Note: In looking at the frequency tables below, please note:

1. *number of subjects who fall on the diagonal - i.e., the pre and pair scores are the same.*
2. *number of subjects who fall above the diagonal - i.e., the pair is doing better than the pre.*
3. *number of subjects who fall below the diagonal - i.e., the pre is doing better than the pair.*

Primary Efficacy Analysis: Report # 488 /Phase 3 (Pivotal) Protocol # 1177-95-03.03

Cross Tabulation of Border Delineation Score Recorded* by Blinded Readers on "Pre" and "Pair" - OptiMARK™ (n = 132)

Border Delineation Score - "Pre"	Border Delineation Score - "Pair" 1	2	3	4	5	6	7	8	9	10
1	22				1			3		
2		1				1	1			
3			1	1			1	1		1
4	1			1		2	2	1	1	1
5					1	2	1			2
6	1		2	2	4		4	4	2	1
7	1					2	1	4	3	3
8		1			1	3		5	1	4
9							2	1	3	6
10								1	1	20

*Empty cells are cells where the frequency is zero. Table prepared by FDA Statistician.

Primary Efficacy Analysis: Report # 488 /Phase 3 (Pivotal) Protocol # 1177-95-03.03

Cross Tabulation of Border Delineation Score Recorded* by Blinded Readers on "Pre" and "Pair" - Magnevist® (n =68)

Border Delineation Score - "Pre"	Border Delineation Score - "Pair" 1	2	3	4	5	6	7	8	9	10
1	13					1	1			1
2		1						1		
3							1			
4					1			1	2	1
5			1	2	1	1			1	
6				1			1	2	2	
7	1							3		
8						1	1	4	3	4
9							1	1	1	2
10								1	1	8

*Empty cells are cells where the frequency is zero. Table prepared by FDA Statistician.

- The table below summarizes the information from the frequency tables:

Primary Efficacy Analysis
Blinded Readers: Border Delineation: Report # 488 /Phase 3 (Pivotal)

		Decrease	No change	Increase	Total
OptiMARK™	N	23	56	54	132
	%	17.42	41.67	40.91	
Magnevist®	N	11	28	29	68
	%	16.18	41.18	42.65	

Comments on primary efficacy analysis:

1. The various frequency scores for OptiMARK™ and Magnevist® are probably statistically similar (proving no significant statistical difference between the two, and thereby establishing equivalence only if the equivalence interval of –1.5 to +1.5 is acceptable).
2. But it is worthy to note that the majority of the cases in both the groups had no change or actually a decrease (when combined) in all the three primary efficacy end points. This is due to the fact that the cases were largely selective (eg. a pre contrast scan easily shows a post-operative defect even without contrast) and enriched (the out come was known when the qualifying MRI was performed).
3. One should bear in mind, that these observations (the results) are the "effects" and not the "cause". It therefore becomes extremely important and crucial to critically weigh some of the issues discussed above in the enrollment section in determining the validity of these results (which seems acceptable for equivalence claim on a face value if the equivalence interval chosen by the Sponsor is acceptable).
4. The equivalence interval of (-1.5,1.5) has been chosen by the Sponsor. This is a wide interval based on which (and in the opinion of the Statistician), the Sponsor has been able to prove equivalence between OptiMARK™ and Magnevist®. If a narrower interval is chosen, the data then suggests no equivalence. The overall data by itself (for both the agents) does not suggest that the pair is clearly and very strongly superior to the pre. It is beyond the scope of this review to further comment on this aspect, and additionally, the Sponsor is not claiming superiority over the comparator.
5. In concurrence with the Statistician, the reviewer acknowledges that the designation of the primary and secondary endpoints was consistent with the protocol (as in the NDA submission), but the statistical methods being used to analyze these endpoints were not. The efficacy results contained in the NDA are derived using ANOVA for calculating confidence intervals, and an equivalence region defined as –1.5 to +1.5. The protocol calls for the use of t-tests and standard confidence interval methods, but does not define an equivalence region. This is a "wide" region that the Sponsor has chosen, which calls for further careful clinical and statistical relevance and validity. If this region is statistically acceptable, the reviewer concurs that the Sponsor has demonstrated equivalence. Refer to the Statistician's review for additional comments.
6. If, in the review team's opinion it is determined that these concerns are significant and meritorious, either no credit should be given for this claim/indication or appropriate changes in the claim or labeling should be made to reflect these observations such as: "OptiMARK™ is indicated for use in patients who have known CNS pathology (specifically post treatment patients) as opposed to those in whom it is suspected with a high degree or those with non-treatment associated pathology ... and OptiMARK™ is indicated for use after appropriate imaging studies have been obtained with another approved gadolinium agent....."
7. See overview of efficacy for further comments.

