number of patients with increased lesions either from the pre-dose to post-1st dose or the post-1st dose to the post-2nd dose (Table # 15A).

(ii). KEY PIVOTAL PHASE 3

The sponsor proposes these two identical CNS studies, 43,779-9A and 9B, as the pivotal key CNS studies and these two studies will be reviewed in detail in this section.

Studies 43,779-9A	**and**	**43,779-9B**
First patient enrolled	February 1997	April 1997
Last patient enrolled	January 1998	December 1997

(a) Design of Studies 43,779-9A and 9B

Both studies were double-blind, randomized, parallel-group, dose escalating, active controlled, multicenter identical Phase III US studies with Omniscan (0.3 mmol/kg) as the comparator. The 410 eligible patients were adults (205/study) that were highly suspected of having a CNS lesion (brain-348, or spine-61) based on nuclear medicine imaging, contrast enhanced computed tomography (CECT), computed tomography (CT), contrast enhanced magnetic resonance imaging (CEMRI), magnetic resonance imaging (MRI), or angiography. The randomization schedule was stratified according to the patient's suspected pathology to ensure a balance of patients with metastatic or non-metastatic lesions. The stratification was based on clinical information that was available at the time of screening. Both studies randomized patients to either a rapid bolus injection of a combination MultiHance dose of 0.05 + 0.1 mmol/kg (n = 71+69), a combination MultiHance dose of 0.1 + 0.1 mmol/kg (n = 65+71), or a combination Omniscan dose of 0.1+0.2 mmol/kg (n = 69+65). MultiHance or Omniscan injections were given 15 minutes apart. Post contrast MRI scans were performed immediately (within 5 minutes) after the first injection and after completion of both injections. Therefore, only a subset of patients had post-contrast dyanamic images performed after the proposed for market single initial injection dose of 0.1 mmol/kg. There are no delayed images possible after the 1st dose as the second dose is given within 10 minutes of the first and the delayed images are effectively the result of the cumulative dose.. These same patients also had the second proposed dose with immediate and delayed imaging. These key studies thus have a combined relevant sample size of 136 patients (n = 65+71).

Two off site independent blinded readers (neuroradiologists) were appropriately blinded to patient data, study agent, dose, and image procedure results. Both unpaired (unmatched) pre-dose and paired (matched) review sessions were held, with the unpaired review performed first and randomized by patient and dose. No unpaired post-dose readings were performed. The paired reading presented the pre-contrast and either the first post-injection or second post-injection scans.

Lesion tracking was performed as follows:
Each reader generated regions of interest (ROI) on schematic maps illustrating representative brain and spine images. At the completion of the diagnostic assessments,

the lesion tracking spreadsheet is presented. The reference lesion numbers are obtained from the collective review of all image sets. All lesions detected in other assessments are matched to the reference lesions.

a. The unpaired assessment for lesion count consisted of the pre-contrast T1wSE only. Then the PD+T2wSE or T2wFSE images were added to perform these additional assessments: 1). location (intracerebral/intraspinal or extracerebral/extraspinal), 2). maximum diameter, 3). enhancement, 4). classification[1] (primary malignant tumor, metastasis, benign tumor/lesion, inflammation, infarct, vascular lesion, infection, unknown, other) of each lesion, and 5). the maximum diameter of the smallest lesion.

b. The paired assessment for lesion count consisted of pre-dose PD+T2wSE or T2wFSE. Then all the T1 weighted images were added (pre-dose T1wSE and either the post 1st dose T1wSE or the post-2nd dose T1wSE) for all the additional assessments. The same evaluation of is obtained as for the unpaired assessment as well as the following additional evaluations: a 0-2 scale is used to evaluate the additional information obtained from the post-dose images to that of the pre-dose images. This was evaluated for: lesion detection/exclusion, signal enhancement of lesions, lesion characterization. (i.e. visualization of lesion margins, pattern of enhancement, morphology and internal structure), and for loss of lesion conspicuity (yes or no).

These two studies were designed to test the hypothesis that MultiHance was not inferior to a currently available extracellular MRI contrast agent, Omniscan. The statistical assumptions made included a baseline percentage of patients with additional information for Omniscan of 80%, Type I error set at 0.0277 (to adjust for the two primary comparisons), Type II error of 0.20 (power of 80%), a non-inferiority margin of 20%. This resulted in a calculation of 67 patients per group for a total of approximately 200 patients.

The sponsor notes that: the expected efficacy rate (i.e. 80%) was based on a published study comparing two other approved gadolinium agents in a similar population.

(b) Critical Design Flaws of Studies 43,779-9A and 9B:

There are several design flaws that adversely effect the interpretability of the studies.

- [redacted]
- [redacted]
- [redacted]

- One of the imaging techniques used as an inclusion criterion was also used as a gold standard (MRI). This occurred for an unknown number of patients. It is not known whether these same images were used in the blinded reading.

MO Comment: If not, then a saturation enrichment problem could exist. If so, then these should be deleted from the analysis.

- The sponsor justifies not performing a unpaired reading of post-dose compared to unpaired pre-dose by stating that "the post dose images were not evaluated alone as pre-dose images are always utilized in clinical practice and it is recognized that the post-dose images are intended to augment the pre-dose images." [pg 69 vol 55].

MO Comment: The primary analysis should compare the unpaired non-enhanced pre-dose images to the unpaired enhanced post-dose images, which the sponsor did not do. The sponsor was not consistent in applying this justification, as the pediatric and other pivotal CNS studies do perform and report unpaired post-dose readings.

- For both studies, the sponsor submitted an amendment after the start of the original off-site blinded readings. The two identical amendments (#3) included an additional [new] blinded read protocol and changed the primary efficacy endpoints. The sponsor noted that "although the amendment took place after enrollment in the study had been initiated, no study blind was compromised and no interm review of patient data had been performed, apart from the necessary one during study monitoring. None of the off-site assessments had taken place prior to the amendment." [page 8 104 volume 56 and page 8 164 volume 66]

MO comment: There is still suspicion as to why there were changes to the efficacy assessments at this late time-point.

On April 27, 2001 the final statistical analysis plan in the NDA was submitted in Amendment #3 with the date November 6, 1997

- The primary assessment of efficacy was changed:

- Some secondary questions (regarding the nature of the information) were added at this time. For example, confidence in lesion detection/exclusion was replaced with an assessment of whether or not a lesion was an enhancing lesion or not.

MO Comment: Should the changes affect the sample size. Was there knowledge of any of the results prior to submitting the revisions included in amendment 3?

- One of the 4 attachments eliminated the unmatched (unpaired) post-contrast reading.

MO Comment: Therefore, the preferred unmatched (unpaired) analysis of pre- and post-contrast images could not be performed.

(c) Trends obtained from Studies 43,779-9A and 9B:

M-7

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_____ § 552(b)(5) Draft Labeling

(2) Lesion detection [secondary endpoint]

The sponsor has reported the total number of CNS lesions found and the mean number of CNS lesions/patient (± STD) found for Pre-dose, Post-1st, and Post-2nd doses scans, comparing the two MultiHance arms to Omniscan, for each of two readers in both studies (Table #20).

