remain the same since all pre dose scans are still part of the set. Thus the score for the paired read can go up or remain the same but will not go down. For the whole population of lesions, the score for the paired read is virtually guaranteed to be higher than the pre-dose read. On the other hand on a pre dose vs. post dose read, the score can go down if the post is worse than the pre and since the score can go either up or down for each lesion the result may be positive or negative. These visualization endpoints although they have been used previously do not determine whether the post dose scan is clinically useful or not. Changes between the pre and post scans may be as important in making a diagnosis as properties of the individual scans. An important criterion in making a diagnosis is whether a lesion enhances or not (malignant lesions tend to enhance) This can only be determined by comparing the pre T1 to the enhanced T1. If a lesion doesn't enhance this fact may be important in making a diagnosis even if the lesion is not well visualized on the post T1. Thus a comparison between pre dose and paired reads, while appropriate for a ***diagnostic*** *endpoint would not be appropriate for the three* ***visualization*** *endpoints used in this study.*

Results:

MH-105

Primary outcome variables: By lesion analysis, pre-dose vs. post –dose, Lesion Border Delineation, Visualization of Internal Morphology, Contrast Enhancement

Pre vs. Post all lesion analysis

Table 6 Scores for Lesion Border Delineation Mean ±SD by individual lesion (table 3-4 p149 v24) MH-105			
	MultiHance		Omniscan
	0.05mmol/kg	0.1mmol/kg	0.1mmol/kg
Reader 1			
N**	297	363	350
Predose score (mean ± SD)	1.7±1.05	1.7±1.05	1.6±1.08
Postdose score (mean ± SD)	1.7±1.33	1.8±1.40	1.8±1.34
p	0.393	0.286	0.010
Reader 2			
N**	355	381	373
Predose score (mean ± SD)	1.6±1.01	1.7±0.99	1.6±106
Postdose score (mean ± SD)	1.6±1.42	1.6±1.44	1.8±1.48
p	0.742	0.729	0.171
Reader 3			
N**	245	271	282
Predose score (mean ± SD)	1.9±1.06	1.8±1.19	1.8±1.13
Postdose score (mean ± SD)	1.6±1.53	1.8±1.59	1.7±1.50
p	(0.009)*	0.936	0.713

*p values in parenthesis mean that pre-dose had a higher score than post-dose

** Total number of lesions seen by reader on all scan sets

Table 7 Scores for Visualization of Internal Morphology Mean ±SD by lesion analysis (table 3-5 p150 v24) MH-105			
	MultiHance		Omniscan
	0.05mmol/kg	0.1mmol/kg	0.1mmol/kg
Reader 1			
N*	297	363	350
Predose score (mean ± SD)	1.8±110	1.8±103	1.6±106
Postdose score (mean ± SD)	1.8±135	1.8±137	1.8±131
p	1.00	0.697	0.029
Reader 2			
N*	355	381	373
Predose score (mean ± SD)	1.7±108	1.8±106	1.6±109
Postdose score (mean ± SD)	1.7±102	1.7±150	1.9±156
p	0.897	0.642	0.034
Reader 3			
N*	245	271	282
Predose score (mean ± SD)	2.0±1.07	1.9±1.21	1.9±1.15
Postdose score (mean ± SD)	1.6±1.56	1.9±1.64	1.8±1.53
p	(0.002)	0.979	0.679

* Total number of lesions seen by reader on all scan sets

Table 8 Scores for Contrast Enhancement Mean ±SD by lesion analysis (table 3-6 p151 v24) MH-105			
	MultiHance		Omniscan
	0.05mmol/kg	0.1mmol/kg	0.1mmol/kg
Reader 1			
N*	297	363	350
Predose score (mean ± SD)	2.1±1.19	2.1±1.19	1.9±1.25
Postdose score (mean ± SD)	2.0±1.44	2.0±1.48	2.1±1.42
p	(0.636)	(0.449)	0.229
Reader 2			
N*	355	381	373
Predose score (mean ± SD)	1.7±1.08	1.8±1.09	1.7±1.14
Postdose score (mean ± SD)	1.7±1.51	1.7±1.51	1.9±1.56
p	0.712	(0.374)	0.257
Reader 3			
N*	245	271	282
Predose score (mean ± SD)	2.4±1.17	2.2±1.33	2.2±1.29
Postdose score (mean ± SD)	1.7±1.60	2.0±1.65	2.0±1.62
p	(<0.001)	(0.113)	(0.131)

* Total number of lesions seen by reader on all scan sets

Reviewer's Comment: It is interesting to note that on contrast enhancement, pre dose gets a higher score than post dose in the majority of cases

- For the primary outcome variables, a statistically significant difference in favor of the post dose scans does not occur for any of the three parameters for any of the three blinded readers for the pivotal trial. Efficacy has not been demonstrated

- No statistically significant difference between the scores for the two MultiHance doses is seen for any of the three visualization outcome variables, for any of the three clinical trials

MH-106

Study MH-106 Supportive study (Re-read of study B19036/020)

B19036/020 was a European randomized double blind study testing two dosing regimens, each consisting of three sequential doses of MultiHance given at 15 minute intervals. The regimens were

1. 0.05 + 0.05 +0.1 mmol/kg
2. 0.1 + 0.1+ 0.1 mmol/kg

149 patients (74 regimen 1 and 75 regimen 2) were available for re-read

Reread Results: Primary outcome variables pre-dose read vs. post dose read

There was no active comparator in this study

The blinded read was performed in the same way as for MH-105

Table 9 Scores for Lesion Border Delineation: Mean ±SD (By Lesion analysis) MH-106 (table 3-36 p200v24)			
	MultiHance		Omniscan
	0.05mmol/kg	0.1mmol/kg	0.1mmol/kg
Reader 1			
N*	142	250	N/A
Predose score (mean ± SD)	1.0±0.85	0.7±0.81	N/A
Postdose score (mean ± SD)	2.3±1.13	2.4±1.09	N/A
p	<0.001	<0.001	N/A
Reader 2			
N*	180	274	N/A
Predose score (mean ± SD)	1.2±1.18	1.0±1.10	N/A
Postdose score (mean ± SD)	2.5±1.18	2.6±1.19	N/A
p	<0.001	<0.001	N/A
Reader 3			
N*	171	259	N/A
Predose score (mean ± SD)	1.3±1.14	1.0±1.10	N/A
Postdose score (mean ± SD)	2.5±1.32	2.9±1.14	N/A
p	<0.001	<0.001	N/A

* Total number of lesions seen by reader on all scan sets

Table 10 Scores for Visualization of Internal Morphology: Mean ±SD (By Lesion analysis) MH-106 (table 3-37 p200 v24)			
	MultiHance		Omniscan
	0.05mmol/kg	0.1mmol/kg	0.1mmol/kg
Reader 1			
N*	142	250	N/A
Predose score (mean ± SD)	1.1±0.98	0.8±0.98	N/A
Postdose score (mean ± SD)	2.5±1.11	2.5±1.10	N/A
p	<0.001	<0.001	N/A
Reader 2			
N*	180	274	N/A
Predose score (mean ± SD)	1.3±1.20	1.2±1.21	N/A
Postdose score (mean ± SD)	1.7±1.51	2.6±1.13	N/A
p	<0.001	<0.001	N/A
Reader 3			
N*	171	259	N/A
Predose score (mean ± SD)	1.6±1.39	1.2±1.21	N/A
Postdose score (mean ± SD)	2.9±1.29	3.2±1.04	N/A
p	<0.001	<0.001	N/A

* Total number of lesions seen by reader on all scan sets

Table 11 Scores for Contrast Enhancement Mean ±SD(By Lesion analysis) MH-106 (table 3-38 p201 v24)			
	MultiHance		Omniscan
	0.05mmol/kg	0.1mmol/kg	0.1mmol/kg
Reader 1			
N*	142	250	N/A
Predose score (mean ± SD)	1.0±0.93	0.7±0.84	N/A
Postdose score (mean ± SD)	2.5±1.12	2.6±1.06	N/A
p	<0.001	<0.001	N/A
Reader 2			
N*	180	274	N/A
Predose score (mean ± SD)	1.4±1.31	1.2±1.24	N/A
Postdose score (mean ± SD)	2.6±1.10	2.7±1.13	N/A
p	<0.001	<0.001	N/A
Reader 3			
N*	171	259	N/A
Predose score (mean ± SD)	1.4±1.20	1.1±1.24	N/A
Postdose score (mean ± SD)	2.7±1.27	3.05±1.65	N/A
p	<0.001	<0.001	N/A

* Total number of lesions seen by reader on all scan sets

- In this study the difference between post dose scores and pre dose scores is statistically significant for both doses, for all three readers for al three visualization endpoints. This result is contradictory to the result of the pivotal trials
- In this study, there was no statistically significant difference between the two doses for any of the three readers for any of the three visualization endpoints. This result is in agreement with the result of the pivotal trials

MH-112 is a reread of pediatric study B19036/036

F. Conclusions

1. Efficacy has not been demonstrated for the primary outcome variables for the re-read of the pivotal trials.
2. A difference in efficacy has not been demonstrated between the 0.05 mmol/kg dose and the 0.1 mmol/kg dose in any clinical trials in adults
3.