SECONDARY EFFICACY ANALYSIS FOR BLINDED READERS: INTENT-TO-TREAT

- **Secondary Endpoints:** [p. 12.0557 - 12.0558, Vol. 2.48]

The secondary end points were:

a) "the proportion of patients for whom the final clinical diagnosis agreed with the diagnosis from the pre-contrast plus post-contrast images (i.e., sensitivity and specificity);"
b) "the image score for the ability to distinguish edematous tissue from pathology pre-contrast plus post-contrast compared to pre-contrast;"
c) "the score for the degree of confidence that the total number of lesion(s) exist pre-contrast plus post-contrast compared to pre-contrast;"
d) "the number of lesions per patient pre-contrast plus post-contrast compared to pre-contrast;"
e) "the proportion of patients for whom the next anticipated management choice suggested for the patient was altered pre-contrast plus post-contrast compared to pre-contrast; and"
f) "the proportion of patients for whom the contrast agent impaired the ability to visualize lesion(s) or pathology."

- An additional independent reader compared the final clinical diagnosis -('a' above) and the number of lesions -('b' above) as determined/provided by the principal site investigator to the masked readers' diagnosis. This independent reader subsequently determined an agreement between the two- ***Agreement with Final Diagnosis***. These (a and c above) are the secondary end points that the Sponsor has pursued in the efficacy analysis.
- The table below (incorporated from the application) provides these results. Pseudo Sensitivity and Specificity results were also derived by combining the Not Evaluable, No Agreement, and Partial Agreement into a Do Not Agree category (in the shaded area in the table) and the Basic Agreement and Absolute Agreement categories into an Agree category.

Secondary Efficacy Analysis: Report # 488 /Phase 3 (Pivotal) Protocol # 1177-95-03.03
Table: Agreement with Final Diagnosis – Blinded Readers

OptiMARK™	Pre-Contrast Diagnosis N(%)				
	Not Evaluable	No Agreement	Partial Agreement	Basic Agreement	Absolute Agreement
Disease	1 (0.8)	65 (53.3)	14 (11.5)	11 (9.0)	31 (25.4)
No Disease		5 (71.4)			2 (28.6)
	Pre- plus Post-Contrast Diagnosis N(%)				
Disease	1 (0.8)	57 (46.7)	18 (14.8)	13 (10.7)	33 (27.1)
No Disease		5 (71.4)			2 (28.6)
Magnevist®	Pre-Contrast Diagnosis N(%)				
Disease		25 (39.7)	9 (14.3)	9 (14.3)	20 (31.8)
No Disease		1 (50.0)			1 (50.0)
	Pre- plus Post-Contrast Diagnosis N(%)				
Disease		25 (39.7)	7 (11.1)	9 (14.3)	22 (34.9)
No Disease		1 (50.0)			1 (50.0)

General comments on secondary efficacy analysis:

1. Refer to the Statistician's review for additional comments.
2. The Final Diagnosis: The Principal Investigator followed each patient for up to 30 days to determine the final diagnosis. If at the completion of this interval a final diagnosis was not available, the clinical diagnosis at 30 days was used. Factors contributing to the final diagnosis were recorded and included but were not limited to one or more of the following:
   CT (with or without contrast), Prior MRI (with or without contrast); also the non-contrast MRI from this trial, Myelography, Clinical course, Physical exam, Lab evaluations, Biopsy and/or Surgery, Histology, Autopsy.
3. As commented above in the final diagnosis section, note that the un-enhanced part of the images from this study was incorporated as one of the factors contributing to the final diagnosis. The reviewer acknowledges that the enhanced images were not included in determining final diagnosis.
4. The Blinded Review Extent of Agreement Appraisal (between the principal investigator's final diagnosis and the blinded readers' final diagnosis and number of lesions) completed by the fourth blinded reader included the following:

   "**Not Evaluable**: Information from the pre and post-contrast MRI record cannot be compared to the final clinical diagnosis (e.g., the images were not technically satisfactory)."
   "**No Agreement**: No agreement in the diagnosis(es) indicated from the pre and post-contrast record compared to those indicated in the final clinical diagnosis record."
   "**Partial Agreement**: Incomplete or fractional agreement in the diagnosis(es) indicated from the pre and post-contrast compared to those indicated in the final clinical diagnosis record."
   "**Basic Agreement**: Basic agreement supported by identical diagnosis(es) yet different number of lesion(s) detected from the pre and post-contrast compared to the final clinical diagnosis record."
   "**Absolute Agreement**: Total agreement based on identical diagnosis(es) **and** same number of lesion(s) detected in the pre and post-contrast record compared to the final clinical diagnosis record."

5. Table 11.4.1.5-3 (Vol. 2.46, p. 12.0052) provides the data on the Agreement with Final Diagnosis (see modified table above). Here again, although the Sponsor has demonstrated that the proportion of patients with disease that had agreement on the post-contrast diagnosis with the final diagnosis was similar for both OptiMARK™(37.7%) and Magnevist®(49.2%); the majority falls into the Do Not Agree category.

PRIMARY & SECONDARY EFFICACY ANALYSIS FOR PRINCIPAL INVESTIGATORS

- The primary efficacy end points were also evaluated and analyzed for the principal investigators for each site. Using similar methodology as for the blinded read data, equivalency between OptiMARK™ and Magnevist® was established. As anticipated, (due to the fact that the principal investigators were not blinded to the patient's history and other pertinent information) there was 91% in Absolute Agreement.

SAFETY SUMMARY:

Refer to the overall safety review section for detailed comments.

General Comments/Concerns

A. **Medical History**:

1. History of Allergy to Iodine Contrast

- Total with history of allergy to iodine/other agents: 10 (10/201 = 5%)
  OptiMARK™ group: 6 (6/133 = 4.5%)
  Magnevist® group: 4 (4/68 = 5.9%)
- Two of patients with the above history who received OptiMARK™ and two of patients who received Magnevist® developed adverse events to the gadolinium complex.

  Patient K-009 reported nausea and chills to OptiMARK™, and anaphylaxis to iodine
  Patient K-024 reported rash to OptiMARK™, and rash and swelling to iodine
  Patient K-011 reported rhinitis to Magnevist®, and nausea, vomiting and retching to iodine Patient A-041 reported taste perversion and asthenia to Magnevist®, and swelling/itching to iodine (Vol. 2.46, pp. 12.0040-12.0041; Vol. 2.53, Appendix 16.2.4-6, pp. 12.2385-2394)
- 4/201 (~1.99%) patients had a history of allergy to iodine contrast (10/201, 5%) also experienced adverse events when exposed to a gadolinium compound. The significance (4/10, 40%) of this at this time is not clear and may call for a larger study. However, at this time, appropriate instructions in the label should be provided to reflect this concern (such as, greater caution should be exercised in patients with known history of allergy to iodine agents...). Similar observations have been made in other trials/studies of this application. See comments in the overall safety section.

2. Concomitant medications:

Sponsor's tabie 11.2-3 (Vol. 2.46 p12.0043) and Appendix 16.2.4-7 (Vol. 2.53, pp. 12.2395-12.2413) lists the summary and the details of concomitant medications.

- ~28 (~13.9%) patients (out of 201, includes both groups) received either steroids or antihistamines (for various reasons) amongst other medications during the study period (24 hours prior through 48-72 hours post). Steroids, by various known and unknown mechanisms, can alter the various pathological sequelae associated many

disease processes (e.g. edema, enhancement, etc.). This can result in changes in the images.

- Both steroids and antihistamines can mask (or decrease or curb) some of the symptoms and signs of drug reactions. In fact, it is a well known and an accepted practice in clinical medicine to administer these drugs to treat allergic reactions to drugs. The observed adverse reactions in this study may therefore not reflect the true incidence or severity of the event/s. These projected values are probably lesser (in number and severity) than what might have been the actual occurrence. See overall safety section for additional comments.

3. Exclusion criterion-hemoglobinopathies:

- No screening or lab tests were performed to rule out hemoglobinopathies other than medical history. Many of the hemoglobinopaties may be asymptomatic and clinically silent and therefore appropriate screening lab tests should have been incorporated since this was an exclusion criterion.