Table #20 Number of CNS Lesions

Study 43,779-9A						
	Reader #1			Reader #2		
Cumulative Dosing Regimens	Pre-Dose[a]	Post-1st Dose[b]	Post-2nd Dose[c]	Pre-Dose[a]	Post-1st Dose[b]	Post-2nd Dose[c]
0.15 mmol/kg MultiHance	N=71 patients			N=71 patients		
# of lesions	138	148	159	153	198	188
mean ± SD	1.9±2.7	2.1±2.9	2.2±2.9	2.2±2.8	2.8±3.4	2.7±3.2
0.2 mmol/kg MultiHance	N=65 patients			N=65 patients		
# of lesions	168	183	174	187	227	226
mean ± SD	2.6±3.2	2.8±3.1	2.7±3.0	2.9±3.4	3.5±3.8	3.5±3.7
0.3 mmol/kg Omniscan	N=66 patients			N=68 patients		
# of lesions	144	139	153	181	190	205
mean ± SD	2.2±2.8	2.1±2.8	2.3±2.9	2.7±3.3	2.8±3.4	3.0±3.4
Study 43,779-9B						
	Reader #1			Reader #2		
Cumulative Dosing Regimens	Pre-Dose	Post-1st Dose	Post-2nd Dose	Pre-Dose	Post-1st Dose	Post-2nd Dose
0.15 mmol/kg MultiHance	N=67			N=66		
# of lesions	105	122	122	97	139	125
mean ± SD	1.6±2.2	1.8±2.3	1.8±2.4	1.5±1.9	2.1±2.4	1.9±2.3
0.2 mmol/kg MultiHance	N=67			N=68		
# of lesions	110	131	136	131	149	159
mean ± SD	1.6±2.2	2.0±2.4	2.0±2.4	1.9±2.2	2.2±2.4	2.3±2.4
0.3 mmol/kg Omniscan	N=65			N=65		
# of lesions	100	135	136	177	189	211
mean ± SD	1.5±2.4	2.1±2.6	2.1±2.6	2.7±3.3	2.9±3.2	3.2±3.4

[a]T1wSE [b]pre-dose PD + T2wSE or T2wFSE + post-1st dose T1wSE
[c]pre-dose PD + T2wSE or T2wFSE + post-2nd dose T1wSE

The following Table #21, lists the corresponding p-values for the three different comparisons of mean number of lesions seen for each dosing regimen for each of two readers in both studies.

Table #21 Corresponding P-values

Study 43,779-9A						
	Reader #1			Reader #2		
Cumulative Dosing Regimens	Pre[a] vs Post 1st Dose[b]	Pre[a] vs Post 2nd Dose[c]	Post-1st Dose[b] vs Post-2nd Dose[c]	Pre[a] vs Post 1st Dose[b]	Pre[a] vs Post 2nd Dose[c]	Post-1st Dose[b] vs Post-2nd Dose[c]
0.15 arm MultiHance	P=0.8	p=0.5	p=0.7	p=0.2	p=0.3	p=0.8
0.2 arm MultiHance	p=0.7	p=0.9	p=0.8	p=0.3	p=0.3	p=0.9
0.3 Omniscan	p=0.9	p=0.8	p=0.7	p=0.8	p=0.5	p=0.7
Study 43,779-9B						
Cumulative Dosing Regimens	Pre[a] vs Post 1st Dose[b]	Pre[a] vs Post 2nd Dose[c]	Post-1st Dose[b] vs Post-2nd Dose[c]	Pre[a] vs Post 1st Dose[b]	Pre[a] vs Post 2nd Dose[c]	Post-1st Dose[b] vs Post-2nd Dose[c]
0.15 arm MultiHance	p=0.5	p=0.4	p=0.9	p=0.1	p=0.2	p=0.7
0.2 arm MultiHance	p=0.4	p=0.3	p=0.9	p=0.5	p=0.3	p=0.7
0.3 Omniscan	p=0.2	p=0.2	p=0.9	p=0.8	p=0.4	p=0.6

[a]T1wSE
[b]pre-dose PD + T2wSE or T2wFSE + post-1st dose T1wSE
[c]pre-dose PD + T2wSE or T2wFSE + post-2nd dose T1wSE

From Table #20, for the 0.15 arm of the MultiHance group (rows 5 and 14), two out of four readers (both reader #2 column 7) saw fewer lesions, one out of four readers saw the same mean number (reader #1 row 14 column 4), and only one out of four readers saw more lesions (reader #1 row 5, column 4), on the post-2nd dose images than on the post-1st dose images . But all readers found more lesions on the post 1st dose images than the pre-dose images.

From Table #20, for the 0.2 arm of the MultiHance group (rows 7 and 16), both readers from Study 43,779-9A saw fewer lesions on the post-2nd dose than on the post-1st dose, but still more than the pre-dose images, while both readers from 9B saw more lesions on the post-2nd dose than on the post-1st dose.

From Table #20, for the 0.3 cumulative Omniscan group (rows 9 and 18), there was progressively more lesions seen on the post-2nd dose than the post-1st dose and predose images for three of the readers from both studies.

From Table #21, for both MultiHance arms and the Omniscan arm, there was no statistically significant change (no p values < 0.05) in the mean number of lesions identified when pre-dose was compared to post-1st dose, pre-dose compared to post-2nd dose, or post-1st dose compared to post-2nd dose.

MO Comment: Therefore, there is no benefit found for the use of either MultiHance or Omniscan for the detection of mean number of CNS lesions. In addition, the standard deviation (STD), which is even larger than the mean, is an indication of the wide variability in number of lesions per patient. A major design flaw, is that there was no gold standard (histopathology or CECT) used to determine the true number of lesions present. The sponsor gives the following explanation: "Gold standard confirmation is often not possible because of the nature of the disease and patient management constraints and therefore it is necessary to use a relative measure of —— efficacy as opposed to absolute efficacy measures. For this study Omniscan was used to provide a relative measure of —— efficacy". [pg 85 vol 55]

There was no matching of individual lesions, it is not known if the lesions identified for one reading were the same ones or different ones for another reading. Similarly, comparison of individual lesions cannot be made between readers. Merely evaluating the mean number of lesions hides the details for the individual lesions by combining new lesions, unchanged lesions, and obscured lesions into one figure. A lesion seen on the baseline pre-dose scan may not have been seen on either post-dose scan. This would suggest that MultiHance or Omniscan enhancement may obscure a lesion. Without a gold standard, it is unknown whether the pre-dose or post-dose finding is the true one. A lesion seen on a post-dose scan, may not have been seen on the baseline pre-dose scan. These lesions are the more important ones, but cannot be verified without a gold standard.

(3) Other secondary CNS efficacy assessments in Studies 43,779-9A and 9B will not be evaluated in detail. A brief summary and comments are provided for some of them.

(a)

(b) Signal Enhancement Characteristics

The sponsor acknowledges that "the only subjectivity involved is the placement of the regions for measurements which was undertaken by an independent radiologist." [pg. 73 vol 55] and "one of the primary sources of variance in these measurements is not the procedure itself, but the range of signal values for various pathologies." [Pg 73 vol 55]

MO Comment: Both of these admissions by the sponsor indicates flaws with the methodology and the endpoint. Therefore this efficacy parameter does not support a CNS indication.

(c) Loss of Conspicuity

The sponsor states that: "post contrast images alone should not be used in routine practice" and acknowledges that: "loss in conspicuity cause by uptake of contrast by hypointense lesions turning them less conspicuous." [pg. 74 vol 55]. The sponsor concludes that: "overall, there was no evidence of loss of conspicuity for either of the off site reviewers when comparing predose versus postdose images sets in all study agent groups." [pg 74 vol 55]

MO Comment: There was no tracking of lesions. Therefore this efficacy parameter does not support a CNS indication.

d. Pediatric CNS study

Study B19036/036

(a) Design of Study B19036/036

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D. Summary of Efficacy Review

1. CNS

a.

b. The sponsor has provided data in adults showing that neither Omniscan or MultiHance has the ability to improve the detection of number of lesions over non-contrast MRI alone. (a secondary efficacy endpoint claimed by the sponsor). [Phase II/III studies 43,779-9A and 9B].

c

d.

e. There are numerous critical fatal design flaws for the evaluation of efficacy. Some major ones include lack of proper lesion tracking, lack of prospective definitions, lack of appropriate gold standards, lack of proper and/or complete statistical analyses, and lack of objective clinically relevant endpoints. [Phase II/III studies 43,779-9A and 9B, and B19036/020].

f. The sponsor did not analyze the data for intra-axial ("brain") versus extra-axial ("spine") CNS lesions. The sponsor did not provide the number of intra- and extra-

axial lesions for each dosing regimen or for each agent in the adult studies [Phase II/III studies 43,779-9A and 9B].

g. The sponsor does not adequately discuss the clinical benefit of an enhanced MRI for patients with known or suspected CNS lesions after modality (including enhanced MRI) has already identified a suspicious lesion.

h. The sponsor did not provide a breakdown of patients by diagnosis (i.e. metastases) for each dosing regimen, for each MRI agent, for each age group [Phase II/II studies 43,779-9A and 9B .

i.

