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%)

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.

a smaller number of patients with preexisting liver dysfunction, who would be more likely to suffer clinically significant liver damage will receive the drug. clinically Thus of the 197 patients in the adult MultiHance patients population with cirrhosis, 195 were in the liver imaging studies (p49v2). 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

5. 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

6. 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.

C. 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.

D. 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 [redacted]
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 [redacted] 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 is [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
4/7/04 12:47:09 PM
MEDICAL OFFICER
Review of resubmission of Multihance NDA

Ramesh Raman
4/7/04 12:52:52 PM
MEDICAL OFFICER
Concur in essence with the recommendations. Additional details are contained in my memo to file and the primary statistical review.

George Mills
4/9/04 11:59:54 AM
MEDICAL OFFICER

HFD-160 Clinical Team Leader's Memo to File

NDA 21-357 (MULTIHANCE)

Letter Date:	April 27, 2001
Sponsor:	Bracco Diagnostics, Princeton, NJ
Drug Name:	MultiHance (Gadobenate dimeglumine)
Class:	Gadolinium Contrast Agent for MRI
Route:	Intravenous as rapid bolus or infusion
Indication:	For Central Nervous System (including the spine) in Adult
Dose:	CNS Adult- 0.1 mmol/kg

HFD-160 Team:	Medical	Dr. Roger W. Li, MD
	Statistics	Shahla S. Farr, MS
	Chemistry	Dr. David Place, PhD
	Biopharm/Tox	Dr. Tushar Kokate, PhD
	Pharmacology	Dr. Hyun Kim, PhD
	Microbiology	Stephen Langille, PhD
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Ramesh Raman, MD
Clinical Team Leader

Concurrence

Patricia Love, MD, MBA
Division Director

CONTENTS

EFFICACY SUMMARY[A]

A= The numbers in this Summary section and in the Overview of MultiHance Clinical Section includes the updates, where as those in the respective review sections does not include the updated information.

Recommendation

Non Approval for CNS (adult [redacted] indications. The sponsor has not submitted adequate data that could validate and support the sought claims. The basis and the reasoning for this decision rested in the concerns on the following identified issues:

A. Nature of the Trials
B. Adequacy of Sample Size- Number of Evaluable Patients
C. Protocol Design Flaws
D. Robustness of Results
E. Additional Related Issue/s- Mechanism of Action of MultiHance with respect to the [redacted]

A. Nature of the Trials

The submitted data was a conglomeration of trials that were of Phase 2 caliber, including the key studies, the design of which provided results that were, at best, hypothesis generating. Specifically, the key trials generated results that were typical of dose-ranging and pharmaco- [redacted] studies. Even in these situations, the results were neither supportive of the stated objectives nor were they consistent. These inconsistencies not only questioned the value of these results with respect to the currently sought claim, but also raised further concerns on the extent of their applicability for future development of this program. The trial design, the stated objectives, and the primary end-points were discordant with each other and were not intricately and cohesively weaved to yield results that were robust to validate the sought indication. The chosen primary end-points were either subjective or technical and not clinically meaningful.

B. Adequacy of Sample Size- Evaluable Patients

Several study design flaws, the cumulative dosing regimen, the discordance between the sought dose and use of the non-marketed formulation, the data in a limited number of patients in whom the effects of MultiHance for the sought dose was captured, were all contributory factors that severely restricted the number of evaluable patients. Specifically,

1. Only ~ 136 patients (65 from study 9A and + 71 from study 9B) from the pivotal trials (out of the 1041enrolled) that received the 0.1 mmol/kg as the first dose could be evaluated for the primary efficacy end-point for the CNS indication (see tables E1A, E1B, E1C, E2A, and E2B).

2. [redacted]

3. [redacted]

C. Protocol Design Flaws

There were several additional concerns that restricted the value that one could place on the results that stemmed from this narrow database with very few patients. These were:

1. Enrollment bias/enrichment- all enrolled patients were with known disease and had received another imaging study as part of inclusion criteria.

2. Several protocol deviations and changes were made during and after the completion of study, for which the justification with adequate scientific reasoning was not provided. These retro analyses and changes, amongst others, included- concerns on patient population and the randomization methods (treatment bias), changes in the definition of the primary efficacy end-point from initial study proposal and the report in the adult studies.

3. [redacted]

4. Image Acquisition and Blinded Reader Methodology- Impact on Results

(a) Image acquisition methods were variable and different sequences were used for blinded reader evaluations between and within the trials. There were no uniformity in the comparative analyses between the image reads and this was reflected in the inconsistent and variability in the results for the same end-point. Specifically, in the pivotal CNS trial 9A and 9B, post-contrast T1 images were not evaluated in the unpaired read as they were in the other CNS trials [redacted]. These variations in the imaging methodology resulted in different results. Specifically, the results seemed to be better with contrast when a single sequence of the pre-contrast image (e.g. pre-T1) was compared with the post contrast T1 image. But when additional pre-contrast sequences (e.g. T2 and or PD) were included with the T1 as part of the pre-contrast set, the use of MultiHance added very little benefit and the results were significantly inferior from those that had a single pre-contrast sequence (see tables E1I, E1J, E1K, and E1L). The sponsor analyzed and the presented the data without providing details on which sequences constituted the pre-contrast image/s and at times may have chosen sequences that yielded better results (as illustrated in table E1I). It was not possible to determine if indeed the stated (as proposed) sequences were acquired (during imaging), what images (and the order) entered the blinded reader methodology, and finally, what images and sequences entered in these analyses. Therefore, meaningful interpretation was arduous. On these grounds, the sponsor failed to reliably and consistently demonstrate that "the drug" (MultiHance) could provide beneficial information over the "device". [redacted]

(b) The magnitude of the concerns on the inconsistencies on the sequences and the variability in the results as discussed above for the CNS trials are superseded by a greater problem in the [redacted] trials. Specifically (as discussed above in the adequacy of sample size), the [redacted] results were not duplicated as they stemmed from a single trial. Therefore, any comments on variations are inconsequential.

5. Prospective Imaging Criteria:

The lack of specific imaging criteria for the blinded reads that could characterize the various listed diagnoses in the CNS trials, and the lack of information on how benign lesions were differentiated from the malignant ones in the [redacted] studies, led to blinded reader assessments that were subjective. Therefore, the value and the reliance that one could place on the "assessments-scores/levels" that were so generated, and hence the results, was curtailed.

6. Whether the "representative" population were enrolled and studied (despite the enrichment) in an "appropriate" fashion to ensure that similar results could be reproducible when used in the targeted population in the community was not possible to determine. Specifically, the required information on the enrolled subjects' medical diagnoses was not presented which would have helped determine congruence between the disease categories as listed in the CRFs (for the CNS indication) and disease prevalence.

D. Results

Barring these issues, the results in itself lacked robustness, consistency and failed to validate the sponsor's claims. These are discussed below under CNS ——— :

I. CNS

1. Primary Efficacy End-point:

(a) The results from the pivotal CNS studies (9A and 9B) failed to demonstrate efficacy for both the primary endpoint of "diagnostic information" and the secondary endpoint of "lesion detection-by number". The application of the observed marginal improvement in the results for the 1st dose over baseline with the 0.1 mmol/kg dose (but inferior to the comparator) in determining effectiveness was severely limited by the subjective scales or criteria that were employed in the scoring. Furthermore, the sponsor failed to demonstrate non-inferiority over the comparator as proposed. The criteria for the chosen confidence interval in the adult pivotal studies were statistically unacceptable and the agency statistics reviewer identified several methodological problems. Furthermore, the parallel study design rendered such comparisons irrelevant. Even under these conditions, the results indicated that MultiHance was inferior to the comparator. Therefore, the category of "diagnostic information" was not validated by these criteria and methods, and efficacy was not established.

(b) ———

(c) The dose-to-image interval was 5 minutes and the dose-to-dose interval was 10-15 minutes in the CNS trials (see schema). Justification for the sought timing- ——— ' for the CNS indication was not provided.

2. Secondary End-point:

With respect to the secondary endpoint of "lesion detection-number", the number of lesions that increased with MultiHance was limited and not statistically significant. Further, the clinical importance of these limited observations could not be validated. In the absence of information on patients' history and the diagnoses, it was not possible to determine if the CNS trials (pivotal adult and pivotal pediatric) were seriously flawed due to the lack of enrollment of the appropriate patient population and therefore attempts on such an assessment on "lesion number" was probably futile (discordance between enrolled patients and study design). However, as discussed above (Cd) the results was not strong even when the right population was studied (the CNS mets study) clearly indicating that the chosen end-point was inappropriate and clinically irrelevant. For reasons alluded to in the review (approach to methods in assessments- see below), the results on the clinically meaningful subset of patients with 0 or 1 or 0-4 lesions at baseline failed to demonstrate the usefulness of MultiHance.

3. Dose Validation:

Validating data to justify the sought 0.1 mmol/kg dose was at best questionable. Specifically, the results from the mets study (on the primary end-point of lesion-to-background ratio with the cumulative doses of .05+.05+.1 mmol/kg versus .1+.1+.1 mmol/kg and post-dose comparisons between the cumulative .1 (as .05 + .05) and the .1 single dose for lesion number) indicated that the .05 dose, if any provided comparable results compared to the .1 mol/kg dose. Furthermore, the data did not demonstrate robustness to justify a second dose.