4. Demonstration of efficacy in the supportive European trial alone is not sufficient to support approval

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VII Integrated review of Safety

C. Brief Statement of Conclusions

1.The sponsor has not performed the drug interaction study requested by the agency in the action letter of May 24, 2002

2.The sponsor has not performed the placebo controlled cardiovascular study requested by the agency in the action letter of May 24, 2002

3.In the integrated safety database from the US and Europe the overall incidence of adverse events is higher in the treatment group than in the Placebo group. This difference is statistically significant (p =0.0003). This higher incidence is also seen in some subgroup analyses (e.g. Table LLL p156 v2)

4.The sponsor's analysis of patients taking Glyburide does not directly address the question of drug-drug competition for the CMOAT/MRP2 transporter system. A drug interaction study is required to resolve this issue.

D. Description of Patient Exposure

The sponsor's reanalysis of safety data is based on a review of data from 2892 adult subjects and 110 pediatric subjects in the Europe-US-China database, and 1218 adult subjects in the Japanese database. The sponsor analyzed THE Japanese database of 1218 subjects separately.

1. Patient exposure, deaths and serious adverse events

Table 13 Population Exposed to MultiHance (p 6-11, table I p23, table T p54, table U p55 v 42)

	Adult Subjects		Peds	Total
	US, Europe, China	Japan		
Completed trials	71	11	2	84
Ongoing trials	9	0	0	9
Exposed to MultiHance	2892	1218	110	4220
Adverse events	519 (18%)	49 (4%)	14 (13%)	582 (14%)
Deaths	2 (0.06%)	3 (0.2%)	0	5 (0.15%)
SAEs (including deaths)	14 (0.5%)	6 (0.5%)	2	22 (0.5%)
Discontinuations for AEs	10 (0.3%)	0	0	10 90.2%)

C. Deaths and serious Adverse Events

All deaths and serious adverse events were reported in the previous submission. There were no new deaths or serious adverse events reported in the resubmission The individual patients who died or experienced serious adverse events were discussed in the medical officer's review of the previous submission

2. Deaths and Serious Adverse events in adults re-submission and previous submissions

Table 14 Adults (US, Europe China) (Table P p42, Table I p23 v42)			
	Previous		Re-submission (10/10/03
	Submission (4/20/00)	Safety Update (9/13/01)	
Exposed to MultiHance	1808	2637	2892
Deaths	1	2	2
SAEs	10	14	14
Discontinuations for AEs	8	10	10

There were no new deaths, SAEs or discontinuations re3ported in this re-submission. All deaths, SAEs and discontinuations have been discussed in the medical review of the previous submission

3.Deaths and Serious Adverse events in the pediatric population re-submission and previous submissions

Table 15 Deaths and Serious Adverse events in the pediatric population (table u p55 v42)			
	Previous		Re-submission (10/10/03
	Submission (4/20/00)	Safety Update (9/13/01)	
Exposed to MultiHance	110	110	110
Deaths	0	0	0
SAEs	2	2	2
Discontinuations	0	0	0

There were no new deaths SAEs or discontinuations reported in the re-submission for the pediatric population

7. Deaths and Serious Adverse events in the Japanese studies re-submission and previous submissions.

Table 16 Deaths and Serious Adverse events in the Japanese studies (table v p56 v42)			
	Previous Submissions		This Submission (10/10/03)
	Submission (4/20/00)	Safety Update (9/13/01)	
Exposed to MultiHance	1213	1213	1218
Deaths	3	3	3
SAEs	6	6	6

There were no new deaths SAEs or discontinuations reported in the re-submission for the Japanese population

D. Sponsor's Response to Specific Deficiencies Mentioned in the Action Letter

Safety data contained in this re-submission consisted of re-analyses of data from subgroups of patients contained in the previous submission

1. The sponsor identified 42 subjects taking the diabetes drug Glyburide, which, is excreted by the CMOAT/MRP2 system. AE data on these 42 subjects were analyzed and compared to data from the 2531 subjects who did not take Glyburide (table B p22)

2. Re-analysis of QTc prolongation was based on the 47 subjects (p86) in the cardiovascular study 43-770-12 and on the 25 pediatric subjects who had EKG data from the pediatric pharmacokinetic study 43-779-10 (p121)
3. Data on urinalysis variables is presented in table VV (p133 v2) and WW (p135 v2) The number of subjects for whom data is available varies with both time of measurement and the parameter being measured.

Reviewer's comment: With the number of Patients so variable it is difficult to interpret the data presented by the sponsor. There is no explanation for this variability in this submission

AE data is available from 852 renally impaired (679 mild, 128 moderate and 45 severe)

Urinalysis data is available from 31 renally impaired subjects (11 placebo, 20 MultiHance) from study 43-779-4

85/2637 patients from the US and European studies have been identified with local adverse events.

G. Methods and specific Findings of Safety Review

1) Only a small number of patients taking Glyburide were identified in the database. The adverse event rate was actually higher in patients not taking Glyburide than in patients not taking Glyburide, whereas a drug interaction with MultiHance would be expected to lead to a higher AE incidence in the Glyburide group. Even if MultiHance did interfere with the excretion of Glyburide it is not clear that lower serum glucose or AEs associated with hypoglycemia would occur. The antineoplastic drugs which could also compete for the CMOAT/MRP2 transporter and which probably have a narrower therapeutic index than Glyburide were not studied, because too few patients taking these drugs were identified in the safety database. However MultiHance is eliminated primarily by the kidney with an elimination half -life of 1-2 hours. MultiHance will be given as a single dose. If it is competing with other drugs for the CMOAT/MRP2 transporter, it will only do so for a short period of time. Even for renally impaired patients, the half-life is short compared to that of most drugs metabolized by the liver. In dialysis patients MultiHance will be eliminated. To obtain a definitive answer to this question a pre clinical drug interaction study, as previously requested by the agency, is required.

The agency expressed a concern with potential liver toxicity [redacted] a CNS indication. [redacted] only a minority of patients imaged for the CNS indication would be expected to have hepatic impairment. As stated in the action letter of May 24, 2002 concern was raised because of clinical data showed increase in liver enzymes and bilirubin in patients with pre-existing liver disease and an increased incidence of pruritis in patients with pre-existing cirrhosis. Since only a relatively small number of patients imaged for the CNS indication would be expected to have pre-existing liver disease, this concern could be handled by a warning, and should not be an approvability issue. The sponsor should be asked to identify all patients with liver impairment in the CNS studies and present relevant laboratory values and AEs.

2) The sponsor has not performed the clinical cardiovascular study requested. The sponsor has reanalyzed old EKG data from study 43-770-12 using a questionable individualized correction method. The most commonly used correction methods used are Bazet's and Fredericia's. Correction formulas based on linear regression have been proposed (QTc preliminary concept paper, 11/15/02) The sponsor uses a *non-linear* regression method of individualized correction to reanalyze QT data from study 43-779-12. Data from the entire database was not reanalyzed.