E. Conclusion of Efficacy Review

1. CNS

The sponsor has shown than MultiHance is inferior to Omniscan and did not evaluate non-inferiority to Magnevist. MultiHance is ineffective in improving the evaluation of the mean number of lesions

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

When compared to the other four FDA approved gadolinium MRI agents, MultiHance has a similar chemistry (except for viscosity), pharmacokinetic, and clinical safety adverse event profile for subjects greater than 2 years of age (see Table #1 in Section II. C). Like the other agents, it is mainly excreted in the urine and is readily dialyzable. It's elimination half-life increases with worsening renal function, but does not increase significantly with impaired hepatic function. Transmetalation is detected with zinc but not with iron (ionic calcium, copper, magnesium, and manganese were not studied). No significant metabolism occurs and fecal excretion varies from

There is absence of pharmacokinetic data for infants (0-2 years of age) and there was only 1 child evaluated < 5 years of age. There is a small sample size (n=15) for

evaluation of CNS [redacted]. Therefore, there is insufficient evidence of safety [redacted] infants in the CNS indication.

The sponsor did not incorporate all the dosed subjects in the reported analyses. The data on Japanese subjects, pediatric subjects, and healthy adult volunteers were excluded. Therefore, overall summaries for demographics (age, weight, and height), method of administration (rapid bolus injection and/or slow infusion) and subanalyses (i.e. adverse events) by imaging indication (CNS versus liver), by geographic location (US, Europe, or Japan), by anatomical CNS location (intra- or extra-axial), [redacted] and by age (< and > 65 years old) are required.

QTc evaluation is not assessed for the pediatric population and is insufficient for the adult population. Further ECG analysis and/or study is required.

The details of the deaths and serious adverse events have not been comprehensively provided but are sufficient enough to determine whether or not a possible causal relationship to MultiHance administration exists.

There is a lack of reporting of urinalysis data for both the adult and pediatric populations. The sponsor should provide analyses for any data that they have available, especially for those patients with renal insufficiency, the elderly, and the pediatric population.

Since this agent has the highest osmolality and viscosity of all five gadolinium agents and these chemical parameters have been associated with serious adverse events in the injected limb (i.e. fascitiis, thrombophlebitis, compartment syndrome, amputation, surgical release, infections, etc), the sponsor must provide additional detail and discussion of all such injection site related adverse events.

Since these agents are known to cross breaks in the blood brain barrier and to effect the QTc interval, complete information regarding all seizures and all cardiac arrhythmias associated with QTc changes are required.

Due to the multiple safety deficiencies and the lack of sufficient evidence of efficacy, MultiHance is considered not approvable.

B. Description of Patient Exposure

Safety was evaluated in a total of 3960 subjects dosed with MultiHance. Of these there were n=3850 adult and 110 pediatric subjects. Approximately, 1/6 of the subjects were studied in the US, ½ in Europe, and 1/3 in Japan. The demographics of the safety pool are summarized in the following Table # 41 for the 67 completed adult (n=2637) and pediatric (n=110) studies in the US and Europe and the 11 Japanese (n=1213) studies. The sponsor did not provide the data in a form that separates the demographic data for the US versus European subjects, for the 5 ongoing studies (n=115) and for the post-market surveillance (n=144,224). As shown in table # 42, the majority of the US/European subjects/patients (72%) were adults less than 65 years old. However 743 adults (28%)

were > 65 years of age. Where provided (i.e. sex), the demographics were similar between the US/Europe and Japan. However, most demographic details for the Japanese studies were not provided.

The proposed for market 0.5 M formulation was given to 3542 (89%) subjects; 398 (10%) subjects received the 0.25 M formulation, and for 20 (1%) subjects the formulation could not be determined.

Of the 2637 US/European subjects who received MultiHance, 721 received a slow infusion, 1639 subjects received a bolus, and 277 received a bolus followed by a slow infusion. For the 110 pediatric subjects who received MultiHance, the administration was either a bolus or an infusion based on the Investigator's discretion. Again it is not clear from the submitted synopses, in what manner MulitHance was administered to the 1218 Japanese subjects. The sponsor did not specify the rate of injection, and whether the injection was performed by hand or with [redacted]

Placebo was given to 80 subjects, Omniscan to 134 subjects, and Magnevist to 216 subjects. There was an overlap of 76 subjects who received both MultiHance and Magnevist in a crossover study.

Table # 42 Demographics for the Overall Safety pool

Demographic	US/Europe Adult N=2637	%	Japan Adult N=1213	%	US/Europe Pediatric N=110	%
Sex						
Male	1522	57.7	759	62.3	60	55.5
Female	1115	42.3	440	36.1	50	45.0
Unknown	-	-	19	1.6	-	-
Age						
<2	-	-	-	-	15	13.6
2-12	-	-	-	-	69	62.7
>12	-	-	-	-	26	23.6
<65	1894	71.8	NA	NA	-	-
≥65	743	28.2	NA	NA	-	-
Mean	55.9	-	NA	-	7.5	-
Range	18-88	-	NA	-	4D-17	-
Race						
White	2451	92.9	-	0	82	75.0
Black	75	2.8	-	0	7	6.0
Hispanic	29	1.1	-	0	21	19.0
Asian	30	1.1	1213	100.0	0	0
Other	7	0.3	-	0	0	0
Missing	45	1.7	-	0	0	0

Weight						
<60	395	15.0	NA	NA	-	-
61-90	1911	72.5	NA	NA	-	-
>90	331	12.6	NA	NA	-	-
Mean (kg)	73.7	-	NA	-	30.6	-
Range	40-136	-	NA	-	4-87	-
Height						
Mean (cm)	169.5	-	NA	-	122.7	-
Range	120-210	-	NA	-	49-179	-
Scheduled Dose						
<0.05	161	6.1	50	4.1	-	-
0.05[a]	558	21.2	269	22.1	-	-
0.10[b]	1170	44.4	668	54.8	110	100
0.15	140	5.3	-	-	-	-
0.20	520	19.7	226	18.6	-	-
>0.2	88	3.3	-	-	-	-
Formulation						
0.25	398	15.1	-	-	-	-
0.5[c]	2219	84.1	1213	100.0	110	100.0
Missing	20	0.8	-	-	-	-
Method Admin						
Infusion	721	27.3	NA	NA	25[d]	22.7
Bolus	1639	62.2	NA	NA	-	-
Bolus, Infusion	277	10.5	NA	NA	-	-
Either	-	-	NA	NA	85[e]	77.3
Location						
US	624	15.7	-	-	25	0.6
Europe	2013	50.7	-	-	85	2.1
Japan	0	0	1218	30.7	-	-

NA=not available
[a]Proposed for market dose for the [redacted]
[b]Proposed for market dose for the [redacted]
[c]Proposed for market formulation [redacted]
[d]Given over 5 minutes
[e]Determined by the investigator but ranging from 10 mL/min to 2 mL/sec or greater.

Overall, of the 2637 adult subjects/patients in the US/Europe, 502 (19%) reported at least one adverse event. Of the 1213 adult Japanese subjects/patients, 49 (4%) reported at least one adverse event. Of the 110 pediatric US/European subjects/patients, 14 (13%) reported at least one adverse event.

Of all these adverse events, there were 5 Deaths, 17 SAEs, and 10 Discontinuations

1. Deaths (n=5) - 2 European, 3 Japanese, no US or pediatric

- Patient 04R00 (CNS study B19036/020; site 10; Investigator [redacted]

34 year old white European female patient with a history of lung and cerebral metastases, headache, vomiting, coordination disorders, thyroidectomy, and taking methyprednisolone, ranitidine, levothyroxine, stediril (OC), lormetaxepam as concomittant medication and receiving radiotherapy as concomitant therapy. The patient had undergone radiotherapy 48 hours after study administration for 2 consecutive days.
Seven days post administration of 0.194 mmol/kg MultiHance, the patient experienced intracranial hypertension. Despite appropriate treatment the patient died on day 8.
Given the 1 week temporal separation from study agent administration, the Sponsor believes that there is no relationship to MultiHance. This MO concurs.