II. [redacted]

[redacted]

E. **Additional Related Issue/s- Mechanism of Action**

[redacted]

The Next Steps

These intrinsic trial design flaws, non-validated imaging methodology/s and variations, the lack of data to justify the .1 CNS dose, [redacted] or the repeat .1 CNS dose as the best doses, concerns on the mechanism of action, amongst others, sets tone for the requirement of new adequately well-controlled trials rather than a re-analyses of existing data. Specifically, because several of these corrective changes if attempted, would be radical, involving the primary end-point (one that is clinically useful and assessed objectively), secondary end-point, image read methodology, statistical methods, and others, conducting new prospectively designed studies would be the "logical" approach. As a preliminary required step, the best dose for each of the sought indication should be established. Preliminarily, the following suggestions are made:

Adult CNS:

[redacted]

CNS:

END OF EFFICACY SUMMARY

SAFETY SUMMARY

Recommendation

Approvable. The basis for this recommendation is due to several issues and concerns that were identified and discussed in the safety review section below. The sponsor is required to address these outstanding clinical and pre-clinical issues prior to approval. The essence of these concerns are summarized below:

1. QT prolongation and CVS related AEs

   QT/QTc prolongation was noted in 40-47% of patients of < 30msecs magnitude (over baseline) across the several time points it was measured starting from the immediate post dose period to > 24 hours post dose (see table S2). Most of the monitoring that was performed reflected cumulative effects of the various doses that the patients received. The monitoring in the immediate post dose period may potentially include those patients in whom QT/QTc was measured after the first dose. Therefore, re-analyses of this ECG data (QT/QTc) will be required. Furthermore, this program did not include continuous monitoring. None of the pediatric patients were monitored with ECG. Therefore, continuous ECG monitoring is recommended in all the on-going studies. Also, ECG data on pediatric patients may additionally be required.

   As discussed in the safety section below, there were patients who experienced various cardiac arrhythmias (see table S3) including ventricular arrhythmia and PVCs. Complete details on these patients are required- medical history, associated ECG changes, associated labs, etc.

2. Liver and Elevated Liver Enzymes

   MultiHance is different from the other gadolinium agents in that it is eliminated via the biliary/fecal route and is lipophilic. The sponsor claims (not validated) that a specific hepatocyte uptake of MultiHance is the basis for its liver imaging. Furthermore, the pre-clinical safety data showed hepatic necrosis and vacuolization in several animals in several of the studies. The clinical database showed elevated liver enzymes in several patients over baseline across several measured time points (see table S1). Furthermore, one patient experienced a serious adverse event- necrotizing pancreatitis. In addition, hyperbilirubinemia was noted in the adults with metabolic liver abnormalities (icterus intermittans juvenilis and V Willibrands disease). These concerns, in aggregate, suggests that the patient population for which MultiHance was developed for use may also be the targeted population for its adverse effects. Therefore, complete re-analyses of those patients with elevated LFTs is recommended.

3. Osmolality

MultiHance has the highest osmolality amongst all the class agents. Phlebitis, thrombophlebitis, compartment syndrome and amputations have been observed with drugs in this class- all presumed due to osmolality. Although the general injection site reactions for MultiHance was comparable to the others, specific details and additional information is recommended from these cases. One patient with history of recent MI and possibly CHF experienced acute pulmonary edema within 10 minutes after 30 mL of MultiHance administration. Whether this is related to the osmolality (and or volume) is a concern. Details on all such patients with a history of or active CHF who may have experienced any adverse events is recommended.

4. Pediatric Safety

Adequate pediatric safety has not been established. Specifically, the PK profile in subjects less than 5 years has not been established (but the sponsor proposes to use in ages [redacted] or older). There were only 15 patients who were less than 2 years of age. None of the pediatric patients had ECG monitoring or urine analyses. [redacted]

5. Other concerns

Although direct relationship could not be established, certain patient populations may be at risk when exposed to MultiHance. These are discussed in the safety review below. For purposes of relevance they are listed here and they should be reflected in the label (under warnings/precautions):

(a) Caution in patients with renal disease.
(b) Patients receiving hemodialysis should be dialyzed within an appropriate time after MultiHance administration to ensure its prompt elimination as in subjects with normal renal function.
(c) Caution in patients with hepatic disease.
(d) Caution in patients with metabolic hepatic abnormalities.
(e) The effects of MultiHance in patients with coexisting hepatic and renal disease is not known.
(f) The effects of MultiHance in patients with porto-caval shunting is unknown.
(g) Caution in patients with seizure disorder/s.
(h) Caution in patients with CHF.

Therefore, based on the aforementioned reasons, the grounds upon which the approvable recommendation is made, is justified.

Label: A complete labeling review is premature in the context of an overall non-approval recommendation. However, specific comments are made in several sections of this review as relevant. See comments in safety above on precautions/warnings.

Other Recommendations: [redacted]

END OF SUMMARY

General Introductory Comment

Based on the complex nature of the presented material and the arduousness encountered by the review team, the focus of this review will be on the efficacy section, which will be approached comprehensively. Dr. Li has reviewed safety comprehensively and only the relevant safety issues will be briefly addressed. For purposes of relevance and completeness, an overview of the MultiHance program will be first presented, which will be followed by an important section titled " Approach to the methods in Assessments". Based on the problems with the study design, protocol, the parallel group cumulative dosing, the subjective end-points, and the "looseness" of the trials which were not cohesive to provide reproducible and consistent results, it was imperative to develop an approach to the review with the intentions of seeking and identifying the "best" data possible (although not identified by the sponsor). These are discussed in the "approach to the methods in assessments" below. This will be followed by comprehensive CNS efficacy ——— comments. The number differences that may be observed between the overview section of the review and the respective review sections are due to the fact that the overview section of the review incorporated information from the updated data extracted from the primary clinical review of Dr. Li (the numbers in the review sub sections were from the data submitted prior to the update).

Overview of the MultiHance Clinical Program

MultiHance, a gadolinium paramagnetic i.v. contrast MRI agent, was submitted for review as a NDA with ——— (CNS ———) in two patient populations

———

The data stemmed from 78 completed clinical trials (3960 subjects) and data on additional subjects (totaling 4075 subjects). The safety database evaluated 3960 subjects (no safety from the on-going trials- 5 trials, 115 subjects). The data stemmed from trials across the world- US based ~ 1/6, Europe ~ ½, and ~ 1/3 from Japan. The data from the Japanese trials were not submitted for full review. The relevant efficacy database (—— subjects) consisted of 1034 subjects in 21 CNS trials and —— in the liver trials. The 5 on-going trials were not included in the efficacy analyses.

———

Four other marketed gadolinium agents are approved for use in the US (OptiMARK for adult CNS and adult Liver, Magnevist for adult and pediatric CNS and adult & pediatric whole body, Prohance for adult and pediatric CNS only, Omniscan for adult and pediatric CNS and adult and pediatric whole body) and the physico-chemical properties of MultiHance are comparable to the others with the exception that MultiHance has the highest osmolality and viscosity. The general AE profile of MultiHance appears to be comparable to with the others. The proposed dose of MultiHance is also comparable to [redacted] adult indications. The fecal/biliary elimination profile of MultiHance is different than the others (others are not eliminated so) and MultiHance is additionally lipophilic. How these differences may affect safety and efficacy is discussed in the appropriate sections.

MultiHance is marketed in 16 different countries for CNS and liver indications.

Approach to Methods in Assessments

As discussed in the summary section and as identified in the primary clinical and statistical reviews, several flaws and deficiencies were ubiquitously ingrained in the trials that rendered the data and hence the results not supportive. Barring these issues the methods that were employed in these assessments and the rationale for such an approach were:

A. The claim (as indicated in the label) on a clinically useful end-point of "number of lesions", although considered secondary by the sponsor, was the focus of the clinical and statistical reviews, because of concerns on the subjective primary end-point.

B. For the CNS evaluation, based on the study design, the number of patients in whom the efficacy of [redacted] `0.1 mmol/kg could be evaluated rested in ~ 136 patients. These were the patients who received the 0.1 mmol/kg dose as the first dose following which imaging was performed. Therefore, the focus of the analyses was on the pre-dose MRI (baseline) versus the first post-dose MRI. The schema illustrates this further.

C. [redacted]

D. A design flaw further limited the database, which steered the focus and the methods of these analyses. When one attempted to compare the test results with those of the approved comparators, the same doses (considering that these drugs are comparable)

were not administered. In particular, comparisons between the 2nd post 0.1 MultiHance results with the 2nd post Omniscan results were not matched because, the administered doses were 0.1 mmol/kg and 0.2 mmol/kg respectively. Although such information may demonstrate that MultiHance may be as efficacious as Omniscan at lower doses, whether the use of Omniscan at these higher doses (although approved for the 0.3 mmol/kg dose) may in fact have caused signal changes in the images leading to lower scores (in this patient population) is unknown.

E. Besides the "subjectivity" of the primary efficacy endpoint, the lack of truth standard, and the problems with the "non-inferiority" trial design, the results stemming from the assessments on the primary efficacy endpoint of neither robust nor supportive of the sought claim. However barring these concerns, the data did indicate that there was some benefit (but inferior to the comparator) with the use of the drug in comparison to the un-enhanced MRI images (see table E1E below). The question was whether this positive trend and observation could be implemented to support the secondary end-point of lesion detection (number of lesions).