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A. Clinical Safety Database

Table 17 83 Clinical Studies in Clinical Safety Database (MO review first cycle table 8 p27)					
Study	location	Imaged Organ	Patients completed	comments	Number of studies
43,779-9A, 43,779-9,B placebo controlled studies	USA	CNS	276	Pivotal	2
B19036/020	Europe	CNS	150		1
B19036/036	Europe	CNS	85	pediatric	1
Other European	Europe	CNS	144		14
Japanese	Japan	CNS	379		3
US Liver Studies	USA	Liver	317		4
European Liver Studies	Europe	Liver	935		22
Japanese Liver Studies	Japan	Liver	485		5
Other US (pediatric and renal dialysis)	US	Liver	56		3
Other European (PK, Cardiac, MRA, Breast)	Europe		784		21
Other Japan	Japan		352		3

Reviewers Comment:

Subjects who received MultiHance

In the US-Europe- China studies, there were 2785 adult patients, and 107 adult normal volunteers for a total of 2892 adult subjects

In the Japanese studies there were 1196 adult patients, 22 adult volunteers for a total of 1218 Japanese adult subjects

In the pediatric studies, there were 85 patients and 25 normal volunteers

Table 18 Subjects Dosed with MultiHance (tables VVV p191 v2, table WWW p192 v, table PPP p176 v2, table LLLp166 v2)			
	Adult	Pediatric	Total
US and Europe	2653	110	2763
Japan	1218	-	1218
China	132	-	132
US Europe, China	2785	110	2895
US Europe, China and Japan		110	4113

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Table 19. Adverse Events by Subgroup Adult Patients Dosed With MultiHance (US, Europe and China) (table VVV p191 v2, table LLLp166 v2)			
	Number of patients	Number with AEs	Percent with AEs
All	2785	493	18%
Male	1585	262	17%
Female	1200	231	19%
Age < 65	2005	382	19%
Age > 65	780	111	14%
White	2498	444	18%
Black	79	24	30%
Hispanic	29	4	14%
Asian	162	19	11%
Other	11	2	18%
Missing?	6	0	0%
Europe	2006	253	13%
US	647	230	36%
China	132	10	7.6%
Adverse Events by Age in Pediatric Subjects Dosed With MultiHance Table WWW p192			
Total	110	14	13%
Age < 2	15	2	13%
2 < age < 12	69	8	12%
>12	26	4	15%
Adverse Events in Japanese Subjects Dosed with MultiHance (analyzed separately by sponsor and not included in above totals (table PPP p176 v2)			
Japan	1218	49	4%

B. Safety deficiencies identified in the action letter of May 24, 2002

1. "The application lacks sufficient data to fully assess the risk of MultiHance on the liver"

a) MultiHance is excreted by the liver through the ATP dependent canalicular multispecific anion transporter (cMOAT). This may result in competition for cMOAT with other drugs eliminated by the same mechanism. The effect of MultiHance on the pharmacokinetics of such drugs may be clinically significant for drugs with a narrow therapeutic index

"Appropriate drug interaction studies are needed. Please submit protocols for FDA comments prior to initiation of these studies"

b) The stated mechanism of action [redacted] is hepatocellular uptake. The preclinical observation of hepatic vacuolization and necrosis raises concern about the hepatocellular safety of MultiHance

2) "The application lacks sufficient data to fully characterize the safety of MultiHance on the cardiovascular system"

1) "Conduct placebo controlled studies in patients using higher than indicated doses of MultiHance (at least 4x) to determine QT effects. We recommend that you submit your proposed protocol. It will be consulted to the Division of Cardio-Renal Drug Products to assess the acceptability in evaluating QT effects

3) The application lacks sufficient data in adults and pediatric patients to determine the effect of MultiHance on the renal system

4) The application lacks sufficient data on local adverse events

5) The application lacks the case report forms (CRFs) for patients who died during clinical trials

6) The application lacks the required reporting of all patients in the Integrated Safety summary

Reviewer's Comment: The action letter of May 24, 2002 specifically asked for two new clinical studies.

1) "Appropriate drug interaction studies are needed. Please submit protocols for FDA comments prior to initiation of these studies"

2) "Conduct placebo controlled studies in patients using higher than indicated doses of MultiHance (at least 4x) to determine QT effects. We recommend that you submit your proposed protocol. It will be consulted to the Division of Cardio-Renal Drug Products to assess the acceptability in evaluating QT effects"

C. Sponsor's Response to r the action letter.

This submission reports on no new clinical trials. It contains no new clinical data. The sponsor maintains that a review and reanalysis of data from previously submitted studies will be sufficient to meet FDA concerns. Below the sponsor's response to each safety deficiency listed in the action letter is discussed separately.

1. Drug-Drug interaction –Competition for the cMOAT transporter

a. The sponsor has performed no new clinical or preclinical drug interaction studies and has submitted no new clinical data. The sponsor has reviewed previously submitted data and has found a total of 61 patients in the MultiHance safety database of 2574 adult patients who had been taking one of 6 drugs which had 40% or more excretion by the cMOAT pathway and which might pose a safety concern. The number of patients taking each drug is given below

Table 20 Patients in US and Europe Safety Database (N = 2574) Taking cMOAT excreted drugs when imaged with MultiHance (p19v2)	
Drug	Number of patients
Glibenclamide (Glyburide)	43
Tamoxifen	7
Doxorubicin	4
Paclitaxel (Taxol)	3
Daunorubicin (adriamycin)	1

Reviewer's comment: Glyburide is the only one of the above drugs taken by a substantial number of patients. Data for the other drugs are available for such small numbers of patients as to be considered as anecdotal. Even for Glyburide, there are too few patients for an analysis of AEs by Costart category. Glyburide is a drug used to treat type 2 diabetes. Tamoxifen is used in the hormonal treatment of breast cancer. Doxorubicin, Daunorubicin and Paclitaxel are cancer chemotherapy agents.

The sponsor speculates that if MultiHance interfered with the excretion of Glyburide there would be a difference in the incidence of hypoglycemia in the treatment group vs. the placebo group. The sponsor has reanalyzed the data in the safety database looking for evidence of such a difference in the data for adverse events. The sponsor first considered adverse events by Costart categories. The total number of adverse events were:

Table 21 Totals for All Adverse Events US. and European studies table B p.022 v.2			
	All Patients N = 2574	Glyburide Patients N = 43 (1.7%)	Non Glyburide patients N = 2531 (98.3%)
Number of Adverse Events	845 (on average 0.328 events per patient)	1 (on average 0.023 events per patient)	844 (on average 0.333 events per patient) p = .0000
Number of Patients with Adverse Events	478 (18.6%)	1 (2.3%)	477 (18.8%) p = .0003

These differences are statistically significant

The sponsor also looked at laboratory values for 4 subgroups of patients. For the Glyburide patients the laboratory value of greatest interest is serum glucose

1) Patients taking Glyburide with the baseline value within the normal range
2) Patients taking Glyburide with the baseline value outside the normal range
3) Patients not taking Glyburide with the baseline value within the normal range
4) Patients not taking Glyburide with the baseline value outside the normal range

Patients whose value either remained in the normal range or remained outside the normal range were not considered.

The most relevant parameter in this context is serum glucose, which should be expected to decrease in Glyburide patients if Glyburide excretion is impaired

Table 22 Number of patients with change in serum glucose values with normal values at baseline (table C p27, table F p 30 v2)			
	3 hours	24 hours	72 hours
Glyburide normal to high	0	0	0
No Glyburide normal to high	57/233 (24.5%)	261/1344 (19.4%)	26/147 (17.7%)
Glyburide normal to low	0	0	0
No Glyburide normal to low	10/233 (4.3%)	29/1344 (2.2%)	5/147 (3.4%)

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Table 23 Number of patients with Change from in serum glucose values with abnormal values at baseline(table E p29, table G p 31 v2)			
	3 hours	24 hours	72 hours
Glyburide high to normal	0	5/35 (14.3%)	0
No Glyburide high to normal	19/57 (33.3%)	183/559 (32.7%)	21/69 (30.4%)
Glyburide low to normal	0	0	0
No Glyburide low to normal	8/14 (57.1)	43/53 (81.1%)	9/13 (69.2%)

There is no clear pattern in these data. These changes may merely reflect daily variations in serum glucose. The normal range for serum glucose is given for fasting patients. These changes may merely reflect the timing of meals. The total patient population from which the data was drawn for each time point is not clear. The fact that denominators are consistently higher at the 24 hour time point than at the other two may indicate that blood was not have been drawn for all patients at all time points, and that more patients had blood drawn at 24 hours than at any of the other two time points.