- Patient 425 (MRA study B19036/042; site 4; Investigaor ———)
  A European female had a carotid MRA and died from a pulmonary embolism. The sponsor did not provide any additional narrative or information on this patient.
- Patient #26169-1 ———————)
  56 Year old Japanese male died 35 days post-dose from suspected adult respiratory disease syndrome which began 32 days post-dose. No additional information was provided by the sponsor.
- Patient # 13120-2 ———————)
  55 Year old Japanese female died 12 days post-dose from cachexia caused by progressive carcinoma. No additional information was provided by the sponsor.
- Patient #26169-5 ———————)
  59 Year old Japanese male died 15 days post-dose from cardiac failure caused by cancerous pericarditis which began 5 days post-dose. No additional information was provided by the sponsor.

2. Serious Adverse Events (n=17) – 5 Related, 5 Possible Related, 7 Unrelated

12 were in US/European adult subjects (see Table #43) 4 Related + 2 Possibly Related + 6 Unrelated.

- Patient #2223 Seizure in a 39 year old asian male, which began 17 minutes post-dose and lasted for 5 minutes. Treated with phenytoin and lorazepam. (CNS study 43,779-9B). Related.
- Patient #1038 CABG occlusion in a 57 year old male, which began immediately post-dose and recovered after emergency cardiac surgery. (study B19036/044). Related
- Patient #1414 Laryngospasm in a 51 year old female, which began immediately post-dose and recovered by 6 hours post-dose. Treated with epinephrine and benedryl. ——— Related
- Patient #14 Acute Pulmonary Edema in a 65 year old male, which began 10 minutes post-dose and recovered by 24 hours post-dose (study PT73E). Related.
- Patient #10 CVA in a 65 year old female, which began 35 hours post-dose requiring hospitalization. Outcome unknown. (study PT71E) Possible Related.

3 were in Japanese adult subjects – 1 Related, 1 Possible Related, 1 Unrelated

- Facial edema in a 30 year old female, which began 1 minute post-dose and lasted for 30 minutes. ——————— Related.
- Myocardial infarction in a 79 year old male, which began 15 hours post and lasted

a few hours ( ). Possibly related.

- Hemorrhage in a 53 year old female, which began 4 days post-dose and was of unknown duration and outcome (CNS study E7155-J081-221). Not related.

2 were in the Pediatric population – 2 Possible Related

- Vomiting worsened (center 3, 5 yo. Black male), began 4 ½ hours post-dose. On chemotherapy for mesencephalic glioma. Treatment given 26 hours post-dose and symptoms stopped 2 hours later. No sequalae. Possible Related.
- Hypoxia, (center 5, 11 month old while male), began 30 minutes post-dose and lasted 3 hours. There was a pre-existing condition (dyspnea) due to laryngeal edema associated with premedication (barbiturates and chloral hydrate). Treated with glucocorticoids. Hospitalized for two days in intensive care. Recovered without sequlae. Possible related.

3. Discontinuations (n=10 see Table # 43 column 6)

4 were due to serious adverse events that were described above:
Seizure, Laryngospasm, Acute Pulmonary Edema, Pulmonary embolism (died)
6 were due to non-serious adverse events.

- Patient #20 Injection Site Reaction This patient also had a constellation of symptoms that were consistent with an anaphylactoid reaction (nausea, vomiting, fecal and urinary incontinence, hypotension, dizziness, sweating and pruritus).

- The other five non-serious AEs with discontinuation were for: Nausea (2), Syncope (1), Hypertension (1), and one subject with Rash, tachycardia, and tremor

There were no pediatric discontinuations due to adverse events the sponsor did not provide information about Japanese AE related discontinuations in the synopses.

Table # 43 Serious Adverse Events, Deaths, and Adverse Events Leading to Discontinuation in the US/European Adult Population

Study #	Center/ Patient #	Adverse Event by COSTART Term	Death	SAE	DC'd
Central Nervous System (CNS) Studies					
B19036/020	10/04R00	Intracranial hypertension	X	X	
B19036/020	02/05R01	CNS depression		X	
B19036/020	09/07R00	Hemiplegia		X	
43,779-9B	22/2211	Rash, Tachycardia, Tremor			X
43,779-9B	22/2223	Seizure Facial paralysis		X	X X
PT79	01/10	Pulmonary embolism (PE)		X	
PT84	01/4	Aphasia/Hemiplegia		X	
Liver Studies					
	14/1414	Laryngospasm Rhinitis, Dyspnea, Respiratory disorder, Urticaria, Pruritus, Eye disorder, Facial edema		X	X X
	01/20	Nausea, Vomiting, Incontenence, Hypotension, Dizziness, Sweating, Pruritus, Urinary Incontenence, Injection Site reaction			X

[redacted]	03/20	Nausea			X
	08/15	Necrotizing pancreatitis		X	
[redacted]	03/1	Nausea			X
Cardiac Studies					
PT71E	05/10	Cerebrovascular accident (CVA)		X	
PT73E	07/14	Acute pulmonary edema Bilirubinemia-increase total and indirect		X X	X
B19036/005	01/11	Severe chest pain		X	
B19036/005	01/30	Hypertension			X
B19036/005	01/48	Syncope			X
MRA Studies					
B19036/042	04/425	Pulmonary embolism (PE)	X	X	X
B19036/042	04/428	Congestive Heart Failure (CHF)		X	
B19036/044	10/1038	CABG Occlusion		X	

Adapted from sponsor's Table L from the 4 month Safety Update pg 9-38 volume 1.
DC'd = discontinuations

4. Post-marketing Surveillance

Periodic Safety Update Reports have been issued from July 31, 1997 (international birth date corresponding with approval in the United Kingdom) to July 31, 2000. In addition, CIOMS forms are available for events reported between August 1, 2000 and February 28, 2001. All spontaneously reported adverse events received by Bracco in the countries where the compound was launched into the market have been entered into the company's worldwide adverse event database. Both serious and non-serious adverse events regardless of the causal relationship between study agent administration and the adverse event are reported. All spontaneous adverse event reactions are reported to Bracco S.p.A. directly by users or via subsidiaries and distributors worldwide and reviewed by in-house physicians working in the Bracco S.p.A. Drug Safety Unit.

Because MultiHance is administered most often as a single administration, an estimate of patient exposure is calculated on the basis of the number of single dose vials sold in the period from the launch into the market (October 1998, Germany) to February 28, 2001. A total of [redacted] units have been sold, and the number of units sold is used for estimating the number of patients exposed to MultiHance. All patients exposed received a single injection of MultiHance.

Of the [redacted] patients exposed to MultiHance, 28 patients (0.019%) experienced adverse events; 10 patients (0.007%) experienced serious adverse events, and 18 patients (0.012%) experienced non-serious adverse events. No deaths have been reported.

The post-marketing adverse events included 2 injection site pain cases (non-serious), 1 case of syncope (serious), 1 case of back pain (serious), 2 cases of cardiac arrest, 1 case of angina pectoris.

C. Methods and Specific Findings of Safety Review

1. Time and Event Schedules

The monitoring of safety parameters varied for the multiple studies. In general monitoring occurred at baseline (pre-dose) and at 24 hours post-dose. Some parameters were monitored at additional or more frequent time periods and will be noted as necessary for each individual parameter.

2. Adverse Events

The sponsor provided the data in a disjointed fashion, which required teasing out the details to develop the following tables. The sponsor did not provide the data in a fashion that allowed readily achievable subset analysis by geographical location (i.e. US versus European), by for market dose [redacted] 0.1 mmol/kg), by indication (CNS [redacted]; by age (< or > 65 years old), by method of administration (bolus or infusion), by anatomical CNS location (intra- or extra-axial), by [redacted] or by formulation (0.25M or 0.5M). Such a breakdown was requested of the sponsor by fax (August 2, 2001) and by teleconference (August 23, 2001). The sponsor (October 24, 2001 letter) stated that they would submit the entire adverse event database in electronic excel format by the second half of November, but this was never received.