F. First some general comments on "lesion detection" assessments:

1. Lesion detection may mean improvement in number of lesions and or better characterization of lesions. In this program, lesion detection referred only to number of lesions.

2. Since its inception, the technology of MRI has rapidly advanced to the extent that the role a contrast agent may play with respect to the number of lesions is limited. In particular, with the use of the various un-enhanced sequences such as T1, T2, PD, FSE, etc., abnormalities in terms of the numbers are generally adequately detected by these non-contrast sequences. The benefit margin that the drug may have over the device is narrow. Therefore, demonstration of benefit of a contrast agent with MRI in terms of numbers requires trials that should be designed carefully to address the following:

3. Improved Detection- Number of Lesions

In this context, clinically relevant benefit is when the enhanced MRI shows any number of lesions greater than the un-enhanced MRI when the latter identifies no lesion. When the baseline shows 3 or more lesions, a further improvement in number alone with contrast does not offer any additional clinical benefit in terms of patient management particularly in patients with CNS metastatic disease. These comments are based on the relationships and comparisons between the un-enhanced MRI and the enhanced MRI. Demonstration of more lesions (for e.g. >3) via MRI with contrast may be relevant when comparisons are made between MRI and another

technique such as CT, where the resolution of the latter is lower. Historically, such "number" endpoints were relevant during the infancy stages of MRI development when the studies were conducted to demonstrate superiority of MRI over CT. Therefore, the true clinically meaningful value of lesion number end-point was assessed in a subset of patients in whom the baseline showed four or less lesions and in those in whom the post dose continued to show 0-4 lesions.

4. Improved Detection- Better of Lesions

Benefit with contrast MRI may be considered clinically useful even when multiple lesions are detected with un-enhanced MRI if the lesions can be better such as better enhancement, better border delineation, pattern of enhancement, etc.

A final word on the "lesion number issue"- lesion "tracking" (which was not performed in these trials) would add valuable information and further strengthen the database.

Based on the aforementioned issues and rationale, the review focused on the the data for the sought indications and the results are discussed. The conclusions and recommendations are based on these findings.

EFFICAY REVIEW

CNS INDICATION

CNS Proposed Indication

"MultiHance is indicated for intravenous magnetic resonance imaging (MRI) of the Central Nervous System (brain, spine and surrounding structures).

Proposed CNS Dosing

0.1 mmol/kg (0.2 mL/kg) as an iv bolus or rapid infusion

Overview of Key CNS Trials

In aid of the CNS indication, and in conjunction with the sponsor, the agency clinical and statistical primary reviewers identified the following trials: 2 adult pivotal (of similar design), one adult supportive metastatic study, and one pediatric study. These are discussed separately below. The table E1A below provides an overview of all the CNS studies undertaken in this drug program and table E1B provides a comprehensive overview and summary of the 4 key trials for the CNS indication. Table E1B is broken into several parts for purposes of easy reference.

TABLE E1A: MULTIHANCE- ALL CNS STUDIES IDENTIFIED				
All Studies[1]	58		N= 2221	
	ADULT		**PEDIATRIC**	
Total Completed CNS Trials[1]	16		1	N= 174
Key Controlled Studies[2]	2 (43,779-9A & 9B)	N= 410	1 (B19036/036)	
Key Uncontrolled Studies[3]	1 (B19036/020)	N= 150	None	
Other Uncontrolled Studies	13	N= 120		
1= Performed in US and Europe (does not include Japanese studies) 2= Considered Key by both Sponsor and Agency Reviewers 3= Not reviewed by Agency Stat Reviewer				

TABLE E1B: MULTIHANCE-CNS-ALL KEY ADULT AND PEDIATRIC STUDIES SUMMARY/OVERVIEW			
	ADULT		**PEDIATRIC**
	43,779-9A & 9B	**B19036/020**	**B19036/036**
Key Controlled	Yes	No	Yes
N	410 (276 MultiHance and 134 Omniscan)	150	174 (85 MultiHance and 82 Magnevist)
Study Location	US	Europe	Europe
Study Design	See below[1]	See below[2]	See below[3]
Known Disease or Abnormality based on Imaging Prior to Entrance for Eligibility[4]	Yes[4]	Yes[4]	?
Truth Standard	None	None	None
Area of Evaluation	~ 85% Brain ~15% Spine	?	Not Reported
1= Phase 3, Multi-center, Double-blind, Randomized, Parallel-group, Comparative, Dose-escalating 2= Phase 2, Multi-center, Double-blind, Randomized, Parallel-group, Dose-controlled 3= Phase 3, Multi-center, Double-blind, Randomized, Parallel-group, Comparative, Single-dose 4= Entrance Eligibility Imaging included- MRI (with or without contrast), CT (with or without contrast), Nuclear medicine imaging, Angiography. Breakdown of each by numbers not available.			

TABLE E1B: MULTIHANCE-CNS-ALL KEY ADULT AND PEDIATRIC STUDIES SUMMARY/OVERVIEW			
	ADULT		PEDIATRIC
	43,779-9A & 9B	B19036/020	B19036/036
Demographics (all subjects)			
Sex	Male: 200 (48%) Female: 210 (52%)	Male: 88 (58%) Female: 62 (42%)	Male: ~84 Female: ~78
Age	Mean age: 48.2 years Range: 18-88 years	Mean age: 57.75 years Range: 23-82 years	Mean age: 7.2 years Range: 4 days-17 years
Race	White: 331 (80.7%) Black: 37 (9.02%)	White: 150 (100%) Black: 0 (0%)	White: 96% Black: 3%
Weight	Mean: 78 kgs Range: 39-136 kgs	Mean: 73 kgs Range: 47-130	Mean: 29.3 kgs Range: 4-95 kgs
Primary Efficacy Endpoint/s			
Definition			
Criteria			
Secondary Efficacy End Point/s[6]			
Lesion Detection: Number of Lesions	Yes	Yes	
Drugs, Dosing Regimen and Dose (mmol/kg)			
Formulation (0.5 M)	Proposed Marketing	Proposed Marketing	
Comparator	Yes- Omniscan (N=134)	None	
Testing Hypothesis with Comparator	Yes- Non Inferiority	Not Applicable	
Number of Dose/s	Multiple	Multiple	
Interval between dosing	15 minutes	10 minutes	
MultiHance	.05 + .1 (~ 33%, N=140)	.05+.05+.1 (~ 50%, N=74)	
	.1 + .1 (~ 33%) N=136 (65+71)	.1+.1 +.1 (~ 50%, N=76)	
Omniscan	.1 + .2 (~ 33%, N=134)	Not Applicable	
Magnevist	Not Applicable	Not Applicable	

6= ~~Of the~~ several (both on-site and off-site) secondary end-points, the number of lesions has been the end-point that the sponsor has pursued in support of the claim. Therefore, the agency reviewers also analyzed this secondary end-point.

TABLE E1B: MULTIHANCE-CNS-ALL KEY ADULT AND PEDIATRIC STUDIES SUMMARY/OVERVIEW			
	ADULT		PEDIATRIC
	43,779-9A & 9B	B19036/020	B19036/036
Imaging and Reads			
Blinded Readers			
Sequence[7] Read For Primary End-point			
Sequence[7] Read For Secondary End-point	Unpaired[8] T1 only Paired[10] PD+T2+PostT1	[11]Unpaired Pre T1/T2 only and Post T1 Paired Post T1 + ?	Similar to primary[9]

7= Usually the unpaired read was followed by the paired read. T1= T1 weighted, T2= T2 weighted, PD= Proton Density, FSE= Fast Spin Echo. The listed sequences are what the sponsor proposed (Vol. 1.1, p. 31, 251).
8= Note that the unpaired read did not include the enhanced MRI.
9=

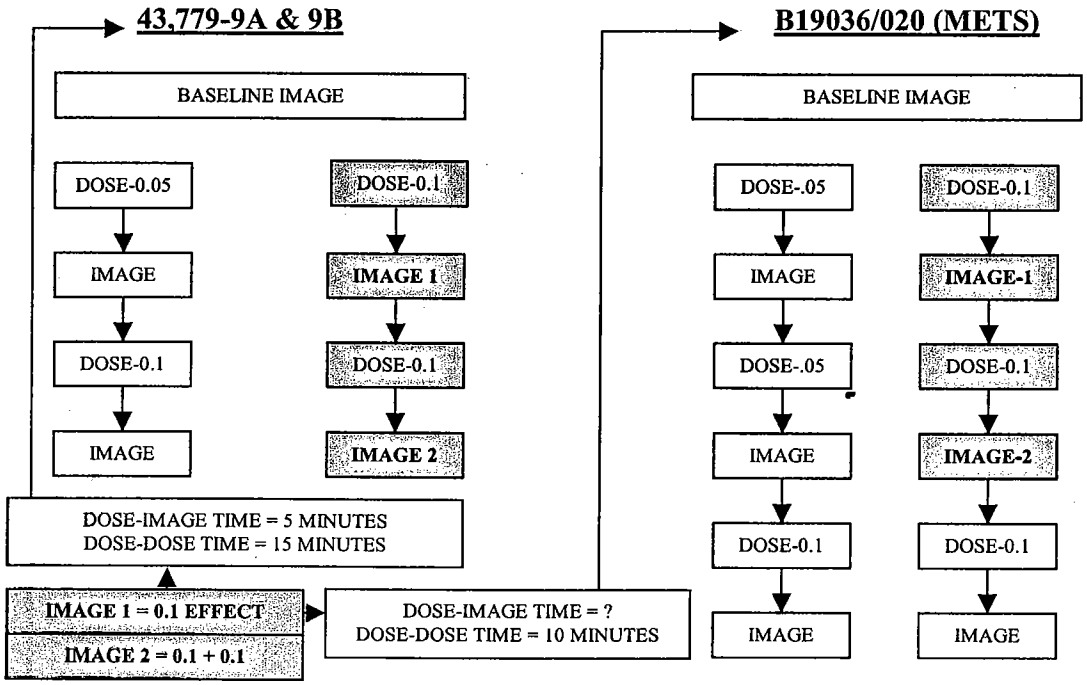
10= Note that Pre T1 was not part of the Paired read.
11= The details for the paired reading is not known.