B. **Assessments of safety**:

Safety assessments and data were collected at various time points as mentioned below. By large, the Sponsor chosen parameters and timings for labs and vital signs are acceptable (except that there was no monitoring during dosing or imaging). EKG frequency, timings and the parameters are all inadequate and clinically meaningless. See below and overall safety review section for further comments.

1. Physical Examination:

- Physical examination changes-clinically significant with "medical relevance"- was not further elaborated by the Sponsor. It would have been important at least to provide examples since "medical relevance" may be subjective (to the evaluating individual) and therefore interpretable differently resulting in variations in observation, documentation and care. The patient population studied consisted of complicated cases (sick with significant findings) with a multitude of problems. It is only ethical, fair, and appropriate to have the appropriately trained person with the appropriate background to make such comments and determinations. Given the 'subjectivity' of this issue, the reviewer has deferred to make additional comments.

2. Vital signs:
Vital signs monitoring do not include temperature. There is no monitoring while on the scanner or during dosing.

3. Labs:
   a. Serum bicarbonate was not included in the measured parameters.
   b. Urinalysis does not indicate if centrifuged or uncentrtifuged samples were analyzed.

c. The presence of urobilinogen (positive) in urine may be normal in normal people, but the Sponsor considers a positive result as extreme.
d. The Sponsor needs to differentiate between males and females when considering >10/HPF WBC or >100/HPF as extremes because these values may be a considered normal in some females, and values less than these are abnormal in males.

4. EKG:

a) As indicated in the overview of safety, the qualifications and background of the EKG readers (for the other trials) is being verified. The Sponsor indicated that the majority of the EKGs were read by the site principal investigator/s. It was noted in this pivotal phase three study (#488) and others, that all the site principal investigators had radiology and or neurology training/background.
b) The tracings are not included in the application.
c) Additionally, the information whether the tracings were read manually or were automated readings is in the process of being furnished by the Sponsor to the agency (upon request from the agency). Its importance rests with the clinical significance that QT changes/intervals are not measured accurately in the phase of associated hypocalcemia and hypokalemia by automated readings and therefore cannot have clinical meaningfulness.
d) The Sponsor chosen parameters (see above) are too wide.
e) Interpretations were portrayed without actual baseline values.
f) ~60/201=~30% (includes OptiMARK™ and Magnevist®) patients' EKG records were incomplete (majority without QT measurements). There were 2 patients in the OptiMARK™ group with EKG changes that were reported to have changes from baseline but the Sponsor felt that these were not clinically significant. These included QT prologation and T wave inversion.
g) Besides the baseline EKG, the only other evaluation occurred at 24 hours post-dosing, which is clinically meaningless (by itself) based on the PK of OptiMARK™.

5. Dosing:

Sponsor does not state whether OptiMARK™ and Magnevist® are physically similar (color, viscosity, etc.) so that person injecting drug and assessing patient remains blinded to its identity.

6. Time events:

Safety data was collected at various time points as shown in the table below:

SAFETY: 433-PHASE 3-PIVOTAL: TIME EVENTS: OptiMARK™ NDA # 20937								
Time	Med Hx	Meds	Physical	Vitals [1]	EKG [2]	Labs [3]	AE	Tolerability
within 14 days pre	X							
within 24 hrs pre		X	X		X	X		
immed pre		X		X				
MRI - non-contrast		X						
DOSE		X					X	
MRI - post-contrast		X						
immed post image		X		X			X	X
2 hrs post		X		X		X	X	
24 hrs post		X	X	X	X	X	X	
48 hrs post (phone)		X					X	
3 days post		X		X		X	X	