Table # 44 Summary of Adverse Events (67 completed US/European studies)

	# of subjects/ patients	# of AERs	# of patients	Rate
All Completed Studies	2747	924	516	18.8
Adult Population	2637	905	502	18.5
Adult Patient Population	2574	845	478	18.6
CNS	546	236	140	25.6
Liver	971	377	202	20.8
Cardiac	186	100	67	36.0
MRA	393	NA	34	8.7
Breast	142	NA	18	12.7
Renal Impairment	20	9	5	25.0
Renal Dialysis	11	19	11	100.0
Hepatic Impairment	11	1	1	9.1
Healthy Volunteers	63	60	24	38.1
Pediatric Population	110	19	14	12.7
CNS	85	15	11	12.9
Healthy Volunteers	25	4	3	12.0

The following three tables (# 45-48) includes summaries of the demographics and adverse events for the 67 completed US/European and 11 completed Japanese studies.

Table # 45 US/European Adult Demographics and Adverse Events

Demographic	#	%	Adverse Events (# of patients)	Rate
Overall	2637	100.0	478/2574	18.6
Sex				
Male	1522	57.7	251/1467	17.1
Female	1115	42.3	227/1107	20.5
Age				
<65	1894	71.8	370/1832	20.2
≥65	743	28.2	108/742	14.6
Mean	55.9		56.5	
Range	18-88		18-88	
Race				
White	2451	92.9	440/2428	18.1
Black	75	2.8	24/75	32.0
Hispanic	29	1.1	4/29	13.8
Asian	30	1.1	9/30	30.0
Other	7	0.3	1/6	16.7
Missing	45		0/6	0
Weight				
<60	395	15.0	79/389	20.3
61-90	1911	72.5	323/1855	17.4
>90	331	12.6	76/330	23.0
Mean (kg)	73.7		73.8	
Range	40-136		40-136	
Height				
Mean (cm)	169.5		169.3	
Range	120-210		120-210	
Scheduled Dose				
<0.05	161	6.1	31 (57)	19.3
0.05[a]	558	21.2	128 (225)	22.9
0.10[b]	1170	44.4	156 (282)	13.3
0.15	140	5.3	45 (71)	32.1
0.20	520	19.7	124 (227)	23.8
>0.2	88	3.3	22 (43)	25.0
Formulation				
0.25	398	15.1	87/371	23.5
0.5[c]	2219	84.1	389/2183	17.8
Missing	20	0.8		
Method Admin				
Infusion	721	27.3	128/678	18.9
Bolus	1639	62.2	336/1619	20.8
Bolus, Infusion	277	10.5	14/277	5.1

Table # 46 US/European Pediatric Demographics and Adverse Events

Demographic	#	%	Adverse Events # of patients (# of events)	Rate
Overall	110		14 (19)	12.7
Sex				
Male	60	55.0	9 (12)	15.0
Female	50	45.0	5 (7)	10.0
Age				
<2	15	13.6	2 (3)	13.3
2-<12	69	62.7	8 (10)	11.6
>12	26	23.6	4 (6)	15.4
Mean	7.5	-	-	-
Range	4 D-17	-	-	-
Race				
White	82	75.0	NA	NA
Black	7	6.0	NA	NA
Hispanic	21	19.0	NA	NA
Asian	0	0	NA	NA
Other	0	0	NA	NA
Weight (kg)				
Mean	30.6	-	-	-
Range	4-87	-	-	-
Height (cm)				
Mean	122.7	-	-	-
Range	49-179	-	-	-
Scheduled Dose				
0.10	110	100.0	14 (19)	12.7
Formulation				
0.5	110	100.0	14 (19)	12.7
Method Admin				
Bolus or Infusion	110	100.0	14 (19)	12.7
Location				
US	25	22.7	3 (4)	12.0
Europe	85	77.3	11 (15)	12.9

NA = not available

Table # 47 Japanese Adult Demographics and Adverse Events

Demographic	# N=1218	%	Adverse Events (# of patients) N=48	Rate 4.0%
Sex				
Male	759	62.3%	NA	NA
Female	440	36.1%	NA	NA
Unknown	19	1.6%	NA	NA
Age				
<65	NA	NA	NA	NA
≥65	NA	NA	NA	NA
Mean	NA	NA	NA	NA
Range	NA	NA	NA	NA
Weight				
<60	NA	NA	NA	NA
61-90	NA	NA	NA	NA
>90	NA	NA	NA	NA
Mean	NA	NA	NA	NA
Range	NA	NA	NA	NA
Height				
Mean	NA	NA	NA	NA
Range	NA	NA	NA	NA
Scheduled Dose				
<0.05	50	4.1%	0	0
0.05	269	22.1%	4	1.5
0.10	668	54.8%	36	5.4
0.20	226	18.6%	8	3.5
>0.2	5	0.4%	0	0
Formulation				
0.5M	1218	100%	48	4.0
Method Admin	NA	NA	NA	NA

Table #48 Summary of Demographics and Adverse Events by geographical location

Demographic By Location	#	%	Adverse Events (# of patients)	Rate
ADULT				
US	624	16.2	225/624	36.1
Europe	2013	52.2	253/1950	13.0
Japan	1213	31.6	49/1213	4.0
PEDIATRIC				
US	25	22.7	3/25	12.0
Europe	85	77.3	11/85	12.9

Table (#49) lists the adverse events that have an overall rate >0.5% based upon the adult US/European subjects/patients. Since the Japanese overall rate (4%) and the pediatric individual rates (all < 0.5%) are significantly lower than either the US or European rates, they are not used to determine the relevant adverse events (>0.5%) to be reported in this table. This is a more conservative approach to compiling this list of adverse events because inclusion of the pediatric data and Japanese data would decrease the overall rates.

Table #49 Summary of Most Frequent Individual Adverse Events
(list is based on those with an overall rate >0.5% for the US+Europeans adults, column #3)

Multihance	US+ Europe pts	US+ Europe %	US pts	US %	Europe pts	Europe %	Japan pts	Japan %	Overall Total	Overall %
# Subjects	2637	68.5%	624	16.2	2013	52.2	1213	31.6	3850	100.0
# Subjects with AERS	502	19.0	225	40.8	277	13.8	49	4.0	551	14.3
# of AERS			361				64		969	
BODY SYSTEM										
Body as a Whole	**200**	**7.6**	**93**	**14.9**	**107**	**7.6**	**10**	**0.8**	**210**	**5.4**
Headache	64	2.4	37	5.9	27	1.3	1	0.1	65	1.7
Injection Site Rxn	43	1.6	8	1.3	35	1.7	0	0	43	1.1
Laboratory Test Abn	21	0.8	0	0	21	1.0	0	0	21	0.5
Pain	16	0.6	11	1.8	5	0.2	0	0	16	0.4
Fever	13	0.5	7	1.1	6	0.3	1	0.1	14	0.4
Cardiovascular	**88**	**3.3**	**49**	**7.9**	**39**	**1.9**	**1**	**0.1**	**89**	**2.3**
Hypertension	18	0.7	8	1.3	10	0.5	0	0	18	0.5
Tachycardia	14	0.5	13	2.1	1	<0.1	0	0	14	0.4
Digestive	**75**	**2.8**	**36**	**5.8**	**39**	**1.9**	**21**	**1.7**	**96**	**2.5**
Nausea	47	1.8	21	3.4	26	1.3	11	0.9	58	1.5
Hemic & Lymphatic	**44**	**1.7**	**13**	**2.1**	**31**	**1.5**	**0**	**0**	**44**	**0.1**
Hypochromic anemia	13	0.5	2	0.3	11	0.5	0	0	13	0.3
Metabolic & Nutritional	**70**	**2.7**	**10**	**1.6**	**60**	**3.0**	**0**	**0**	**70**	**1.8**
Nervous	**99**	**3.8**	**43**	**6.9**	**56**	**2.8**	**11**	**0.9**	**110**	**2.9**
Vasodilation	31	1.2	11	1.8	20	1.0	4	0.3	35	0.9
Paresthesia	23	0.9	5	0.8	18	0.9	4	0.3	27	0.7
Dizziness	19	0.7	15	2.4	4	0.2	1	0.1	20	0.5
Skin and Appendages	**42**	**1.6**	**27**	**4.3**	**15**	**0.7**	**14**	**1.1**	**56**	**1.5**
Rash	14	0.5	11	1.8	3	0.1	0	0	14	0.4
Respiratory	**25**	**0.9**	**17**	**2.7**	**8**	**0.4**	**3**	**0.2**	**28**	**0.7**
Special Senses	**33**	**1.3**	**27**	**4.3**	**6**	**0.3**	**0**	**0**	**33**	**0.9**
Taste perversion	25	0.9	20	3.2	5	0.2	0	0	25	0.6
Urogenital	**28**	**1.1**	**8**	**1.3**	**20**	**1.0**	**0**	**0**	**28**	**0.7**
Musculoskeletal	**14**	**0.5**	**11**	**1.8**	**3**	**0.1**	**0**	**0**	**14**	**0.4**