There are no apparent differences in the changes in LFTs in Glyburide patients and non-Glyburide patients.

It should be noted that the incidence of adverse events in patients not taking Glyburide is actually higher than in patients taking the drug.

b. FDA was concerned about liver toxicity because of preclinical studies showing hepatic necrosis and vacuolization. Subset analysis of bilirubin and liver enzymes in liver impaired patients was performed. The sponsor presents no new data on hepatic safety, but has reviewed previously submitted data.

Patients receiving MultiHance for the CNS indication may have co-existing liver morbidity

(patients with brain metastases can also have liver metastases), but these will only be a fraction of patients imaged.

The sponsor has presented multiple tables comparing changes in bilirubin, protein albumin and liver enzymes(tables K-P p 50-57 v2) There are 3 time points at which values were obtained, 3 hours, 24 hours and 72 hours after dosing respectively. It should be noted that the denominators (the number of patients for which data is available) vary both for different time points and for different laboratory measurements. This pattern has already been noted for laboratory data related to Glyburide. The largest number of patients has data from the 24 hour time point. The number of patients for time points 3 hours and 72 hours is always much less. Even at 24 hours, the number of patients is always significantly less than the total number of patients in the US and European trials. The data in these tables would be more meaningful if data were available for all patients at all time points. With data presented for only small subsets of patients and no knowledge of how these subsets were formed it is not clear what conclusions could be drawn from these tables. Perhaps the most clinically significant table is the P (p57 v2) which shows the number of patients with large changes in LFTs that are most likely to be clinically significant. The sponsor considers the following changes to be "markedly abnormal:

Table 24 "Markedly Abnormal" Changes in Laboratory Parameters as Defined by Sponsor (table J p 48 v.2) Table	
Parameter	"sponsor's "markedly abnormal change from baseline
Total protein	> 30% baseline value
Albumin	> 25% baseline value
Bilirubin, direct bilirubin, SGOT, SGPT	> 150% baseline value
GGT	> 100% baseline value
Subgroup	Range of percent of patients with marked abnormal values (all LFTs) @ 24 hours
Entire population	0.1%-0.5%
Liver impairment no cirrhosis	0.1%-0.8%
Liver impairment mild cirrhosis	1.5%
Liver impairment severe cirrhosis	2.2%- 4.3%%

The incidence of "markedly abnormal" changes in LFTs is highest in subjects with severe cirrhosis. For subjects without cirrhosis, even if they have liver impairment, the incidence is < 1%

Reviewer's comment: Concern about liver toxicity can be addressed with a warning concerning patients with cirrhosis

2. FDA was concerned with QTc prolongation

"The application lacks sufficient data to fully characterize the safety of MultiHance on the cardiovascular system"

It was recommended that the sponsor perform additional clinical and preclinical studies. In particular it was recommended that an additional placebo controlled clinical studies at doses up to 4x the clinical dose to study QTc effects. The sponsor has performed no additional clinical studies and submitted no additional data. The sponsor has performed an additional pre-clinical study in monkeys, at doses up to 10x the clinical dose with no effect seen (see Pharm-Tox review and Pharm-Tox section of this review)

The sponsor has reanalyzed from study 43,779-12 (43 patient crossover study) by using another method of calculating QTc. Defining RR =HR/60bpm there are two standard methods of defining QTc:

a) Bazett's $QTc = QT/(RR)^{1/2}$

b) Fridericia's $QTc = QT/(RR)^{1/3}$

An individualized linear regression model can also be used

The sponsor has proposed to use an individualized correction based on each individual patients Pre -dose EKGs. The sponsor uses the formula

c) $QTc = QT/(RR)^{\alpha}$

Where α is different for each patient and is obtained by a non-linear regression of the patients pre –dose QT values vs. RR to find the slope. If QTc is a constant, β as RR changes, then

$$QT = \beta(RR)^{\alpha}$$

The sponsor takes the logarithm of this equation

$$\ln(QT) = \ln(\beta) + \ln(RR)$$

and performs a least squares fit to the logarithmic equation

Reviewer's comment: the problem with a logarithmic transformation is that differences at large values of RR are reduced and differences at small values are magnified. If a patient's α is in the range $1/3 < \alpha < ½$ then that's patient's correction will be intermediate between Bazett's and Fridericia's but for patients with $\alpha > ½$ the correction will be greater than Bazett's. The mean, SD and range of the values of α obtained through this calculation are not provided by the sponsor.

The results of this analysis are presented graphically in figures 2 through 5 (p91-94 v2).

Reviewer's comment: Comparing fig 3 with fig 5, it appears the early mean increase in QTc (first 5 minutes after dosing), in the MultiHance patients, using the Bazet correction, disappears when the individual patient correction is used. However, fig 1 shows that the uncorrected QT interval actually decreases in the MultiHance patients in the first 5 minutes after dosing so that the increase in QTc is mostly do to the increase in heart rate in the MultiHance patients in that time interval. Thus the patients with larger values of α

would be expected to have the largest increase in QTc. Since these patients would also have the highest corrections in the individual method, these large values would be brought back to baseline. Since historically Bazet's correction is the most common method used in the literature and previous analyses of the relationship between QTc and Torsades are based on this method, it is not clear that the individual method is justified. However the sponsor has used a similar method for Sonoview and this was found to be ok by Cardiorenal.

This result, the lack of any post-marketing reports of Torsades arrhythmias in Europe and the results of the monkey study make the of QTc prolongation leading to Torsades a remote possibility which can be dealt with a warning in the labeling

The sponsor admits that EKGs were not obtained during the pediatric CNS study (p121 v2) The sponsor notes that EKGs were obtained during the pediatric pharmacokinetic study. The pharmacokinetic study had only 25 patients and had no placebo group. EKGs were obtained. QTc values are given are given in table PP p122. The mean QTc values at 1,2, 4, and 24 hours are all less than the value at baseline.

3 Effect on the renal system

Data on urinalysis variables is presented in table VV (p133 v2) and WW(p135v2) The number of subjects for whom data is available varies with both time of measurement and the parameter being measured as shown below

Table 25 Number of Subjects with Data by Parameter and Time of Measurement After Dosing (table VV-table XX p133-136 v2)			
Parameter	3hr	24 hr	72 hr
Urine glucose	268	1398	210
Urine protein	245	1385	210
Urine blood	93	1221	210
Urine ketones	270	1415	210
Urine pH	278	1345	210
Urine Specific Gravity	280	970	211
Urine WBC	248	237	
	207	205	
Microscopic			
Urine RBC	207	205	
Urine WBC	248	237	
Urine casts	204	207	
Urine microscopic cylindroids	91	91	

Reviewer's comment: since the number of patients for whom urinalysis data is presented varies with both the parameter being measured and the time of the measurement no conclusions can be drawn from this data

The sponsor has also presented AE data from study 43-779-4 for renally impaired patients and from study 43-779-5 for dialysis patients

Table 26 Number of Renally Compromised and Dialysis Patients with Adverse Events (table RR p128 v2)			
Renally Compromised Patients, Study 43-779-4 n= 32			
Placebo n = 12		MultiHance n=20	
Total	Related	Total	Related
5 (42%)	2 (17%)	5 (25%)	0
Dialysis Patients, Study 43-779-4 n= 17 (table SS p129 v2)			
Placebo n = 6		MultiHance n=11	
Total	Related	Total	Related
3 (50%)	2 (33%)	11 (100%)	7 (^$%)

Reviewer's Comment: The fact that in the renally compromised patients, there is a higher incidence of AEs and Related AEs in the placebo Group than in the MultiHance group may be due to the small number of patients in these studies. No conclusions can be drawn from this data. A warning in the labeling concerning renally compromised patients may be needed

6. The application lacks sufficient data on local adverse events

The sponsor has presented a table of local adverse events from the US and European database (table HHH p154 v.2). The most common local adverse event was injection site reaction.