The schema below provides an overview of the relationship between dosing and imaging, and understanding this basic plan was critical in several assessments that included:

a) The rationale for the sought dose
b)

c) Formed the basis on which one could estimate the number of evaluable subjects within each trial in whom "relevant" efficacy information resided (see table E1C below).
d) Formed the basis upon which the adequacy, relevance and appropriateness of the timing of safety monitoring were assessed with respect to dosing and provided an estimate of the number of subjects in determining dose response

MULTIHANCE DOSING SCHEMA: ADULT CNS



Note that the hatched boxes in the schema marks 0.1 mmol/kg dose either as a first dose, or as a second dose that followed the first 0.1 mmol/kg dose, and the relevant imaging that could potentially identify the effects of the single dose or the cumulative dose.

Based on the sought dose of 0.1 mmol/kg for the CNS indication) and from the schema above, it is quiet obvious that none of the patients in these key CNS studies received the 0.1 mmol/kg dose as a single dose. Furthermore, it is evident that based on the known PK profile of MultiHance and the interval of 10 or 15 minutes between doses, any effects on the images after any second dose would be due to the cumulative effect of all the preceding doses. The true effects of each dose following the first dose were therefore not captured. These are indicated in the shaded and hatched boxes in the schema for dosing. IMAGE 1 indicates the "pure" effects of a single 0.1 mmol/kg dose and IMAGE 2 indicates the cumulative effects of a 0.1 mmol/kg dose preceded by another 0.1 mmol/kg dose. Therefore, differences in the assessments between IMAGE 1 and IMAGE 2 may indicate if a second dose provides any additional benefit.

The table below summarizes these findings and provides an estimate of the actual number of evaluable patients for the — adult ——— CNS doses.

TABLE E1C: MULTIHANCE- CNS EVALUABLE ADULT ——— PATIENTS (N)		
	All Studies	**Key CNS Studies (N)**
Total CNS Study Subjects	1041	NA
Adults- Single 0.1 mmol/kg dose ———	406	None
Adults- First Dose of 0.1 mmol/kg for ——— Assessment (Primary endpoint)	NA	N ≈ 136 (65 in 9A + 71 in 9B) (76 evaluated — ratio as ——— endpoint in mets study)
Adults- All 0.1 mmol/kg as First Dose (potential for secondary endpoint of lesion number for single dose)	NA	N ≈ 202 (136 from 9A & 9B+76 from mets study)
Adults- First 0.1+ Second 0.1 mmol/kg for Mets	NA	N ≈ 76
Adults- All First 0.1+ Second 0.1 mmol/kg doses (potential for lesion number with 2nd dose)	NA	N ≈ 202 (136 from 9A & 9B+76 from mets study)
Ref: Clinical and Statistical reviews, See schema above NA= Not applicable		

CNS EFFICACY FINDINGS

43,779-9A & 9B (Adult Pivotal)

As indicated earlier, the primary efficacy parameter used to compare MultiHance and Omniscan was the off-site assessment of increase in the level of ——— based on a three-point scale from pre-dose images (unpaired pre-dose only) to pre-dose plus post-first dose images (paired- pre plus post). The differences in the proportions of patients whose level of — information increased were assessed by a one-sided confidence interval. ——— ——— ——— As discussed in the "approach to methods of assessments" section of this review, the results of the subset of patients who received the 0.1 mmol/kg dose as the first dose and the subset of patients who received a 0.1mmol/kg as second dose that was preceded by a 0.1 mmol/kg dose are discussed in depth because these results are directly relevant to the sought dose.

The efficacy findings and results were therefore assessed at the following levels:

A. ——— Information (primary end point)- Increase in level predose versus predose + post-first 0.1 mmol/kg dose and predose + post 1st dose + post 2nd dose of MultiHance (and Omniscan), by readers (2 for each study) for the two pivotal CNS studies 9A and 9B. These were presented as shifts in value at the three levels of scoring, % changes in comparison to Omniscan, and confidence interval differences.
B. Lesion Detection- number of lesions- Increase in number pre-dose, post 1st dose, and post 2nd dose.

Pre-Interpretation Comments:

It is important to note the following before interpreting these results:

a) All subjects were with known disease based on several imaging studies (including enhanced MRI) that were performed as inclusion criteria (enrichment concern).
b) There were no imaging criteria that were prospectively defined for the various categories (therefore subjective).
c) There were no gold standards that could adequately validate the .
d) There was no lesion tracking nor were the lesions matched.
e) The chosen primary efficacy end-point and the scales that were used to score were subjective .
f) The sequence for image reads was different for these two trials (the enhanced image was not read in the unpaired read).
g) Protocol changes and deviations were observed. These are discussed in the medical and statistical reviews.
h) Several patients received an excellent score at baseline, indicating that the drug may add no further benefit. These were not counted in these analyses.

M-2

1 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

The table below provides a summary of the results for "lesion detection- number of lesions" analyses for studies 9A and 9B. The conclusions that one may draw on "lesion detection" are summarized below.

1) See pre-interpretation comments above.
2) As discussed elsewhere, the lesions were not broken down by numbers and in particular, the clinically useful measure of the post contrast outcome of those lesions that were 0 or 1 at baseline were not provided. Furthermore, lesion characterization (an integral component of "lesion detection") was not performed. Caution should be exercised when one interprets these results and the true clinical meaning of these should be gauged critically.
3) The lesions were not matched or tracked. Therefore, it was not possible to determine the extent of this improvement across the patients and within patients. This lack of information could be a serious limitation in the determination of clinical usefulness (see below).
4) The Omniscan arm used higher cumulative dose of 0.3 mmol/kg. Therefore, these results were not included here. They may be found in the primary clinical and statistical reviews.
5) Inter-reader variability [redacted] influenced any conclusions that could be made.
6) The results indicated that there was no statistically significant change (although the readers found more number of lesions after the 1st dose compared to the baseline) in the mean number of lesions identified, when the baseline image was compared to the post 1st dose or the 2nd dose image, and the 2nd dose provided no additional beneficial information greater than the 1st dose, with either MultiHance or Omniscan.

TABLE E1F: MULTIHANCE-CNS-ADULT-STUDIES 9A & 9B
LESION DETECTION- NUMBER OF LESIONS*
DOSE = 0.1mmol/kg[1]

		Reader 1			Reader 2		
Study		**Baseline**	**Post 1st Dose**	**Post 2nd Dose**	**Baseline**	**Post 1st Dose**	**Post 2nd Dose**
9A[2]	N	168	183	174[A]	187	227	226[A]
	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
	P-Value	0.7	0.9	0.8	0.3	0.3	0.9
9B[3]	N	110	131	136[B]	131	149	159[B]
	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
	P-Value	0.4	0.3	0.9	0.5	0.3	0.7

* Ref: Clinical and Statistical Reviews. All lesions.
1= As first dose and second dose (total 0.2 mmol/kg)
2= N= 65 subjects for both readers
3= N= 67 subjects for reader 1 and 68 for reader 2
A= 174 reported as 194 and 226 reported as 233 by the Sponsor (Vol. 1.1, p 100)
B= 136 reported as 140 and 159 reported as 166 by the Sponsor (Vol. 1.1, p 100)

Despite that the "lesion number" was a secondary end-point and that the results (as discussed above) on the number of lesions (as a total without information on the "spread or frequency" of the improvement across patients and the "magnitude" of improvement) were not supportive for this claim from this database, for reasons alluded to above, data on a subset of these patients (from 9A and 9B) with baseline number of lesions 0-4 were further analyzed separately to determine if there was a trend for improvement with MultiHance either with the 1st or 2nd 0.1 mmol/kg dose over baseline. This is presented

below. It is important to remember that the value that one can place on these assessments and hence the findings were limited due to the following reasons:

a) The small sample size
b) Studies 9A and 9B were probably not primarily designed to assess lesion numbers and the uncontrolled CNS metastatic study (B19036/020) was potentially a better study for this type of assessment. Furthermore, the break down of the study population by disease and diagnoses was not available for 9A and 9B. This would have provided an estimate of the sample size of those patients in whom lesion number would be relevant (e.g. brain mets).
c) For purposes of relevance, the limited sample size, and that the 2nd dose of Omniscan was not 0.1 mmol/kg but 0.2 mmol/kg, such evaluations on the 0-4 lesions for Omniscan were not performed. Furthermore, perhaps the more relevant B19036/020 study that evaluated "lesion number" in 150 subjects did not include Omniscan as a comparator. Therefore, such information on Omniscan stemming from these two trials would neither in itself be relevant nor could it be reinforced from other sources within this database (i.e. the mets study).