The overall adverse event profile for the US (41%) is generally much greater than for Europe (14%) or Japan (4%). The individual adverse events with overall rates > 0.5% (column 3) are: headache (2.4%), nausea (1.8%), injection site reaction (1.6%), vasodilation (1.2%), paresthesia (0.9%), taste perversion (0.9%), dizziness (0.7), laboratory test abnormality (0.8), hypertension (0.7), tachycardia (0.5), rash (0.5), and hypochromic anemia (0.5). Most of these individual adverse events are have a higher reporting rate in the US compared to Europe. The adverse event profile for Japanese adults finds that only nausea (0.9%), vasodilation (0.3%), and paresthesia (0.3%) occur in > 0.1% of the subjects.

MO Comment: The sponsor should provide for each body system and individual adverse events similar geographic breakdown sub-analyses by imaging indication (CNS vs Liver), by formulation (0.25 M vs 0.5 M), by dose, by administration method (bolus vs infusion).

MultiHance has injection site adverse event profile is comparable to that reported in the Magnevist, Prohance, Omniscan, and OptiMark package inserts (see Table # 48)..

Table # 50 Comparison of Most Common Adverse Events (%)

	MultiHance	Magnevist*	ProHance*	Omniscan*	OptiMARK*
Headache	1.7	5.5	-	<3%	8.4
Nausea	1.5	2.5	1.4	<3%	3.0
Injection Site Reaction	1.1	2.8	-	<1%	1.2
Vasodilation	0.9	-	-	-	2.3
Paresthesia	0.7	-	-	-	2.1
Taste Perversion	0.6	-	1.4	-	4.4
Dizziness	0.5	<2%	-	<3%	3.1
Laboratory Test Abnormality	0.5	-	-	-	-

*data obtained from package insert

3. Clinical Laboratory Evaluations

For studies in the Adult Patient Population, the scheduled time-points at which parameters were measured varied across the studies. Generally, clinical laboratory tests for the majority of patients were obtained within 24 hours prior to the first injection of study agent and at 24 hours post-dose. In several uncontrolled CNS, liver, and cardiac studies data were also obtained at 3 hours post-dose and in the special population studies laboratory evaluations were also obtained at 72 hours post-dose. The sponsor provided the range of normal values and the prospectively defined changes required for a substantial change in laboratory parameters. The sponsor presented shift tables for patients with values outside the normal range and for parameters groups (hematology,

hepatic function, renal function, and iron metabolism). In addition, the sponsor noted patients that had a marked abnormality which is defined as a change from baseline that was outside the substantial change limit and outside the normal reference range.

The sponsor did not incorporate into the overall MultiHance safety reports (NDA submission's Integrated Summary of Safety and the 4 month Safety Update), the 1218 Japanese patients, the 110 pediatric subjects, or the 63 healthy European volunteers. Therefore, a complete evaluation of safety is compromised and limited only to the 2574 adult US/European subjects.

MO *Comment: the sponsor will need to reanalyze and revise the ISS report and 4 month safety update to include all subjects who received MultiHance.*

a. Complete Blood Count

Less than 1% of the subjects had a "marked abnormality" for hematocrit, hemoglobin, RBC count, WBC count, and platelet count. Almost all the post-dose evaluations were obtained only at 24 hours post-dose. No consistent trends were identified.

b. Clotting Function Panel

Clotting function was not evaluated.

c. Chem-Screen Panel, Electrolytes, Hepatic Function Panel

Only glucose had "marked abnormality" changes of >1%. However, these were not fasting glucose values and glucose is known to fluctuate depending on the time is was obtained after a meal. No consistent trends were identified for sodium, potasssium, total bilirubin, direct bilirubin, AST (SGOT), ALT (SGPT), GGT, LDH, creatinine, total protein or albumin.

d. Iron Metabolism Panel

At 24 hours post-dose:
Total iron had "marked abnormality" increases of 3.3% and decreases of 2.4%.
Ferritin had "marked abnormality" increases of 2.2% and decreases of 0.3%.
Transferrin had "marked abnormality" increases of 0.2% and decreases of 2.3%
No consistent trends were identified.

e. Urinalysis

Although the sponsor collected data (pH, specific gravity, protein, glucose, ketones, blood) for the adult population and pharmacokinetic data for the pediatric population, the sponsor did not provide any narrative or statistical analysis of the data and did not obtain microscopic data (i.e. casts).

4. Vital Signs

No clinically meaningful trends were noted. For each of the parameters, the percentages of patients with increases from baseline of potential importance were very similar to or the same as the percentage of patients with decreases.

5. Electrocardiograms

ECG normal range of values [pg 78 vol 127]

PR	115-196	>32
QRS	79-118	>16
QT	326-445	>48

October 13, 1999 - A teleconference was held. This was a follow-up to the pre-NDA meeting of June 17, 1999. The following information was obtained from the FDA meeting minutes, the FDA had the following recommendations regarding the reporting of EKC data from the various clinical sources (the data should be tabulated by parameter, PR interval data should be displayed for prolongations of ≤ 200 msec or ≥. 201 msec, QRS ≤ 100 msec and ≥ 101 msec, QT absolute ≥ 450 msec, and QTc ≤ 30 msce, ≥ 31 msec, ≤ 60 msec, ≥ 61 msec. At the request of the FDA, the sponsor stated that it would include some images from the study for the FDA to view in the planned submission.

October 21, 1999 - A teleconference was held as a follow-up to the teleconference of October 13, 1999. The reason for this T-con was to clarify the presentation of EKG data and the normal/abnormal range of parameters in the NDA.

For the PR Interval	≥ 201 msec
For the QRS Interval	≥ 101 msec
For the QTc & QT Interval	≥ 450 msec (post-dose with MultiHance)
For the QTc/QT change from baseline (magnitude of change)	≤ 30 msec, ≥ 31 msec, ≤ 60 msec, ≥ 61 msec

The FDA asked the sponsor to comment on the presence, change, appearance in either the T or U wave. For each patient that had prolongation of any parameters of the EKG, comments should be made that may be relevant (other parameters, vitals, medical history, medications, etc.).