1 includes systolic and diastolic blood pressure, pulse, and respiratory rate (no temperature)
2 12-lead EKG
3 includes hematology, chemistry (note: serum Ca^{+2} measured using atomic absorption assay as Sponsor states that OptiMARK™ interferes with colorimetric assay), serum Gd, and urinalysis; all labs in USA and Canada shipped to NDA[redacted]
all labs in Europe shipped to[redacted]
AE = adverse event monitoring for two hours post-dose, then at discrete times as indicated
Tolerability: patient will be asked about sensations of heat, cold, or pain at injection site and whether it was mild, moderate, or severe
– *Reviewers' Note: the submitted CRF's pertaining to: enrollment [p.12.0890, Vol 2.48]; demographic record [p.12.0891, Vol 2.48]; medical and surgical history [p.12.0892, Vol. 2.48]; concomitant medications [p. 12.0893, Vol. 2.48]; physical examination-baseline [p.12.0894, Vol. 2.48], 24 hours post-contrast [p.12.0908, Vol 2.48]; vital signs [p.12.0895, Vol. 2.48]; EKG-baseline[p. 12.0896, Vol. 2.48], 24 hours post-contrast [p.12.0909, Vol 2.48; clinical labs-baseline [p. 12.0897, Vol. 2.48], 2 hours post-contrast [p.1.0900, Vol 2.48], 24 hours post-contrast [p.12.0910, Vol 2.48], 3 days post-contrast [p.12.0911, Vol 2.48]; drug administration record [p.12.0898, Vol 2.48]; adverse events [p. 12.0912, Vol. 2.48]; and tolerability assessment [p. 12.0898, Vol. 2.48] have been noted.*

7. Other comments/concerns:

- OptiMARK™ and Magnevist® were well tolerated in this comparative study at 0.1mmol/kg dose.
- There were no statistically significant differences between the treatment groups with respect to adverse event frequency; but the patients in the Magnevist® group experienced more severe adverse events (see below).
- There were no serious or unexpected changes in labs, vitals, EKGs, or physical examinations.
- There were no deaths, serious adverse events, dropouts due to adverse events or post-dosing dropouts.
- 1 patient in the OptiMARK™ and 3 patients in the Magnevist® group experienced severe adverse events (see comments in other studies and in the overall safety review section regarding the issues on the terminology of serious and severe adverse events and the implementation of these in the application) in this study. Patient 488-F-015 who received OptiMARK™ developed an UTI, which was considered to be the severe adverse event.
- There were 24 patients who required medical treatment due to adverse events (14 in the OptiMARK™ group and 10 in the Magnevist® group). Only one of these was attributed to the study drug in the OptiMARK™ group (ecchymosis and edema).
- Statistically small but clinically insignificant changes in vital signs from baseline were noted in both groups.

- The table below summarizes the demography, disposition, AE and dosing information for both the drugs:

SAFETY:488:PHASE 3 –PIVOTAL: OptiMARK™ NDA # 20937 PATIENT ENROLLMENT/DISPOSITION/AE/DOSE			
		Treatment Group 0.1mmol/kg	
		OptiMARK™	Magnevist®
Number of patients			
Entered study		136	70
Exposed to drug		133	68
Completed study		133	68
Evaluated for Safety		133	68
Evaluated for Efficacy		133	68
Dropped pre-dosing		3	2
Dropped postdosing (non-AE)		0	0
Serious AE		0	0
Dropped for adverse event		0	0
Demography			
Age (Years)	N	133	68
	mean	44.9	45.2
	range	18-80	20-73
Drug volume			
Total volume (ml)	N	133	68
	mean	15.1	15.9
	range	9.1-23.4	9.5-22.9

- The table below summarizes some of the safety findings:

SAFETY: STUDY 488: PHASE 3:OPEN-LABEL:OptiMARK™ NDA # 20937			
ADVERSE EVENTS:			
OptiMARK™		Magnevist®	
PATEINTS (N) EXPOSED = 133 DEATHS (N) = 0 PATIENT (N) WITH SERIOUS ADVERSE EVENTS = 0 DROPPED (N) DUE TO ADVERSE EVENTS = 0 POST-DOSING NON-AE WITHDRAWAL (N)= 0 PATIENTS (N) WITH ADVERSE EVENTS= 38 (28.6%) TOTAL (N) ADVERSE EVENTS = 81 PATIENTS WITH SEVERE ADVERSE EVENTS= 1		PATEINTS (N) EXPOSED = 68 DEATHS (N) = 0 PATIENT (N) WITH SERIOUS ADVERSE EVENTS = 0 DROPPED (N) DUE TO ADVERSE EVENTS = 0 POST-DOSING NON-AE WITHDRAWAL = 0 PATIENTS (N) WITH ADVERSE EVENTS= 19 (27.9%) TOTAL (N) ADVERSE EVENTS = 35 PATIENTS WITH SEVERE ADVERSE EVENTS = 3	
	Dose (0.1mmol/kg) Treatment Group		
	OptiMARK™	Magnevist®	
N (RECEIVED DOSE)	133	68	Comments for OptiMARK™
N (PATIENTS WITH AE)	38 (28.6%)	19 (27.9)	• Most frequent: headaches (9.8%); taste perversion (3%)
N (ADVERSE EVENTS)	81	35	• Onset within 2 hours of dosing, lasted ~ 2.05 (± 4.31)
INTENSITY OF AE MILD (N) MODERATE (N)	80 (98.8%)	32 (91.4%)	• Others : nausea, dizziness
SEVERE (N)	1	3	
EKG & PE			
No clinically significant changes between the two groups			
VITAL SIGNS			
Statistically small but clinically insignficant changes in both groups			
LABORATORY EVENTS			
	Statistically significant		Clinically significant
Parameters affected	Phosphorus >80% of reference range in 5% of patients Others-very small		no
Dose related	?		?
Time related	?		?
Resolution time	?		?