The results from these preliminary analyses (by the agency clinical and statistical teams) on this subset of patients with 0-4 lesions from studies 9A and 9B were not encouraging and it was difficult to determine the clinical usefulness of MultiHance with respect to "lesion detection-number" based on these values. Furthermore, the few improvements between the baseline to 1st dose and 1st dose to 2nd dose occurred in the same patients and in some instances, the shifts occurred in lesions that were 3 in number at baseline, diminishing its clinical value.

TABLE E1G: MULTIHANCE-CNS-ADULT-STUDIES 9A & 9B NUMBER OF LESIONS[1]- SUBSET-SUBJECTS (%)- 0.1 mmol/kg[2]

		9A		9B	
Drug	**Reference Points**	**Reader 1 (n=65)**	**Reader 2 (n=65)**	**Reader 1 (n=67)**	**Reader 2 (n=65/67?)**
MultiHance	Baseline-Post 1st Dose	12 (18%)	8 (12%)	14 (20%)	10 (15%)
	Post 1st Dose-Post 2nd Dose	2 (3%)	4 (6%)	6 (9%)	6 (9%)

* = Ref: Agency Statistician
1= Defined as 0-4 at baseline and 0-4 after the 1st dose. Improvement was defined as any improvement over baseline with the 1st dose and any improvement with the 2nd dose over the 1st dose.
2= As first dose and second dose of MultiHance.

Summary of Studies 9A and 9B:

In summary, the data from studies 9A and 9B have failed to demonstrate efficacy for both the primary endpoint of _____ ' and the secondary endpoint of "lesion detection-by number".

The database that was relevant for assessments and analyses was narrow and was of the Phase 2 "caliber". In particular, the flaws in the trial design, the incongruity between the trial design, the sought indication and chosen end-points, yielded information that could not be validated. When one attempted (despite the flaws) to find "common" grounds that brought congruity, the evaluable subjects were substantially reduced in numbers and the results were insufficient to drive an indication.

The application of the observed marginal improvement in the data for the 1st dose over baseline with the 0.1 mmol/kg dose in determining effectiveness is severely limited by the subjective scales or criteria that were employed in the scoring. Furthermore, the sponsor failed to demonstrate non-inferiority over the comparator as proposed. Therefore, the category of [redacted] is not validated by these criteria and methods and such a claim is not established.

With respect to the secondary endpoint of "lesion detection-number", the number of lesions that increased with MultiHance was limited and not statistically significant. Further, the clinical importance of these observations could not be validated and it is plausible that these two trials did not enroll the appropriate patient population and therefore such an assessment on "lesion number" was probably futile. [redacted]

B19036/020 (Mets Study)

For purposes of easy reference, this study is referred to as the mets study. See CNS indication above. In addition, the following language in the proposed label (Dosage and administration section, Vol. 1.1, p 109) is noted-

. . .

[redacted]

An overview of the study design and the protocol is comprehensively provided in Table E1A. Several of the comments that were made for the two pivotal studies are also relevant for this trial. The "pre-interpretation" comments above for studies 9A and 9B are additionally applicable.

The "pre-interpretation" issues and concerns related to this study is summarized below for completeness:

a) All patients were with "known" disease based on entrance CT or MRI, the details of which were not provided.
b) The chosen primary end-point was "technical" and this was a Phase 2 "uncontrolled" European trial that attempted to shoulder a heavy burden of validating the "lesion detection" claim [redacted] Although this latter claim of lesion detection (number of lesions in this case) was a secondary end-point, for reasons alluded to above (approach to methods in assessments), and in particular, the failure of the two pivotal trials to demonstrate efficacy on their primary end-points of [redacted] and based on the preliminary results on a similar secondary endpoint of "lesion detection" in patients with 0-4 lesions, this study was critically analyzed.

c) The issues on "lesion number" in relationship to- a) the clinical relevance and the importance of assessments of 0-4 or less in number, and b) [redacted] as an end-point for lesions >4 in number, as discussed above in the pivotal trials, are of importance.
d) The lack of a truth standard, a comparator and lesion tracking [redacted] restricted the value of the results.
e) Although 150 subjects were enrolled in this trial, only ~ 76 were evaluable with respect to the sought dose of 0.1 mmol/kg and the repeat dose of 0.1 mmol/kg (see table- CNS Evaluable Subjects, above).
f) [redacted]
g) The interval between the doses of 10 minutes and image acquisition within 5 minutes after dosing (see schema above) is discordant with the language in the label as mentioned above. Justification for such a claim is not validated.
h) The blinded reads methodology was different for this study in comparison to the two pivotal trials. In particular, the issue was the unpaired enhanced MRI read. The enhanced MRI was not assessed in the unpaired read for studies 9A and 9B, but was included in such assessments in this and other CNS studies. [redacted] The sponsor has argued (Vol. 1.1, p 250) in favor of why the post dose images were not read alone based on current clinical practices. Without entering the issue of whether such an approach was rationale, the sponsor did not maintain consistency in the image read methodology across the trials rending such arguments "mute". The impact of this deviation is highlighted specially when the database is already "truncated".

As discussed above in the "approach to methods in assessments", the focus was on those patients who received the 0.1 mmol/kg dose (both as 1st and 2nd dose) and if these doses improved "lesion detection".

The results from this mets study were analyzed on the basis of the following:

A. Quantitative Measures of [redacted]
B. Qualitative Measures- i.e., Lesion Detection- described as changes in number of lesions (Secondary End-point, but clinically relevant).

[redacted]

1.

[redacted]

The results of "lesion detection-number" evaluations may be tabulated and summarized as follows:

TABLE E1H: MULTIHANCE-CNS-ADULT-METS STUDY* INCREASE IN NUMBER (%) OF LESIONS: 0.1 mmol/kg[1]			
		Reader 1 (N=74)	**Reader 2 (N=74)**
Baseline - Post 1st Dose[A]	Increase	22 (30)	24 (33)
	No Change	33 (46.5)	39 (53.4)
	Decrease	16 (23)	10 (14)
	Not recorded	3 (4)	1 (1)
Post 1st Dose - Post 2nd Dose[B]	Increase	24 (32)	19 (25)
	No Change	45 (61)	48 (65)
	Decrease	2 (3)	6 (8)
	Not recorded	3 (4)	1(1)
*Ref: Clinical Review (tables 14A, 14B); Vol. 1.1, pp.267-268, table L 1= As 1st and 2nd dose- a subset of the .1+.1+.1 arm A= Effect of 0.1 mmol/kg as first dose (see schema) B= Cumulative effect of 0.2 mmol/kg dose (0.1 first dose + 0.1 second dose [see schema])			

1) See "pre-interpretation" issues/concerns above.
2) In the absence of information on lesion "tracking" the value of these results is limited.
3) As discussed above (studies 9A and 9B), the lesions were not broken down by numbers and in particular, the clinically useful measure of the outcome of those lesions that were 0 or 1 at baseline that improved post-contrast were not provided.

4) The 2nd dose offered very limited improvement over the 1st, the clinical and statistical significance of which could not be established. The results further demonstrated that the majority of the patients remained unchanged after the 2nd dose with no added benefit over the first dose.
5) When one dichotomously categorized the results into those that improved (increase) and those did not (by collapsing the no change and the decrease) as indicated by the hatched areas in the table above, 64-73% of the patients showed no improvement for both doses (mean of 66% for the 1st dose for both readers and 68.5% for the 2nd dose for both readers).
6) However, greater improvement following the first dose is observed in this trial when compared to the number of lesions assessments from studies 9A and 9B

As discussed above in the 9A and 9B trial sections, the importance of evidence of improvement in lesions that are 0-4 in number at baseline is emphasized. The agency clinical reviewer performed a subset analyses from this database for those patients with 0-1 baseline number of lesions and 0-1 post 1st dose. The results are summarized in the table below (compare with Table E1L below).

TABLE E1I: MULTIHANCE-CNS-ADULT-METS*- 0.1mmol/kg[1]

INCREASE IN LESIONS[2] BY PATIENTS (%) AND NUMBER (SUBSET 0 or 1 at BASELINE and POST 1st DOSE)

	Reader 1 (N=71)			Reader 2 (N=73)		
	Pre T1/Pre T2 versus Post T1[3]					
	0 to > 1	1 to >2	> 2	0 to > 1	1 to >2	> 2
Baseline - Post 1st Dose[A]	½ (50)	6/22 (27)	47	½ (50)	8/31 (26)	40
Post 1st Dose - Post 2nd Dose[B]	0/1 (0)	6/21 (29)	49	½ (50)	4/26 (15)	45
	Pre T1 versus Post T1[3]					
Baseline - Post 1st Dose[A]	7/8 (88)	17/35 (49)	28	½ (50)	17/42 (40)	28
Post 1st Dose - Post 2nd Dose[B]	0/1 (0)	6/21 (29)	49	½ (50)	4/26 (15)	45

*Ref: Clinical Review (Dr. Li)
1= As first and second dose
2= Lesion tracking or matching not provided.
3= The breakdown of Pre T1 and Pre T2 not provided by the Sponsor. The Sponsor stated that the higher of the values were chosen. Whether the paired reading included the Pre T1/T2 is not known.
A= Effect of 0.1 mmol/kg as first dose (see schema)
B= Cumulative effect of 0.2 mmol/kg dose (0.1 first dose + 0.1 second dose [see schema])

1. The second dose does not provide any significant benefit over the first dose.
2. Interpretation of the results with the first dose is restricted by the very small numbers in the 0 to >1 group. Conclusions are further restricted by the lack of specifics with respect to the image sequences and the methodology. The significance of this issue is further discussed below and the data presented in Table E1L highlights the concerns when all the pre-contrast sequences/images are (not) included in the determination of benefits of the drug over the device.
3. As discussed above, the data from this trial with respect to "lesion numbers" was critical in the CNS efficacy assessments. Based on the concerns and the results (from studies 9A, 9B [redacted]) with the [redacted]" end-point, any clinically significant data that potentially could have driven this indication rested in this trial that sought "lesion number" in the right patient population (patients with

mets).