Table 27 Number of patients with local AEs (table HHH p154 v2)				
	Placebo n = 80	MultiHance n = 2637	Magnevist n = 127	Omniscan n = 134
All Local AEs	9 (11%)	85 (3%)	7 (6 %)	7 (5%)
Injection site reaction	4 (5 %)	42 (1.6%)	4 (3.1 %)	2 1.5%)

Reviewer's comment: It would appear that MultiHance has a lower incidence of local adverse events than either Magnevist or Omniscan, but all three imaging agents have a much lower incidence of local adverse events than placebo.

5.Case report forms for patients who died

The sponsor claims that these case report forms were in the original submission in volumes 1.350-1.354. They are resubmitted an appendix in volumes 14-18 of this submission

7. Integrated safety summary

Reviewer's Comment: The sponsor has submitted data from trials performed in Europe, the US, Japan and China but has not submitted an integrated safety summary that includes data from all of these patients. In this submission, the patients from Japan have been carved out and presented separately and additional patients from China have been included in some of the analyses.

E. Adequacy of Safety testing

No new safety data is included in this submission. The sponsor's reanalysis of previously submitted clinical safety data is inadequate to address the safety concerns expressed in the action letter. However because of the new preclinical data submitted on QTc prolongation [redacted], these safety concerns can now bed addressed as labeling issues rather than approvability issues.

F. Summary Critical Safety Findings and Limitations

The sponsor's reanalysis of previously submitted clinical data contributes virtually nothing to our understanding of the safety profile of MultiHance. The only significant changes from the previous submission are:

1. [redacted] It is likely that only a small fraction of patients imaged for the CNS indication will have serious hepatic impairment. The risk of liver toxicity in such patients can be handled with a warning in the label

2. Concern that QTc prolongation could lead to Torsades has been greatly reduced by the negative results of the preclinical monkey study. Concern about QTc can also be handled with a warning in the label

VIII Dosing Regimen and Administration

No difference in safety has been demonstrated between the 0.05 mmol/kg dose and the 0.1mmol/kg dose

IX Use in Special Populations

Hepatically impaired, renally impaired and pediatric patients have been studied. No need for dose adjustment for these groups has been demonstrated.

X Conclusions and Recommendations

A. Conclusions

1. The material contained in the clinical section of the resubmission contains little additional evidence of efficacy for the indication and dose proposed by the sponsor
2. The material contained in the clinical section of the resubmission contains no additional evidence of the superior efficacy of the 0.1 mmol/kg dose over the 0.05 mmol/kg for the indication and dose proposed by the sponsor
3. The material contained in the clinical section of the resubmission contains no additional evidence of safety for the indication and dose proposed by the sponsor.
4. Additional evidence of safety was presented in the pharmacology-toxicology section of this submission. Because of the negative results of the cardiovascular study in primates, at doses up to 30 times the proposed clinical dose, the probability of QTc prolongation leading to Torsade de Pointes arrhythmias can be considered to be low.
5. Additional evidence of safety is contained in the post marketing data review and literature search performed by the sponsor. With approximately [ ] patients dosed in Europe, no cases of Torsade de Pointes have been reported to the sponsor. No cases of Torsade de Points has been reported in the literature for any gadolinium MRI contrast agent. QTc Prolongation can be considered to be a labeling issue rather than an approvability issue

6. On the basis of the previous submission, the NDA was found to be approvable. There is nothing contained in the clinical section of the re-submission that would alter this finding.

B. Recommendations

- The NDA should be found to be approvable for the CNS imaging indication.
- The appropriate clinical dose in adults [redacted]
- An additional robust placebo controlled clinical trial, performed in the US is required to demonstrate efficacy. This study could also be used to produce additional clinical safety data.

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/s/

Robert Yaes
11/23/04 02:03:30 PM
MEDICAL OFFICER

George Mills
11/23/04 02:08:34 PM
MEDICAL OFFICER

HFD-160 Clinical Team Leader's Memo to File

NDA 21-357 (MULTIHANCE) – RESUBMISSION

COVER SHEET

Resubmission Date:	August 2nd, 2004
Sponsor:	Bracco Diagnostics, Princeton, NJ
Drug Name:	MultiHance (Gadobenate dimeglumine)
Class:	Gadolinium Contrast Agent for MRI
Route:	Intravenous as rapid bolus or infusion
Indication: Foot note 1	For Central Nervous System (including the spine) in Adults
	"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."
Dose:	CNS Adult- 0.1 mmol/kg
HFD-160 Team:	

Medical:	Robert Yaes, MD; Ph.D.
Statistics:	Sonia Castillo, Ph.D.
Chemistry:	David Place, Ph.D.
Biopharm/Tox:	Yanli Ouyang, Ph.D.
Pharmacology:	Young-Moon Choi, Ph.D.
Microbiology:	Stephen Langille, Ph.D.
Project Manager:	Diane Smith, R.Ph.

Ramesh Raman, MD
Clinical Team Leader
Expert Reviewer

Concurrence

George Mills, MD, MBA
Division Director

Foot note: 1 = Previously Sought CNS Indications

Cycle 1 - (NDA Submission) Adults and Pediatrics: "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). "

Amended (Major amendment) Adults "MultiHance is indicated for intravenous use in MRI to visualize lesions with abnormal blood-brain-barrier or abnormal vascularity of the brain, spine, and associated tissues."

Cycle 2 – (NDA Resubmission) Adults "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 third cycle review memo is intended to address the following:

Highlight the salient aspects that justified the recommendation for Approval and Labeling. In particular, the purpose is to discuss in detail the basis of the scientific rationale that altered the Agency's previous positions in efficacy determinations leading to the re-assessment of existing data without the need for new studies.

Reference is made to the previous memos, the action letters, the primary medical and statistical reviews and meeting minutes. Because approval and labeling were largely dependent on whether effectiveness was demonstrated, efficacy related issues were most relevant that required critical evaluation. Therefore, efficacy related issues will be the focus of this memo and safety comments will at best be very brief.

REGULATORY BACKGROUND

The salient efficacy related regulatory milestones are summarized below in table 1 below.

TABLE 1- CYCLE III - MULTIHANCE NDA
EFFICACY RELATED REGULATORY MILESTONES

Cycle	Action	Material Reviewed	Recommendation & Basis
Cycle 1	Approvable Letter May 24, 2002	Original Data	New Trials. Results not verifiable
Sponsor proposed a new re-read protocol for an anatomic visualization claim using three visualization endpoints. Success, at a minimum was to demonstrate that the post-contrast MRI was better than the baseline (the primary level) for an adult CNS indication using two CNS studies. This would alleviate the flaws in the original data base, including the need for a truth standard or a comparative trial design.			
Cycle 2	Approvable Letter April 14, 2004	Blinded re-read of original data using new study protocol	New Trials. Failed on agreed primary analysis. Secondary results biased.
Industry Meeting- Sponsor provided scientific justification for reconsideration of existing data for acceptance of primary and secondary level results of cycle 2 re-read data. Letter for re-analyses sent.			
Cycle 3 (Current)	Not applicable	Re-analyses of blinded re-read cycle 2 data	Not applicable

It is beyond the scope of this third cycle review memo to comprehensively provide the complex regulatory details of this NDA since its inception as an NDA in April 2001. The most relevant regulatory aspects related to this third cycle review can be traced to the industry meeting of July 9, 2004 that took place following the second cycle review action and the subsequent letter dated July 23, 2004 that was sent to the sponsor requesting a re-analyses following the meeting with the sponsor and their consultants.