FINAL COMMENTS:

1. This was a phase three pivotal study for the CNS indication and the main objectives were to establish equivalency to another gadolinium agent Magnevist® with respect to efficacy and safety. The trial design and the objectives are similar to the study 525, which is the other pivotal phase 3 study for the CNS indication. The phase 2 studies' (464 and 465) efficacy results were not significant and Sponsor has stated that there were no statistically significant differences between the pre and the post contrast images on several of the primary efficacy end points. The phase 3 open label studies were terminated prior to completion and therefore these are being submitted for safety review only. Therefore, the CNS indication for OptiMARK™ for efficacy rests in the outcome of studies 488 and 525.
2. Efficacy comments:
   A. Detailed comments have been made in the efficacy summary.
   B. The combination of qualifying MRI and the large number of selective patients (post-treatment) has led to a bias and patient enrichment. This has clearly affected all the primary efficacy end points, and the data is clearly driven by these patients. There were no patients in whom 'suspicion' of CNS pathology existed at the time the study started, because all were known to have some pathology (historically and radiologically) as enrollment occurred only after this qualifying MRI.
   C. The post-treatment patients made all the primary efficacy end points easily accomplishable, and this clinical concern has been complemented with statistical confirmation. Despite these enrichments, the data shows that in neither groups the post contrast scores were better than the 'no change + decrease' groups together. This is probably, again largely due to two reasons: a) the even distribution of the post-treatment groups between the two groups and, b) easier recognition of post-op changes on non-contrast images. From this aspect, both OptiMARK™ and Magnevist® did poorly. The Sponsor is not claiming superiority over the comparator.
   D. Finally, if one ignored the above concerns of bias and enrichment of patient population, the Sponsor has proven equivalency (a very 'anemic' score for both the groups) only when an equivalency interval of –1.5 to +1.5 is chosen. If no such interval is chosen or if a narrower one is chosen, the FDA statistician has shown that there would be no equivalence on large component of the data.
   E. Based on these clinical, scientific, statistical, and ethical grounds, the Sponsor has not proven equivalence.
   F. If the equivalence interval is acceptable (then why call it an equivalence trial?), equivalence is established (barely) only on a statistical basis. It is beyond the reviewer's scope to comment further.
3. Safety comments:
   A. There were minor deficiencies in monitoring for safety.
   B. There were no deaths, or serious adverse events, or discontinuations due to OptiMARK™.
   C. The association between history of allergy to iodinated agents or other contrast agents an developing an adverse reaction to OptiMARK™ has been noted here as

in some of the other clinical trials in this program. Labeling should reflect this concern.

D. There were patients on steroids and or antihistamines as noted in several of the patients in this program. The potential masking/curbing of adverse reactions (number and severity) in these patients due to these medications is a very strong possibility. Therefore, the projected adverse event profile is probably more 'benign' appearing than what it might be if these patients were not on these medications. Labeling should indicate this concern and or the fact that several of these patients were on steroids and or antihistamines.

E. The overall adverse event/reaction profile appears similar to Magnevist® with no significant differences. Equivalence is probably established form this point of view.

F. Perhaps the most concerning safety issue is the inadequacies of the EKG as noted across these trials and discussed extensively in the overall safety section.