Therefore, "approvability" based on "lesion number" is not justified.

CNS Proposed Indication

CNS Pediatric

M-3

17 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

SAFETY SUMMARY

Dr. Li has reviewed the safety data comprehensively. Only the salient issues are discussed below. Information on the overall exposure and demographics is discussed in the section "Overview of the MultiHance Clinical Program" above.

Although MultiHance is marketed in several other countries and is generally comparable to the other approved gadolinium agents with respect to the physio-chemical properties and the adverse event profile, the differences in the osmolality, lipophilicity, biliary excretion (therefore liver), renal elimination profile, and in conjunction with the pre-clinical safety findings and concerns, places MultiHance on a different platform that requires further attention. The concerns that stem from these issues and those that are generally known to be associated with gadolinium agents such as on the heart, are discussed below.

A. Osmolality

1. Injection Site Reactions

Of all the approved gadolinium agents, MultiHance has the highest osmolality/viscosity. The related concern, specifically, Magnevist, which has a lower viscosity and osmolality has been associated with phlebitis, injection site reactions, compartment syndrome, fasciitis and amputations. The most likely attributable cause to these events was osmolality, ionicity and/or viscosity. Although such instances were not reported in this program, details regarding those patients who were categorized as "injection site reactions" are recommended with specific breakdown of events (including fibrosis and other compartment syndrome related events). Page 100 of Dr. Li's review provides a breakdown of these reactions by dose. The overall injection site reaction rate was similar to Magnevist and OptiMARK. These concerns are further compounded by the local skin reactions in the pre-clinical studies in animals following "paravenous" injections.

2. CNS Effects

A second concern that may be related to osmolality (and or direct) is the effects on the CNS, particularly in the presence of a disrupted blood brain barrier. The pre-clinical safety pharmacology studies in animals revealed hypoactivity, impaired motor coordination, convulsions and death in which the doses ranged from 0.3 to 3.3 times the clinical dose. Whether these effects were independently attributable to osmolality is not known. There was a report of seizures in a patient listed as a serious adverse event (see below). Although MultiHance may have not have triggered the seizure in this patient, whether it lowered the threshold for pre-existing seizures is a possibility. Magnevist (with the second highest osmolality) label lists seizures under precaution/warning. Furthermore, there was no EEG monitoring in this program. On these grounds, appropriate warning in the label is recommended.

3. CHF-Pulmonary edema

One patient with a history of recent large MI and probably with CHF (was receiving ACE inhibitors and furosemide) developed acute pulmonary edema (listed as SAE) within 10 minutes after administration of 30mL of MultiHance. The high osmolality of MultiHance may have decompensated the heart failure in triggering pulmonary edema. These are additional concerns that require appropriate warning in the labeling.

B. Liver and GI

The relationship between MultiHance and the liver requires further exploration. This concern, based on- its presumed mechanism of action of hepatocelluar uptake and lipophilicity, the pre-clinical observations of hepatic necrosis and pancreatic vacuolization in animals (these are discussed in the review in detail- see liver indication), elevated LFTs in patients, calls for additional safety information.

1. AE-Bilirubinemia

The AE table lists a 0.2 % bilirubinemia in 4 adult patients and 0.6% in overall adult population. There were 5 healthy volunteers who experienced bilirubin elevation as AE of which 3 had a baseline elevation related to medical condition of icterus intermittans juvenilis and V Willibrands disease. The sponsor reports that the post dose increase returned to baseline even with continued administration of the drug (vol. 1.1, p. 312).

2. AE Profile: Special Populations

Hepatically impaired patients were studied in the special population trial (16 patients, male and female, 11 received the 0.1 mmol/kg dose and 4 received placebo). Of the 971 patients who received MultiHance, 180 patients (18.5%) experienced 377 AE of which study agent related AE occurred in 149 (15.3%). These rates appear to be comparable to the general AE profile. The pre-clinical transporter knock out study in rats showed that the renal excretion fraction was significantly increased when the hepatic function was decompensated. In other words, there seemed to be a renal compensation in the presence of hepatic dysfunction. Renal dysfuction may develop in patients with liver disease (the hepato-renal syndrome). Data on such patients with co-existing liver and kidney disease was not collected. Also, the behavior of MultiHance in patients with porto-systemic shunting is unknown. These issues may be relevant in the context that the intended population for use may potentially be the targeted population. The AE profile for the patients enrolled in the liver studies did not reveal any significant changes from the CNS group.

3. LFT Changes from Baseline

Table CC (vol. 1.229, p 96) lists LFT changes from baseline for the adult population. Only the elevations are tabulated below:

TABLE S1- MULTIHANCE- ELEVATED LFTS-ADULTS (%)* CHANGE FROM NORMAL BASELINE			
	3 hour post	**24 hours post**	**72 hours post**
Total Bilirubin	9/260 (3.5)	36/1302 (2.8)	7/178 (3.9)
Direct Bilirubin	6/256 (2.3)	8/677 (1.2)	2/174 (1.1)
AST (SGOT)	3/222 (1.4)	30/1066 (2.8)	5/139 (3.6)
ALT (SGPT)	1/204 (0.5)	46/10170 (4.3)	6/172 (3.5)
Alkaline Phosphatase	2/208 (1.0)	26/1118 (2.3)	3/134 (2.2)
GGT	4/152 (2.6)	36/839 (4.3)	2/129 (1.6)
* Ref: Table CC (vol. 1.229, p 96).			

4. Pancreas

The sponsor reported a case of necrotizing pancreatitis as a serious AE from the ongoing clinical trials (vol. 1.1, p 311). Details on this patient are lacking to make any further assessments, but further exploration is recommended particularly in the context of pancreatic vacuolization in the pre-clinical animal studies.

The sponsor needs to validate the "hepatocellular" mechanism-of-action claim and addtionally, should provide a detailed breakdown of the AE with respect to lab (LFTs) abnormlaities and other AEs related to the GI system (by patient, by dose, changes across different parameters in the same patient, time of resolution to baseline, associated symptoms, and associated renal status)

C. Heart and ECG

Gadolinium agents are known to block the calcium cardiac channels and are associated with QT/QTc prolongation. Based on these concerns, the following comments are made.

1. Adult ECG Clinical Adequacy

The adequacy of the relevant ECG monitoring in this program was not determinable. Specifically, with the frequent cumulative dosing (dosing intervals of 10-15 minutes), it was not possible to isolate those ECGs that were recorded following a single dose that did not reflect cumulative effects. The timing of the ECG recording varied across the trials (table 51, p 98, Dr. Li). 12 lead during the "immediate post-dose" time point was performed in one pivotal study (adult liver, N=97) and overall, a total of 181 patients were monitored at the same time point. The details on the other 84 patients are not provided. The sponsor further states that 30% of these immediate post dose ECG evaluations occurred within 10 minutes post dose and 70% within 30 minutes post dose (vol. 1.229, p 78). The latter time point of within 30 minutes may reflect a cumulative effect if these patients received the cumulative dosing and it was further not possible to determine if this monitoring within 10 minutes post dose was indeed post 1st dose. Therefore, the extent of the database with respect to the most

relevant time-point of monitoring (immediate post- 1st dose) to assess the potential effects of a single dose is unknown.

2. Pediatric ECG Adequacy

There was no ECG monitoring in the pivotal CNS pediatric study.

3. ECG: Pre-clinical Adequacy

According to the memo of the biopharm/tox team leader, the ECG monitoring was inadequate. There was no continuous monitoring during dosing and there were no QT evaluations. Based on several concerns, an overall non-approval recommendation has been made with additional pre-approval studies, including in vitro cardiac electrophysiology studies (effects on potassium channels and action potential duration).

4. ECG Findings

(a) QTc Prolongation

The table (Dr. Li, p 98) indicates all the QT/QTc changes across all the measured time points. The relevant findings are summarized in the table below:

TABLE S2*- MULTIHANCE-ECG-QTc (msec) INCREASE FROM BASELINE-PATIENT (%)

	Immediate Post N = 181	1 h ± 15 m N = 520	2 h ± 15 m N = 519	4 h ± 30 m N = 516	24 h ± 3 h N = 657
≤ 30	73 (40.3)	249 (47.9)	222 (42.8)	236 (45.7)	No record
≥ 30 ≤ 60	6 (3.3)	13 (2.5)	25 (4.8)	12 (2.3)	23 (3.5)
≥ 60	1 (.6)	1 (.2)	3 (.6)	4 (.8)	4 (.6)

* Ref- Dr. Li , table 51

(b) ECG-Changes in Rhythm or Morphology

Table WW, Vol. 1.229, p 135 indicates patients with changes in rhythm and morphology changes in ECG. No meaningful trend was noted. But in conjunction with the other ECG CVS changes, these additional findings suggest that the effects of MultiHance on the heart was global and was observed at different levels and affected different parameters.