The outstanding cycle 2 deficiencies that drove the "Approvable" recommendation were primarily related to the lack of demonstration of effectiveness and the need for new data via new efficacy trials. These cycle 2 results stemmed from a prospectively designed re-read study protocol. The re-read protocol came into existence as a proposal to address the several design flaws and deficiencies identified during first cycle review. Amongst the several flaws in the original study design that were noted during cycle 1 review, perhaps the most important were: a) the absence of a truth standard and or a comparative study design without which the performance of MultiHance could not be verified, b) the discordance between the sought indication [redacted] anatomic indication during the review cycle) and the endpoints (subjective and not prospectively designed or discordant with the sought indication), and c) the lack of justification for the sought 0.1 mmol/kg dose since the 0.05 mmol/kg dose also seemed to perform comparably. Most of the safety concerns had been addressed by the end of second review cycle (both clinical and preclinical) and it was felt that any outstanding safety issues could be addressed in the label, in particular, the QT and CVS arrhythmia concerns and the hyperbilirubinemia / liver concerns. During this referenced meeting, the sponsor agreed to incorporate the QT/CVS safety concerns in the label. The proposed label does include these elements which however required minor editing that were successfully negotiated with the sponsor during the review period.

The focus of the July 9, 2004 meeting was primarily with respect to efficacy and this post cycle 2 agency letter of July 23, 2004 liberally took into consideration on the information that was discussed and presented at this meeting by the sponsor and their consultants. This referenced letter highlighted the type of the recommended re-analyses, the aim of which was: a) to explore if the re-analyses results could support a decision on whether a label could be written without new studies and b) the scope of the indication that the re-analyses could deliver. Precisely, whether the re-analyses would support a broad adult CNS indication for all CNS diseases or a CNS tumor only visualization indication was the focus and basis for the requested cycle 3 re-analyses. Therefore, indirectly, the focus of this third cycle review was related to whether MultiHance effectiveness could be determined with existing data. This position and stance taken by the Agency in considering a re-analyses instead of the requested new studies was radically different from what was communicated in the two previous action letters. Such an approach, in my opinion, is justified and portrays the Agency's receptiveness and flexibility in re-considering new scientific information for approval determinations that was presented in the referenced industry meeting.

Two such important scientific issues of relevance that were discussed during this July 9, 2004 meeting rendering this data re-evaluable were: a) whether the types of MR sequences that constituted a pre-contrast set in the pivotal efficacy trial (Study B) were complete and one that represented the clinical practice in the US, and b) the scientific basis of why the performance of MultiHance was found inferior in one study (Study A) in the agreed primary analyses at a lesion level that involved a pre v/s post comparison while the results suggested MultiHance's adequate performance in either the secondary analyses (pre v/s paired comparisons) or in the pre v/s post analyses on a global lesion level (called patient level by lesion).

Specifically, the concerns on the lack of one of the sequences (Proton Density-PD) in one of the pivotal studies- the metastatic study - Study B (this study will be referred to as Study B here on as in the Agency proposed label and was referred originally in cycle 1 as B19036/020 and subsequently in the cycle 2 as MH 106), were argued as being scientifically justified since in clinical practice, one did not always need the missing PD sequence during evaluation of patients with metastatic disease. If one accepted this practice guideline, then the concern of bias would be alleviated. One important aspect from a regulatory perspective that requires further comment on this issue on sequences pertains to the discordance between what actually the consultants stated as the accepted practice for evaluating metastatic CNS disease and the sponsor's subsequent arguments. Specifically, while it was the consultants' scientific opinion that PD sequence was typically not used and therefore not required in clinical practice in the US when evaluating only patients with known metastatic disease, the sponsor has extended this clinical practice guideline that is meant for metastatic CNS disease only, to all CNS diseases. Of course, such an extrapolation has not affected the data base since the concern on the sequences is related to one of the pivotal studies (Study B only) and not to the second pivotal study (Study A) where, in the latter, representative types of diseases were evaluated with appropriate sequences, one similar to the clinical practice in the US.

The second aspect, a more complex issue, that subsequently also led to the request for re-analyses were based on the following scientific arguments during the discussions:

The patient population in study A included patients with a variety of CNS diseases including patients with CNS tumors. Based on the known pathological behavior for the wide spectrum on CNS diseases that occur in adults, it is expected that several of these CNS diseases will have an intact blood-brain-barrier and therefore these lesions are not expected to enhance when a gadolinium agent like MultiHance that does not cross the intact blood-brain-barrier (BBB) is administered. Therefore, in such comparisons between pre- contrast and post-contrast MRIs (pre v/s post) using a scoring system based on visualization end-points like it occurred in the second cycle blinded re-read analyses, the post-contrast MRI is bound to perform inferiorly compared to the pre-contrast MRI during evaluation of lesions that do not enhance due to an intact BBB.

Another intrinsic benefit to seeking a re-reanalysis was if the question on the dose could be answered- specifically if the sought 0.1 mmol/kg dose was the best dose. Since the sought dose of 0.1mmol/kg dose was not shown to be superior or any different in performance than the 0.05 mmol/kg dose during the second cycle review, conceptually, the re-analyses could possibly identify the best dose.

These regulatory and scientific issues clearly influenced the way in which existing data was re-assessed in this cycle 3 review. The efficacy results are discussed in detail in the primary statistical review of Dr. Sonia Castillo. The salient aspects of the results in relation to the aforementioned regulatory issues that justified the current recommendation are discussed below.

RESULTS- DISCUSSION

The overview of the results is summarized in Table 2.

TABLE 2*[E]- CYCLE III – MULTIHANCE NDA EFFICACY RESULTS- 0.1 mmol/kg			
	Pre v/s Post [A1, B1]	**Pre v/s Paired [A2, B2]**	**CYCLE**
BY LESION			
Study A- All Patients	NS		II
Study A- Tumor Patients Subset (N = 65) [C]	S	S	Current (III)
Study A- Non-Tumor Subset (N = 59) [C]	NS (but significant for pre-dose)	S	Current (III)
Study B- All Patients with Mets			II
ALL LESIONS (PATIENT LEVEL)			
Study A- All Patients	S [D]	S [E]	Current (III)
Study B- All Patients with Mets	S [D]	S [E]	Current (III)

* = Source – A1 = Table 3.3; A2 = Table 3.4; B1 = Table 3.5; B2 = Table 3.6; C = Table 3.1 from Dr. S. Castillo's Stat Review

D = Source - From Sponsor's results (acceptable per Dr. Castillo)- Study A : End-of-Text Tables 28.1 - 28.3, pp. 137 - 145 from Vol. 27; Study B: End-of-Text Tables 28.1 - 28.3, pp. 136 - 144 from Vol. 34.

E = Source - From Sponsor's results (acceptable per Dr. Castillo)- Study A: End-of-Text Tables 12.1 - 12.3, pp. 052 - 060 from Vol. 27 and Study B: End-of-Text Tables 12.1 - 12.3, pp. 051 - 059 from Vol. 34.

S = Results Statistically Significant for the Difference in Means for all 3 visualization end-points, for all 3 blinded readers. Significant means in pre v/s post, post is better than pre; in pre v/s paired, paired is better than pre.

NS = Not Significant (if significance criteria not met)

NOTE: Hatched and shaded areas indicate positive results suggesting better performance when MultiHance is administered. The hatched areas were positive results that were demonstrated during cycle 2 and the shaded areas from the present re-analyses.

The salient underlying scientific considerations and its clinical implications will be discussed along with how the results could be justified. Linking these issues to both the positive and negative results is the key in the understanding of the performance of MultiHance and in determining effectiveness. These discussions provide justification for the current recommendation for visualization of all CNS diseases in adult subjects for the sought 0.1 mmol/kg dose.

The first cycle review and second cycle review memos provide comprehensive information on the protocol, study design, and the efficacy database and serve as an excellent prologue. Understanding the salient scientific aspects that are interwoven with the regulatory issues discussed above is critical prior to not only discussing the results but also its acceptance as evidence of effectiveness.