Table # 51 EKG Evaluations in the Adult and Pediatric Studies

	Screening Baseline	Immediately post-dose*	1 hour ±15 min	2 hours ±15 min	4 hours ±30 min	24 hours ±3 hours
43,779-9A & 9B Adult CNS	12 lead <24 hrs	NP	12 lead after 2nd injection	12 lead	12 lead	12 lead
B19036/020 Adult CNS	12 lead < 15 days	NP	12 lead after 3rd injection	NP	NP	12 lead
B19036/036 Pediatric CNS N=85	NP	NP	NP	NP	NP	NP
43,779-10 Pediatric PK N=25	12 lead <1 hour	NP	12 lead	12 lead	12 lead	12 lead
43,779-1 Adult Liver	12 lead	NP	12 lead	12 lead	12 lead	12 lead
B19036/010/039 Adult Liver	12 lead < 7 days	NP	NP	NP	NP	12 lead
B19036/015 Adult Liver N=97	12 lead < 7 days	12 lead	NP	12 lead	12 lead	12 lead
B19036/016 Adult Liver N=113	NP	NP	NP	NP	NP	NP
US/EUROPEAN ADULTS QTc (msec)						
	N=663	N=181	N=520	N=519	N=516	N=657
Mean baseline	420.5	414.5	422.6	422.7	422.6	420.5
Mean Δ	-	2.2	1.5	1.2	1.5	0.8
Minimum	-	-50	-123	-56	-55	-108
Maximum	-	70	66	65	328	180
No Change	-	41 (22.7)	19 (3.7)	28 (5.4)	20 (3.9)	NR
Increase ≤30	-	73 (40.3)	249 (47.9)	222 (42.8)	236 (45.7)	NR
Increase ≥31-≤60	-	6 (3.3)	13 (2.5)	25 (4.8)	12 (2.3)	23 (3.5)
Increase >60	-	1 (0.6)	1 (0.2)	3 (0.6)	4 (0.8)	4 (0.6)
Decrease ≤30	-	54 (29.8)	227 (43.7)	227 (43.7)	228 (44.2)	NR
Decrease ≥31-≤60	-	6 (3.3)	9 (1.7)	14 (2.7)	16 (3.1)	14 (2.1)
Decrease >60	-	0	2 (0.4)	0	0	2 (0.3)

*30% were obtained within 10 minutes post-dose and 70% were obtained 30 minutes post-dose (however the sponsor did not clarify which post-dose in regimens with more than one dose)
NP = not performed
NR = not reported

The origin of the immediate post-dose numbers was no provided by the sponsor. The sponsor should have also provided a breakdown by dose, formulation, method of administration, etc. Study B19036/015 used a single dose of 0.05 or 0.1 mmol/kg (0.25 M or 0.5 M formulation, respectively)

MO Comments: The overall ECG analysis and reporting is inadequate. Some of the important point are described below:
The sponsor did not clearly state whether a cardiologist performed the EKG readings, therefore, the results are reliable.
Only 25 pediatric patient EKG evaluations were available but none were obtained immediately post-dose and the QTc intervals were not calculated or analyzed.
Only one adult study evaluated 12 lead EKGs immediately post-dose (B19036/015).
QTc intervals were not subanalyzed by indication (CNS vs Liver), dose (single or cumulative), sex, age, or for changes < 30 msec. The sponsor should subanalyze the data for those patients receiving the proposed single doses of [redacted] 0.1 mmol/kg (CNS) of the 0.5 M formulation, by age, sex, and level of QTc change.
The sponsor did not indicate how many patients with changes had baseline QTc or QT intervals >450 msec at the various post-dose time-points.
By reporting the mean values for baseline and QTc changes, the sponsor has not identified if these were the same or different patients with changes at each of the time points. The sponsor needs to provide the data in a format that can show the individual QTc values for each patient with a QTc change of ≥ 31 to ≤ 60 msec or > 60 msec.
Further detailed ECG analysis and reporting, especially for QT and QTc, is needed.

In the case of a repeat NDA submissiion, the sponsor should indicate the following:
Study, patient #, dose (single or cumulative), formulation, age, sex, weight, cardiologist reading, QT, QTc, QTc change from baseline, and any associated clinically relevant change in vital sign, physical examination, arrhythmias, medications for each time point.At a minimum this information should be provided for the few patients with QT or QTc increases greater than 30 msec.

6. Continuous Cardiac Monitoring

Continuous cardiac monitoring was not performed in any of the key studies.

7. Medical History

Although the sponsor collected data regarding medical history, the sponsor did not provide any narrative or statistical analysis of the data.

8. Physical Examination

Although the sponsor collected data (complete physical examination including neurological examination) regarding physical examination, the sponsor did not provide any narrative or statistical analysis of the data.

9. Injection Site Evaluation

Table # 52 Summary of Injection Related Adverse Events

	<0.05	0.05	0.1	>0.1	EU	US	V	0.25M	0.5M	Bolus	Inf	Peds
n =	161	558	1170	748	2013	624	63	398	2219	1639	721	110
IS Hemorrhage	0	1	0	0	0	1	0	0	1	1	0	0
IS Inflammation	0	1	0	1	0	2	0	0	2	2	0	0
IS Pain	2	3	4	0	3	4	2	2	5	5	2	1
IS Reaction	1	21	10	11	23	16	4	8	31	29	10	0
Contrast Infiltration	0	0	0	3	0	3	0	0	3	3	0	0
Deep Thrombophlebitis	0	0	0	1	1	0	0	0	1	1	0	0
Phlebitis	0	0	1	0	1	0	0	0	1	1	0	0
Application Site Reaction	0	1	1	2	0	4	0	0	4	4	0	0
Totals	3	27	16	18	28	30	6	10	48	46	12	1
%	1.9	4.8	1.4	2.4	1.4	4.8	9.5	2.5	2.2	2.8	1.7	0.9

IS=injection site
EU=European
US=United States
V=healthy volunteers
Inf=infusion
Peds=pediatric

MO Comment: The US has more than 3 times the rate of injection site adverse events than Europe, however, the volunteers have a rate 2 times the US patient population rate. The formulation does not appear to differ. The bolus injection has a rate 1.6 times greater than with infusion. There appears to be a much higher rate of injection site adverse events with the 0.05 mmol/kg dose than any of the others. [a possible explanation to explore include are these cases more likely to have been US patients given a bolus injection?].
Compared to the Magnevist package insert (2.3% for "injection site coldness") and OptiMark package insert (2.7% for "injection site"), the rate of injection site reactions is in the same general range. MultiHance has no reports of limb amputation, compartment syndrome, paralysis, or numbness of the injected arm. Comparison cannot be made to ProHance and Omniscan without performing the same analysis of the combination of injection site adverse events.

10. Protocol Deviations/Premature Discontinuations

The sponsor did not summarize the protocol deviation for all the 83 studies.

Tables # 53 & 54 shows the discontinuation for the enrolled subjects and the dosed subjects, respectively.

Table # 53 Discontinuations (Enrolled subjects)

	Adult US/European Population N=2701	Adult Japanese Population N=NA	Pediatric US/European Population N=136
Discontinued Prior to Receiving Study Agent:	64	-	26
Reason not given	5	-	0
Non-study related reasons	21	-	26
Adverse Event	3	-	0
Unsatisfactory compliance	4	-	0
Protocol violation	2	-	0
Other	29	-	0

NA=not available

Table # 54 Premature Discontinuation* (Dosed subjects)

	Adult US/European Population N=2637	Adult Japanese Population N=1218	Pediatric US/European Population N=110
Discontinued After Receiving Study Agent:	67	6	0
Reason not given	11	6	-
Non-study related reasons	2	-	-
Adverse Event	10	-	-
Unsatisfactory compliance	5	-	-
Protocol violation	8	-	-
Other	33	-	-
Completed Study	2570	1212	110

*A subject may have more than 1 reason for premature discontinuation

D. Adequacy of Safety Testing

a. The sponsor has not provided sufficient evidence of safety to warrant the inclusion of infants in the package insert. The safety and efficacy of infants (——— 2 years old) is based upon 15 CNS patients. For PK analysis, there was only one child (3.2 y.o.) under the age of 5 years. The adverse event profile of these 15 infants was lower than that found for adults and similar to that of children and adolescents. QTc intervals were not evaluated in the 85 pediatric CNS patients.

b. There is insufficient information to determine the effect of MultiHance on QT prolongation. The sponsor has not reported the QT and QTc intervals and the Change in QTc analyses appropriately. A reanalysis of the data should be performed to

include at a minimum, the following: Study, patient #, dose (single or cumulative), formulation, age, sex, weight, cardiologist reading, QT, QTc, QTc change from baseline, and any associated clinically relevant change in vital sign, physical examination, arrhythmias, medications for each time point.

c. The transmetalation effects of MultiHance with copper and calcium have not been evaluated. The potential arrhythmias and cardiac effects, however, are not demonstrated in vivo. The sponsor should perform an additional PK study. Zinc urinary excretion is greatly increased with worsening renal impairment, although similar findings are noted for other gadolinium agents. Iron urinary excretion is not measurable, both pre- and post-dose.

d. The sponsor must incorporate the Japanese safety data into their summary analyses. Some of the missing summary information include: age, weight, height, method of administration (bolus, infusion, both), case reports for all deaths, serious adverse events, and discontinuations, and EKG data.

e. Additional horizontal analysis of abnormal liver function tests (over time) on a per patient basis is required.

f. Microscopic urinalysis is required and complete pediatric urinanalysis is required.

g. Additional information is required for any injection site related adverse events (a search should include the following terms: phlebitis, thrombophlebitis, contrast infiltration, injection site pain, injection site inflammation, injection site infection, injection site reaction, injection site hemmorrhage, application site reaction, numbness, paralysis, compartment syndrome, amputation, and surgical release of injection limb).