(c) Cardiovascular Adverse Events

The sponsor reported cardiovascular related AEs in the adult population (vol. 1.229, p 81). The table S3 below summarizes these findings for the MultiHance group.

TABLE S3*- MULTIHANCE-CARDIOVASCULAR AE-ADULT POST FIRST DOSE (N = 1808)	
Number of Subjects with CVS AE (subject number)	70 (3.9%)
Number of CVS AE (event number)	89 (.05)
Type of Abnormality	**Number of Events**
Supra Ventricular Arrhythmias[1]	32
Conduction System Abnormalities[2]	10
Ventricular Arrhythmias[3]	5
Indicators of MI	3
Q, S, and or T wave abnormalities[5]	7
Others	14

*Ref- Vol. 1.229, p 81.
1 = Includes Atrial Fib/flutter (4), SVT (16), Bradycardia (8), Sinus Arrhythmia (4). Most SVTs (9/16) other than Atrial Fibrillation or Atrial Flutter, occurred less than 4 hours post dose (Vol. 1.229, pp. 83-84). All sinus bradycardias occurred less than 4 hours post dose.
2 = Table X, Vol. 1.229, p 89 lists these abnormalities- includes PR interval changes, AV Blocks, BBB, Ventricular Arrhythmia. In 5/10 patients these occurred less than 4 hours post dose.
3 = Table AA, Vol. 1.229, p. 93 lists all the ventricular arrhythmias. Included PVCs, Ventricular Arrhythmias, Extrasystoles. Occurred 1-hour post dose to 24-hour post dose. In 4 patients, these were associated with other ECG abnormalities. Dose ranged from ~.05 mmol/kg to ~ 0.2 mmol/kg.
5 = Table Y, vol. 1.229, p 91 lists all these abnormalities. In 4 patients these were noted less than 4 hours post dose.

Summary of ECG and CVS

Although there were no deaths associated with ECG changes, these findings along with inadequacies in clinical and pre-clinical monitoring are concerning. Specifically, QTc prolongation was observed across most of the measured time points (table S2). The cardiovascular related AE (table S3), included patients with ventricular arrhythmias and PVCs. Although most QTc prolongation were of the <30 msec magnitude, the frequency of its occurrence across the measured time points (ranged from 40-47%) were additional concerns. Historically, in most drugs that caused malignant ventricular arrhythmias, the magnitude of the change from baseline were not significant. Therefore, the occurrence of most QTc prolongation in the < 30 msec range is not a reassurance. Further pre-clinical and clinical data may be required.

D. Other General Inadequacies in the Safety monitoring

(a) Kidney and Urine

MultiHance's relationship with the renal and urinary system appears to be different when compared to the other gadolinium agents. Specifically, the renal elimination pathway is not the sole route by which the drug is eliminated, but there seems to be a "compensatory" mechanism by which the renal elimination is increased when hepatic dysfuction co-exists. The renal elimination is prolonged in patients with renal dysfunction. The relationship between MultiHance and co-existing hepato-renal disease is not known. Renal vacuolization (in rats, NOAEL was .5 mmol/kg in the acute and repeat tox studies) has been noted with other gadolinium agents including MultiHance, but the associated functional abnormalities (as evidenced by the urinary electrolyte changes in the kidney in the repeat tox studies) are unique to MultiHance, as such an association is unknown with the other agents. Likewise, bladder

vacuolization (epithelial cell vacuolization in the repeat tox study in rats) also appears to be unique to MultiHance.

Complete urine analyses were not performed in these trials. The pediatric population had no urine analyzed. Based on the PK profile of MultiHance (primarily eliminated by the kidneys), and the pre-clinical findings of the importance of the need for this safety monitoring is highlighted. As discussed in the special population above, the relationship between MultiHance and patients with co-existing hepatic and renal disease is not known.

(b) Calcium

Lab assessments did not include ionized calcium levels.

(c) Pediatric Safety

1. The safety [redacted] and older pediatric population was evaluated in 85 CNS pediatric patients who received the 0.1 mmol/kg dose. Of these patients, 15 were <2 years of age (included the following number of subjects in each subset of patients under 2 years age: 4 day old= 1, ~ 6 months old = 3, ~9 months old = 2, one year old = 3, 1 ½ year old = 2, 1 ¾ year old = 2 and 2 year = 2). There was only one subject < 5 years old (3.2 years) who was assessed in the pediatric PK study (none < 2 years of age, 4 years = 2, 5 years = 0 and 6 years = 5). Based on the age groups that were studied, there is no justification to support this claim for the stipulated age group.
2. There were two pediatric patients who experienced serious AE (vomiting 4 ½ hours post dose in a brain stem glioma patient and hypoxia 30 minutes post that lasted 3 hours in a previously intubated patient).
3. As mentioned above in the ECG section, none of the pediatric patients had ECG monitoring.
4. Safety monitoring did not include urine analysis.
5. [redacted]

E. Adverse events

AEs by subgroup were analyzed for the following – sex, age, race, weight, dose, study location, center, formulation, and injection methods. In particular, there were no dose related relationships. Although less number of patients were enrolled in the US based trials, the AE reporting for US based trials was greater than the non-US based trials (594 subjects with 153 [25.8%] drug related AE versus Europe with 1151 subjects with 155 [13.5%]). The bolus injection group also showed a slightly higher incidence of AE compared to the slow injection sub group (bolus in 790 subjects with 183 [23.2%] related AE versus 678 slow infusion with 112 [16.5%]). Within the special population groups, including the pediatric population, no noticeable differences were observed except for the renal group. However, the small number of patients in these renal studies limited any definitive conclusions that could be drawn.

The CVS related AEs are discussed above under the ECG section. The 4-month safety update for all completed studies was submitted. Post-marketing safety data was also submitted.

F. Serious Adverse Events, Deaths, Discontinuations

These are discussed in Dr. Li's review (pp 86-89) and Vol. 1.229, pp. 65-71 of the submission.

1. Deaths

There were 5 deaths and there was no temporal relationship between the dosing of MultiHance and the timing of the death. In 4 of these 5 patients death occurred 7 to 35 days later. In one patient the timing of death with respect to MultiHance administration was not provided- but the cause of death was probably due to pulmonary embolism. The cause of death in the other patients could be attributable to their underlying medical conditions.

2. Serious AE

There were 17 patients who experienced serious AEs (NDA submission = 15 [included 10 adults and 2 pediatric patients from the European and US data-base and 3 patients from the Japanese studies] and update = 2). Five of these were associated with death (see above). Three were associated with discontinuations. The SAEs that are of relevance were:

(a) Convulsions (also seen with Magnevist- ? osmolality related ? direct effects): occurred 17 minutes after the first dose in a patient who had a history of seizures.
(b) Acute pulmonary edema: 10 minutes post dose in a patient with history of large anterior MI 8 days prior to drug administration on several medications including ACE inhibitors and furosemide (? Suggestive of CHF). Total volume of MultiHance was 30mL. The high osmolality of MultiHance may also have been contributory.
(c) Syncope: The syncopal episode occurred ~10 hours post MultiHance following chest pain.
(d) The acute necrotizing pancreatitis was described above (pancreas).

The other unrelated SAEs included: intracranial hypertension, CNS depression, Hemiplegia, PE (20 hours post), Aphasia (3 hours post) Acute Allergic Reaction, and Stroke (34 hours post). The pediatric SAE was discussed above (pediatric safety).

3. Discontinuations: There were 10 patients who discontinued from the studies of which 4 were due to serious AEs. These are discussed in Dr. Li's review.

Safety Summary: See safety summary above.

END OF REVIEW

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
5/24/02 04:16:26 PM
MEDICAL OFFICER
The non-approval recommedation is based on the details contained in the memo. Reference is also made to Dr. Li's review. See addendum to memo to file.

Patricia Love
5/24/02 05:17:43 PM
MEDICAL OFFICER

REVIEW CYCLE #1

Submission Date August 20, 2001/ February 26, 2002

Action: Approvable

NDA #21-357 MEDICAL OFFICER'S REVIEW HFD-160
NDA #21-358
MULTIHANCE

Submissions:	N000-AM	N000-BM	N000-BM
Letter Date:	February 26, 2002	March 8, 2002	March 12, 2002
Date Received:	February 26, 2002	March 12, 2002	March 13, 2002
Date Assigned:	March 6, 2002	March 14, 2002	March 15, 2002
Submissions:	N000-BM	N000-BM	Faxed articles
Letter Date:	March 25, 2002	April 18, 2002	May 1, 2002
Date Received:	March 26, 2002	April 19, 2002	May 1, 2002
Date Assigned:	March 27, 2002	April 24, 2002	May 1, 2002

Date Completed: May 16, 2002

Type of Submission: NDA Amendment
Sponsor: Bracco Diagnostics, Inc
P.O.Box 5225
Princeton, NJ 08543
Division: Medical Imaging and Radiopharmaceutical Drug Products
Medical Officer: Roger W. Li, MD
Team Leader: Ramesh Raman, MD
Statistician: Shahla S. Farr, MS
CSO: Tia Harper-Velazquez