In essence, the question was if the sought visualization claim was one that was appropriate to pursue and if existing data via these re-analyses were driven by adequate and acceptable scientific perspectives that could support such a claim. The salient interconnected milestones that could answer this question resides in the discussions involving the following- a) the evolution of the current visualization claim and its clinical impact, b) the inappropriateness of the pre v/s post comparisons in the non-tumor subset subjects due to the imputation flaws in the blinded reader scoring as a cause for failure during the cycle 2 re-read re-analyses and its impact on the results and the interpretation of the noted positive (significant) results, c) the acceptance of the lack of the PD sequence in Study B and its impact on the results, and d) the acceptance that the performance of the 0.1 mmol/kg dose (the sought dose) was reliable. These core issues concomitantly, not only created a significant regulatory track (discussed above) but were also key modulators that drove the concept of a re-analyses and justified re-visiting the results- both positive and negative.

a) <u>The Evolution of a Visualization Claim (Indication) & its Clinical Impact</u>

Subsequent to cycle one review, it was determined that due to the intrinsic flaws in original trials, existing data, at best, could possibly only support a visualization claim ——— To avoid redundancy, the scientific circumstances that led to a visualization claim that were discussed comprehensively during cycle 2 review, will not be repeated. In essence, these previously discussed scientific issues provided an insight on what type of an indication the existing data without new trials could fetch. The outcome was the currently sought visualization indication. The focus was on whether the re-analyses of the two re-read studies (previously MH 105 and MH 106) - Study A and Study B provided results that could meet the requirement to support a visualization claim.

Therefore, barring the previously noted flaws and deficiencies, the question was if with the administration of MultiHance, one was able to "see" better compared to the baseline non-contrast MRI images. Although efficacy determinations based on "visualization" it is foreseeable that with better visualization physicians can make better image interpretations which in fact can carry over to better patient management. Therefore, an improvement in visualization over baseline images carries an implied value despite the lack of confirmation on what is actually being visualized because physicians can still effectively use the information when they can see better, which ultimately helps in patient management. Secondly, although the true value of better visualization is implied and not confirmed, it is reasonable to formulate that with better visualization one can make better patient management decisions based on the comparable physico-chemical properties between MultiHance and the approved class agents that are also indicated for better visualization but are routinely being used as diagnostics in the clinic. It is beyond the scope of this memo to address the basis of approval for the class agents.

With a visualization indication therefore recognized as one that could provide clinical benefit whether direct or implied, the next steps were if such a claim was validated. Its

validation therefore depended on the acceptance of two other issues (mentioned above in the regulatory section) discussed immediately below under b) and c). Subsequent to cycle 2 review, the sponsor, by identifying the drawbacks in the blinded reader protocol within the previously failed primary level of analyses and by bringing light and dimension on what constitutes current standard US clinical practice while evaluating metastatic CNS lesions, successfully paved the path for further consideration of existing data.

b) The Imputation in the Blinded Reader Scoring as a Cause for Failure in the Non-Tumor Subset Re-read Re-Analyses & Interpretation of Positive Results

Justification

In the cycle two review, it was shown that the re-read results that were derived based on a prospectively designed re-read blinded reader protocol failed to support a visualization claim for the pre-specified primary analysis of pre v/s post comparisons. Subsequent to cycle two review, based on new scientific information as discussed above under the regulatory background section, a re-analyses was requested. Therefore, the premise of these re-analyses was to explore if one could determine the performance of MultiHance (the results) from a perspective that was based on the reasonable scientific justifications provided by the sponsor. Specifically, re-analyses were recommended to explore if these scientific arguments pertaining the performance of contrast agents like MultiHance with respect to the blood-brain-barrier in those non-tumor non-enhancing lesions could be confirmed. The acknowledgement that in such analyses as it was performed previously (cycle 2) involving pre v/s post comparisons, the post-contrast images would be intrinsically handicapped because of lack of enhancement in the non-tumor non-enhancing lesions, was critical. Greater importance (one not provided by the sponsor) was given to the value of how such information when a lesion did not enhance could still provide information that was important and potentially useful in patient management. In other words, lesions always did not have to enhance in order for physicians to effectively manage patients.

Non-Significant Results - Pre v/s Post (Study A and Non-Tumor Subset): By Lesion Level

Such an argument and justification made above is reasonable and scientifically sound when evaluating non-enhancing CNS lesions. The non-significant results in this program are therefore explainable and attributable to the blinded reader scoring methodology for the chosen visualization end-points and are not a reflection of the performance of the drug with respect to its known pharmacodynamics. Hence, it is not possible to either capture or determine evaluable effectiveness – an entity that depends and follows successful enhancement in this program.

The lack of such active pharmacodynamic effects are reflected in the results in the table 2 where the non-significant results (NS) in Study A (all patient analysis and the non-tumor subset analysis) were driven possibly by such non-enhancing lesions (possibly non-

tumor) with an intact blood-brain-barrier. Since all results were based on a difference in scores (means), the negative results can be attributed to the way in which the protocol called for the blinded reader scoring—one that was designed to capture the true pharmacodynamic performance of the drug that depends on the level of integrity of the blood-brain-barrier. Scoring for this subset of patients, via this re-analysis protocol, was designed to provide positive results only for enhancing lesions and for anatomic visualization end-points. Without enhancement, the scores that the post-contrast non-enhancing lesions on the MRI would receive were deemed to be the same or lower than the baseline. Thus, the negative results are not considered reflective of the true effectiveness of MultiHance as contrast agent- one known to assess abnormal vascularity. One can argue further in favor of such a justification that hypothetically, if all the studied subjects had lesions with an intact blood-brain-barrier, the results would most likely demonstrate non-significance at all levels if they were evaluated using the same blinded reader methodology and criteria.

Significant Results - Pre v/s Post (Study A Tumor Subset & Study B): By Lesion Level

The logic itself, i.e., the scoring system was best designed to evaluate and provide superior results for lesions that would intrinsically enhance, is directly evidenced with the positive results in the pre v/s post comparisons. As shown in table 2, the results were significant (S) for all patients with tumors in the two pivotal studies (CNS tumor subset patients in Study A and all patients with CNS mets in Study B)—lesions known and expected to enhance due to break down of blood-brain-barrier in the pre v/s post comparisons. Thus, this pre v/s post positive result in patients with tumors is direct evidence of effectiveness of MultiHance in patients with CNS tumors (both primary and metastatic).

Significant Results - Pre v/s Post & Pre v/s Paired (All Studies): All Lesion/Patient Level

The results discussed thus far relate to a by-lesion-level of analyses (meaning the blinded readers scored each lesion). As indicated in table 2, results were also analyzed (by the Agency Statistician and the Sponsor) at a patient level (although still at a lesion level, the blinded readers provided a single score [probably a mean] for all the lesions that were seen if the subject had more than one lesion). Independent of the type of analyses (i.e., whether pre v/s post or pre v/s paired), the results were significant (positive) suggesting that the post-contrast MRI singly or in combination with the baseline MRI clearly provided better visualization than the baseline MRI alone. As discussed above, better visualization can be translated to better patient management.

Although intriguing it is not surprising that the results were positive across all studies (Study A and B), all subjects (tumors and non-tumors) and all comparisons (pre v/s post or pre v/s paired) at an all lesion level. Two plausible explanations are: a) the number of subjects with more than one lesion drove the results and at least some of these lesions (within that subject) enhanced, sufficient to drive the results and b) in such subjects, the positive score/s that the enhancing lesion/s received, offset the negative score/s that the non-enhancing lesion/s received, and c) with the paired assessments, readers can always

get a better perspective of the nature of the pathological process and hence the score was higher. See pre v/s paired below.