E. Summary of Critical Safety Findings and Limitations of Data

a. MultiHance is mainly excreted via the urine and is readily dialyzable. Its half-life increases as expected with worsening renal impairment. There is no significant change in volume of distribution, elimination half-life, clearance, or mean cumulative urinary excretion with hepatic impairment or for children/adolescents aged 2 to 16. Additional urinalyses (pediatric and microscopic) are required to evaluate potential kidney damage. [redacted] that for dialysis patients, hemodialysis is required within [redacted] hours of MulitHance administration.

b. MultiHance does not cross the intact blood brain barrier, or exhibit significant protein binding. However, the mechanism of hepatocyte uptake and fecal excretion requires further investigation and clarification. Potential hepatic damage must be excluded with additional horizontal evaluation of the existing laboratory data (liver function tests).

c. MultiHance has a general adverse event profile similar to the other four approved gadolinium agents. The injection site adverse event profile is similar to that seen with Magnevist and OptiMark. The adverse event profile for US+European adults finds that only headache (2.4%), nausea (1.8%), injection site reaction (1.6%), and vasodilation (1.2%) occur in more than 1% of the patients/subjects, which is not unlike that of the other approved gadolinium agents. The adverse event profile for Japanese adults does not find any of the adverse events occurring in more than 1% of the patients/subjects. As seen with many other drugs, the overall and individual adverse event rates in general tend to be greater for the US population than for Europeans or Japanese.

VIII. Dosing, Regimen, and Administration Issues

a. In the proposed Key Phase III CNS studies, the sponsor did not prospectively determine, based upon the data obtained from their Phase II studies, the optimal dose, formulation, dosing regimen, , method of administration (bolus or infusion), or imaging parameters (T1 vs T2 vs PD, SE vs GE vs FSE vs , dynamic vs. delayed) to study.

b. The clinical advantage and mechanism of action for a second dose of MultiHance for the specific evaluation of metastatic CNS lesions (as opposed to the other CNS lesions) were not clearly defined or evaluated. It is possible that it is the delayed timing of the post-2nd dose imaging, and not the cumulative dose, that is the important factor in improving the enhancement of CNS metastatic lesions.

c. The clinical advantage and mechanism of action for delayed hepatic imaging has not been clearly identified. Perhaps, for some hepatic lesions, dynamic imaging is required and for others, delayed imaging is advantageous. The sponsor needs to identify the specific situations that require dynamic, delayed, or both types of hepatic imaging and include this information in the package insert.

d. The package insert should indicate that hemodialysis is required within hours post-dose.

IX. Use in Special Populations

a. Renally impaired patient labs were obtained within 24 hours, and at 2, 24, 48, and 72 hours post-dose.
b. Dialysis and hepatically impaired patient labs were obtained within 24 hours pre-dose and at 24 and 72 hours post-dose
c. Pediatric PK labs were obtained between 48-72 hours pre-dose and at 24 and 72 hours post-dose.
d. For all the above subjects, the normal range for serum calcium was 8.4 to 10.3. Ionic calcium was not evaluated. No urine tests for Fe, Zn, Mg, or Cu were obtained.

X. Conclusions and Recommendations

a. The sponsor has not provided sufficient evidence of safety to warrant the inclusion of infants in the package insert. The safety and efficacy of infants (——— 2 years old) is based upon 15 CNS patients. For PK analysis, there was only one child (3.2 y.o.) under the age of 5 years. The adverse event profile of these 15 infants was lower than that found for adults and similar to that of children and adolescents. QTc intervals were not evaluated in the 85 pediatric CNS patients. The true interactive effect of MultiHance on patients with immature kidneys, liver, and blood brain barrier cannot be assessed.

b. There is insufficient information to determine the effect of MultiHance on QT prolongation. The sponsor has not reported the QT and QTc intervals and the Change in QTc analyses appropriately. A reanalysis of the data should be performed to include at a minimum, the following: Study, patient #, dose (single or cumulative), formulation, age, sex, weight, cardiologist reading, QT, QTc, QTc change from baseline, and any associated clinically relevant change in vital sign, physical examination, arrhythmias, medications for each time point.

c. The transmetalation effects of MultiHance with copper, manganese, and calcium have not been evaluated. The potential arrhythmias and cardiac effects, however, are not demonstrated in vivo. The sponsor should perform an additional PK study. Zinc urinary excretion is greatly increased with worsening renal impairment, although similar findings are noted for other gadolinium agents. Iron urinary excretion is not measurable, both pre- and post-dose.

d. MultiHance is mainly excreted via the urine and is readily dialyzable. Its half-life increases as expected with worsening renal impairment. There is no significant change in volume of distribution, elimination half-life, clearance, or mean cumulative urinary excretion with hepatic impairment or for children/adolescents aged 2 to 16. Additional urinalyses (pediatric and microscopic) are required to evaluate potential kidney damage.

e. MultiHance does not cross the blood brain barrier, or exhibit significant protein binding. However, the mechanism of hepatocyte uptake and fecal excretion requires further investigation and clarification. Potential hepatic damage must be excluded with additional horizontal evaluation of the existing laboratory data (liver function tests). The lipophilic structure of MultiHance has not been proven to have a significant imaging advantage.

f. The sponsor must incorporate the Japanese safety data into their summary analyses. Some of the missing summary information include: age, weight, height, method of administration (bolus, infusion, both), case reports for all deaths, serious adverse events, and discontinuations, and EKG data.

g. MultiHance has a general adverse event profile similar to the other four approved gadolinium agents. The adverse event profile for US/European adults finds that only headache (2.4%), nausea (1.8%), injection site reaction (1.6%), and vasodilation (1.2%) occur in more than 1% of the patients/subjects, which is not unlike that of the other approved gadolinium agents. The adverse event profile for Japanese adults does not find any of the adverse events occurring in more than 1% of the patients/subjects.

h. The injection site adverse event profile is similar to that seen with Magnevist and OptiMark. Additional information is required for all injection site related adverse events (a search should include the following terms: phlebitis, thrombophlebitis, contrast infiltration, injection site pain, injection site inflammation, injection site infection, injection site reaction, injection site hemmorrhage, application site reaction, numbness, paralysis, compartment syndrome, amputation, and surgical release of injection limb).

i. In the proposed Key Phase III CNS [redacted] studies, the sponsor did not prospectively determine, based upon the data from the Phase II studies, the optimal dose, formulation, dosing regimen (single or multiple doses), method of administration (bolus or infusion), or imaging parameters (T1 vs T2 vs PD, SE vs GE vs FSE vs [redacted], dynamic vs. delayed) to study.

j. [redacted]

k. The clinical advantage and mechanism of action for delayed hepatic imaging has not been clearly identified. Perhaps, for some hepatic lesions dynamic imaging is required and for others delayed imaging is advantageous. The sponsor needs to identify the specific situations that require dynamic, delayed, or both types of hepatic imaging and include this information in the package insert.

l. [redacted]

XI. Appendix

A. Tables

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/s/

Roger Li
2/22/02 02:19:47 PM
MEDICAL OFFICER
see attached complete NDA MO review

Ramesh Raman
2/22/02 06:56:25 PM
MEDICAL OFFICER
Concur in essence with Dr. Li and the recommendations. See team leader's memo to file for further details.

Patricia Love
2/27/02 03:58:41 PM
MEDICAL OFFICER
This represents the conclusions for materials received before 2/25/02. I agree with the essence, My memo to the file should be seen for other comments. On 2/27, a major amendment was received. Final decision is deferred.