Drug Name: MultiHance
Class of Drug: MRI agent

New and/or Revised Proposals and/or Data Submitted

I. Revised CNS [redacted] Indications and Dosing Regimens
II. Prospective Imaging Criteria Sheets Used by the Blinded Readers (Protocols #43,779 9A/B and B19036/039)
III. New CNS study (BBG/701)
IV. New Literature (1 CNS [redacted])
V. Subset analysis of adverse events in patients with cirrhosis
VI. Subset analysis of adverse events in patients with an allergy history
VII. Subset analysis of ventricular repolarization (Study 43,779-12) in patients on calcium channel blockers

Clinical Review

I. Background and Introduction
II. Conclusions and Recommendations
III. Summary of Clinical Findings
IV. Summary of Safety Findings

TABLE OF CONTENTS

Clinical Review Addendum

I. Background and Introduction

The clinical recommendation (date of review - February 8, 2002) for the original NDA application (dated stamped received - April 27, 2001) was NOT APPROVABLE for the CNS ——— indications. The sponsor was briefed of the pending decision a few days prior to the transmission of the NOT APPROVABLE letter. The sponsor was granted an emergency meeting with the Division on February 25, 2002. At that meeting, the sponsor's request to send in an amendment before the PDUFA date of February 27, 2002 was permitted. The amendment was to contain an additional CNS study, a CNS meta-analysis, and the prospective pictorial image criteria used by the blinded readers to distinguish benign from malignant liver lesions. The amendment was stamped received on February 27, 2002. Multiple additional submissions were also sent in over the following months of the NDA extension.

This clinical review will discuss all the newly submitted items received by May 1, 2002 and determine if they provide substantial new information that could significantly alter the clinical recommendations for the CNS ——— indications.

II. Conclusion and Recommendation on Approvability

1. CNS

The sponsor has not performed proper nor complete evaluations to determine the optimal dose (e.g. single 0.05 or 0.1 mmol/kg or double dose 0.1+0.1 mmol/kg), imaging times (e.g. dynamic and/or delayed), imaging sequences (e.g. T1wSE, T1wGE, T2wSE &/or T2wFSE) for their proposed "visualization" ("detection") indication.

For "detection", the sponsor must further evaluate the ability of MultiHance MRI to identify confirmed new lesions in those patients suspected to have non-metastatic lesions and in those patients suspected to have metastases, with dynamic imaging and with delayed single or double dose imaging, respectively.

The limited additional information provided in the NDA amendment (one literature article, one additional CNS study, one meta-analysis, and reiteration of the portions of the original NDA submission) is not sufficient to advance the original clinical recommendation and therefore, the proposed CNS indication is NOT APPROVABLE.

M-4

1 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Clinical Review of New and/or Revised Proposals and Data Submitted

I. Revised CNS ——— · Indications and Dosing Regimens

A. Revised Indication(s) Proposed by the Sponsor

1. CNS

ORIGINAL VERSION- "In the CNS, intravenous MultiHance ———— ——— additional to that obtained with unenhanced MRI resulting in improved detection and diagnostic assessment of lesions with abnormal vascularity and of lesions thought to cause an abnormality in the blood brain barrier."

NEW VERSION- "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."

B. Revised Dosage/Administration by Sponsor

1. CNS

ORIGINAL VERSION – "0.1 mmol/kg (0.2 mL/kg) administered as a rapid intravenous infusion or bolus injection. In patients with known or suspected brain metastases, a second injection of 0.1 mmol/kg provides a significant increase in lesion-to-normal parenchyma contrast enhancement that is associated with improved lesion detection."

NEW VERSION - "MultiHance should be administered as a bolus injection at a dose of 0.1 mmol/kg (0.2 mL/kg). A second 0.1 mmol/kg dose and the subsequent increase in contrast enhancement is recommended in those patient subpopulations where lesion detectability at MRI should be highest, such as patients with suspected metastatic disease to the CNS."

C. Revised Imaging Times

1. CNS

OLD VERSION - May start up to 20 minutes after the injection of MultiHance.

NEW VERSION – Not specified in the proposed package insert.

II. Prospective Imaging Criteria Sheets Used by the Blinded Readers (Protocols #43,779 9A/B and B19036/039)

1. CNS

The sponsor has provided copies of the Matched Assessment portion (#8-12) and the Lesion Tracking page of the Off-Site Blinded Reading Selected CRF Sheets for Protocols #43,779-9A/B in Attachment 1 of Submission N000-BM dated April 18, 2002.

These CRF sheets ask, in general terms, whether certain parameter(s) (pattern/anatomy of enhancement, number of lesions, signal intensity characteristics including hemorrhage, or other, explain) contributed

and whether lesion detection/exclusion, signal enhancement, or lesion

(i.e. visualization of lesion margins, pattern of enhancement,

morphology and internal structure) on the post-dose images offered additional diagnostic information. Then the reader was to indicate from a list of 10, the primary diagnosis.

MO Comment: These pages of the CRF had already been provided in the original NDA submission. There were no representative pictorial enhancement images available to the blinded reader depicting the prospectively defined specific features of a benign or malignant [redacted] lesion or of an individual CNS diagnosis.

III. New CNS Study BBG/701

Title: "Comparison of the Contrasting Behavior of Gd-BOPTA [MultiHance] and Gd-DTPA [Magnevist] in CNS Indications".

This is a Phase IIIb multicenter (n=2), double blinded, randomized, intra-individual crossover comparison of 0.1 mmol/kg MultiHance (0.5M) to 0.1 mmol/kg Magnevist (0.5M) evaluated in 15 (EFF=efficacy) patients with known intra-axial glioma (WHO grade III+IV) or intra-cerebral metastases from August 10, 1999 to December 13, 1999. Administration of the two agents were separated by at least 48 hours (washout period) and was given intravenously by power injector at a rate of 2 mL/second.

The primary efficacy endpoint was to demonstrate MultiHance's superior "global" assessment of contrast enhancement compared to Magnevist (evaluated on a continuous scale from 0 to 18, with 0 = MR session 1 better than session 2, 9 = both equal, and 18 = MR session 2 better than session 1). Statistically evaluation was performed with the Wilcoxin signed rank test with $\alpha = 5\%$, $\beta = 80\%$, and calculated required sample size of 24 cases. Blinded reading was performed off-site by two independent readers.

Secondary endpoints included [redacted] metastases, other, unknown), and technical quality. The sponsor acknowledged that secondary analyses were to be considered "exploratory" (page 38 of volume 2 Submission N000-BM dated February 26, 2002).

Safety monitoring consisted only of adverse event reporting.

The sponsor reports that MultiHance is subjectively judged to be statistically better than Magnevist in 10 patients, equal in 3 patients, and worse in 2 patients for reader #1 ($p<0.05$), and better in 13 patients, equal in 1 patient, and worse in 1 patient for reader #2 ($p<0.01$).

MO Comment: There are multiple flaws with this clinical trial.

a. *The primary endpoint is totally subjective.*
b. *The efficacy sample size (n=15) is too small to draw any conclusions.*
c. *There was a high percentage of protocol deviations (37.5% = 9 out of 24 patients).*
d. *Could include patients with prior CNS biopsy if <10% of the "initially detected tumor mass" remained.*
e. [redacted]

Conclusion: This Phase III clinical MultiHance study does not add any useful pivotal or supportive evidence for the CNS indication.

IV. New Literature (total n= 13)

1. CNS (n=1)

The sponsor submitted one CNS article with the NDA amendment dated February 26, 2002. It was a retrospective, multicenter, blinded, randomized Phase II analysis of 22 patients with known CNS metastatic lesions proven with either contrast enhanced CT or contrast enhanced MRI. It compares MultiHance (0.2 and 0.3 cumulative doses) to one of three other gadolinium contrast agents (Magnevist, Omniscan, or Dotarem).

Table #1 CNS Article

1° Author	Title	Journal	Year	Volume	Page(s)
Colosimo, C	Detection of Intracranial Metastases	Investigative Radiology	2001	36 (2)	72-81

Comparator (n)	Phase	Readers (#)	Dose Response	# of Centers	Normal Subjects &/or Patients (#)
Magnevist (13) Omniscan (4) Dotarem (5)	II	Yes (2) Blinded Randomized	Yes Three Sequential	8 Retro-spective	22 Pts

Formulation (M)	Dose (mmol/kg)	Rate (mL/s)	Power Injector /Hand	MR Tesla	MRI Sequences
NS	0.05+0.05+0.1 0.1+0.1+0.1 Comparator was 0.1 or 0.2	≥ 2	Bolus at 10 minute intervals	0.5, 1.0, or 1.5	MultiHance PRE-T1wSE, T2wSE or T2wFSE POST-T1wSE Comparator PRE-T1wSE, T2wSE or T2wFSE POST-T1wSE

Dynamic (minutes)	Delayed (minutes)	1° Endpt	2° Endpt	12 lead ECG	Adverse Events
NS	NS	Sens+Spec Lesion/Brain Detection	Lesion # Location	NS	NS

Important Statements made by the Author(s)
MultiHance "has higher relaxivity than equimolar formulations of other approved extracellular contrast agents." "resulting in the possibility of superior contrast enhancement-represents an alternative approach to increasing sensitivity without increasing costs." "Metastatic disease is a relatively slowly evolving pathology, and a mean time interval of 8.2 days between examinations would not be expected to have a significant effect." No truth standard was used. No lesion by lesion comparison was performed. "The small sample population of the study precluded the possibility of performing meaningful statistical analyses on the data."