Significant Results - Pre v/s Paired (All Studies): By Lesion Level, All Lesion/Patient Level

If one accepts science with an open-mind, then acceptance of positive results in the pre v/s paired comparisons requires further comments. As shown in table 2, the results were significant for both studies (A and B) across all subjects in the pre v/s paired blinded reader assessments. Typically, per v/s paired comparisons are performed to make a diagnosis using diagnostic imaging end-points. An enhanced MRI is always read with the un-enhanced MRI (as reflected in the label of all the approved class agents) that helps the physician in patient management. However, such analyses require diagnostic endpoints on the image that the blinded readers evaluate based on a prospective protocol. Such diagnostic end points did not contribute (instead visualization end-points were what was used) to the observed positive results in the pre v/s paired analysis in this database. It is surprising that the paired MRI reads provided better results than the post-contrast MRI reads for the same visualization endpoints that were assessed by the same blinded readers in the non-tumor subset subjects. The paired results for these non-tumor subset subjects therefore suggest implied benefits (since the paired read provides better results than the pre alone) that contrast provides but the re-read analyses were not prospectively designed to make claims on such results. Therefore acceptance of pre v/s paired positive results (not pre-specified) in this program for the non-enhancing subset of subjects would be based on the blinded readers' clinical intuitiveness in interpretation (as discussed above under visualization and the implied benefit it provides) rather than based on the robustness and adequacy of the clinical trial. In a broader sense, retrospectively seeking for the best results by exploring for its residence from any where in a database until it is found is neither scientifically sound nor a reflection of the required and expected standards. Nonetheless, benefit was given to the intrinsic flaw in the way in which the scoring imputation rules potentially affected non-enhancing CNS lesions and influenced the pre v/s post comparisons rending negative results and failure on the prospectively agreed primary analysis during second cycle review.

Such is perhaps not the concern for Study B in which it is expected that enhancement of the lesions will be the rule than the exception since all subjects were with metastatic lesions (see c below).

c) The Acceptance of the Lack of the (Proton Density) PD Sequence in Study B and its Impact on the Results

The underlying scientific justifications are discussed above under the regulatory section. Concurrence on the sponsor's consultants' testimony that PD sequence is not required when evaluating metastatic CNS lesions as an accepted clinical practice guideline in the US, was additionally sought via telephone conversations with specialists in the field of neuroradiology from academic centers such as the National Institutes of Health (reference is also made to the e-mail memo sent subsequent to this conversation at that time). Based

on such information, the results stemming from Study B were subsequently considered viable for evaluation.

A re-analyses was not formally recommended since such analyses at a lesion level were performed and reviewed previously (cycle 2). Also, analyses on all lesion/patient level in Study B from existing database were re-visited (shaded areas in table 2).

These results are presented in table 2. The hatched areas represent positive results from cycle 2 review (for by lesion analyses) and as mentioned above, the shaded areas reflect positive results on an all lesion/patient level. The arguments presented above that justify these results in pre v/s post comparisons also apply to Study B. Since metastatic lesions typically break down the intact blood-brain-barrier causing enhancement, the results are expected to be positive with the administration of MultiHance. These results, in aggregate, provide direct evidence that with MultiHance, there was better visualization over baseline for all levels of comparison (pre v/s post or pre v/s paired) and for all levels of lesion analyses (by lesion or all lesion/patient level) in adults with known metastatic CNS lesions.

d) Dose:

The results presented and discussed were derived with the sought 0.1 mmol/kg dose. As discussed in the primary statistical review, because the performance of the 0.05 mmol/kg dose was not consistent across all readers and for all visualization endpoints, results with the 0.05 mmol/kg dose were not discussed in this memo and further, to prevent the clinicians from using the lower but non-reliable 0.05 mmol/kg dose particularly in the absence of any worrisome safety concerns with the sought higher 0.1 mmol/kg dose,

EFFICACY SUMMARY & CONCLUSIONS

Overall, the following conclusions can be drawn from these results projected in table 2:

Combined, the hatched and the shaded areas in table 2 (previous cycle/s and current cycle) reflect positive results. When the analysis is one that compares the pre v/s paired MRI images, the paired images always provided better results than the pre that was independent of the type of disease. Stated differently, the results were positive for all CNS (and spine) adult lesions for the sought 0.1 mmol/kg dose in the pre v/s paired analysis. While the results were also positive in favor of the post MultiHance MRIs in the comparisons involving the pre v/s post (the pre-specified method) for all patients in Study B (all patients with known metastatic lesions) and for the tumor subset patients from Study A, MultiHance failed to show superiority over the un-enhanced baseline images in the pre v/s post comparisons when the patients' disease was not tumor. Stated differently, MultiHance failed to show effectiveness in non-tumor patients because of the pre-specified blinded reader scoring methodology in pre v/s post comparisons.

Such positive and negative results did not easily and automatically transcribe itself as clear and sufficient evidence in determining effectiveness. The scientific arguments presented above clearly indicated that MultiHance's performance that was determinable via the re-read re-analyses was dependent on the nature of CNS disease and its vascular state (the disease type and its effect on the integrity of the blood-brain-barrier- a fundamental pharmacodynamic attribute) and the type of the chosen analyses. With the appropriate arguments and justifications, it was shown that the overwhelming message conveyed with these results was that better visualization was possible when MultiHance was administered over baseline non-contrast MRI. Some of this evidence was direct and some derived. In imaging, when one is able to see better, it is expected that one will be able to use this better visualization to make patient decisions. MultiHance's performance, as an agent that provides better visualization, has not been and cannot be directly substantiated with existing data. Although it was not possible to demonstrate or confirm the true clinical meaning or the usefulness of better visualization with existing data, its value can be inferred from MultiHance's physiochemical comparability with the current marketed class agents and how the latter drugs are routinely used as diagnostics despite being approved for a visualization indication. Of course the approval basis for these agents was different and the data that supported their respective visualization claims were prospective.

Based on the aforementioned interwoven regulatory and scientific discussions and justifications, the existing data base was found sufficient for review for the sought visualization claim and with the arguments presented above, the results, in aggregate, can be considered as evidence of the effectiveness of MultiHance for a visualization claim.

SAFETY

There were no safety concerns or problems of significance requiring additional data that were identified either during cycle 2 review or in the update. The outstanding safety issues that were identified were of the magnitude that these could be addressed in the label. These were recommended and the sponsor's label was edited for final concurrence from the sponsor, which was successfully accomplished.

RECOMMENDATION

All disciplines have recommended approval with label changes. There are no outstanding preclinical issues that have an impact on clinical safety and efficacy.

Efficacy: Approval for the sought indication with label changes (see below)

Safety: Approval with label changes (see below)

LABEL

The currently proposed label has been edited by all disciplines including clinical safety and efficacy. The entire clinical trials section was re-written to conform to the re-analyses that supported the sought visualization claim and one that integrated the scientific justifications. Like wise, the clinical safety sections (including adverse events) were re-written to conform to the draft guidance for the industry for adverse events. The QT, CVS arrhythmias and Hepatic (cMOAT - drug and inherent metabolic disorders) issues were identified, edited and re-arranged in the appropriate sections (PK, Precautions, Interactions and AE sections). Negotiations with the sponsor on these elements and the label in totality (including the pre-clinical sections) were successfully accomplished.

POST MARKET ISSUES

The sponsor has requested pediatric waiver for the 0-2 year ages and a deferral for PK for the 2-5 year ages in whom safety and efficacy data will addtionally be collected. These are the issues and the recommendations on the sought waiver and deferral:

a) Since there is use for MRI with contrast in the 0-2 year age group, but considering that all the approved class agents are indicated for age 2 and above and that enrollment in this age group may be difficult, the requested waiver may be granted with the understanding that the need for such data in the 0-2 year ages in the future may be required. Hence sought waiver should not be granted as proposed without further modifications providing allowance and provision for studies in the future if required.
b) The requested deferral is not complete with respect to the pediatric drug program. Specifically, in addition to the PK data in the ages 2-5 years, new safety and efficacy data for all age groups is required. With the Phase 4 commitment (the basis for seeking deferral) to collect only PK data in the age 2-5 years, the existing pediatric safety and efficacy data is not sufficient for approval without new safety and efficacy data. Hence sought deferral should not be granted without further modifications in the commitment that would represent the pediatric drug development adequate for review for an indication.

END OF CYCLE 3 MEMO

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

/s/

Ramesh Raman
11/23/04 12:43:22 PM
MEDICAL OFFICER
The attached cycle 3 memo to file provides justification for approval for the use of MultiHance in Adults to visualize CNS lesions with the 0.1 mmol/kg dose. Label changes were successfully negotiated. Pediatric Ph 4 commitment in place.

George Mills
11/23/04 01:49:58 PM
MEDICAL OFFICER

REVIEW CYCLE #2

Submission Date October 10, 2003

Action: Approvable