G. Refer to overall efficacy and safety summary for further comments.

END OF REPORT 488

NDA # 20 937 **OptiMARK™** **Report # 525 /Phase 3 (Pivotal)**
IND# **Protocol # 1177-95-03.03**

- Volumes Reviewed: NDA # 20 937 Volumes # 2.1 - 2.168 and additional information from Sponsor with letter dates 24 April 1998 (Volumes # M7.1 - M7.3), 11 September 1998 (BM), September 23, 1998 (letter correspondence to CSO)
- Primary Volumes for this study: 2.57-2.66

This study was amended one day prior to study end date-to include a CRF page to capture data validation of imaging parameter data (see comments made in the Regulatory Section regarding amendments). These details and other revisions that were made to this study and to the Liver protocols were provided by the Sponsor (upon request by the FDA) on May 14 1998
Study initiated (date first patient received study drug) - 19 June 1996 (Protocol proposed Oct 95, Amendment #1 made in April 1996, Amendment #2 made in November 1996, Amendment #3 Made on May 30 1997-all similar to study 488)
Study ended (date last patient received study drug) – March 17, 1997

This study is similar to study #488. Refer to this section of the review for detailed comments.

TITLE:

"A Multicenter, Randomized, Double-Blind Study to Evaluate the Safety, Tolerability, and Efficacy of OptiMARK™ (Gadoversetamide Injection) Compared to Magnevist® (Gadopentate Dimeglumine Injection) in Patients with Central Nervous System Pathology"

ETHICS:

- Patient Information and Consent: Appendix 16.1.3-2 (Vol. 2.59, pp. 13.0811-13.0941) provides several sample consent forms.

~ Reviewer's comment: Some of the statement/s in the benefits section (on a few of these consent forms) has 'therapeutic implications' that can be interpreted as attributable to the study drug (OptiMARK™ is an investigational diagnostic agent with no direct therapeutic benefits). However, the information stemming form the qualifying MRI, history, physical examination, labs, etc. may be helpful in the treatment and management of the patient.

STUDY DESIGN, OBJECTIVES, AND PLAN:

- This was a multi center, parallel group, randomized, single dose, double blind comparative study (refer to the Study Review Section of study #488) in patients with known or highly suspected CNS pathology the aims of which is stated below.
- The trial aims to compare OptiMARK™ and Magnevist® with reference to safety, tolerability, and efficacy -- [p. 13.0527, Vol. 2.59]

"To show that OptiMARK™ is equivalent to Magnevist® in patients undergoing a MRI of the central nervous system."
"To compare the safety profile of 0.1 mmol/kg OptiMARK™ to 0.1 mmol/kg Magnevist®. Safety will be assessed in terms of clinical signs and symptoms including physical examinations, monitoring of vital signs, electrocardiograms, incidence and nature of adverse events, and clinical laboratory measurements."
"To compare the tolerability profile of OptiMARK™ to Magnevist® by evaluating the incidence of heat, cold, and pain at the injection site during and immediately following intravenous administration."

DRUGS, ADMINISTRATION, DOSES AND COMPLIANCE:

- OptiMARK™ 0.1 mmol/kg IV-supplied as a 20mL single-dose vial (20mL fill) in a concentration of 0.5mmol/mL OR Magnevist® 0.1 mmol/kg IV- supplied as a 20mL single-dose vial (20mL fill) in a concentration of 0.5mmol/mL.
- As proposed, the drugs were hand-administerd as a bolus injection (approximately 1-2mL per second) followed by a normal saline flush (minimum of 5mL). Patient and Principal investigator were blinded as to the agent used. The dose was prepared by 'third party blind' and the drug was administered by a qualified site personnel other than the third party blind (the third party blind did not have contact with the enrolled patients; p13.0544, Vol. 2.59).
- In a majority of the patients, the drug was administered via the antecubital vein (Appendix 16.2.5-1, Vol. 2.63).
- The maximum volume that was administered was 25.4 mL in patient F-009 in the L antecubital vein (Appendix 16.2.5-1, Vol. 2.63, p 13.2159). There were two other patients who also exceeded the stated volume that were exposed to the study drug. See below for comments on protocol violations.
- The table below summarizes some of the dosing information.

Dosing Information:Report # 525 /Phase 3 (Pivotal) Protocol # 1177-95-03.03				
	Patients N (%)	Mean Volume (mL)	Mean Duration of injection (secs)	Mean rate of injection (mL/sec)
OptiMARK™	129 (66.4%)	15.6	15.7	1.38
Magnevist®	65 (33.5%)	15.07	17.6	1.25
~ *Comments (OptiMARK™)*	*Total exposed- 194*	*Maximum volume-25.4ml (variation/violation)*	*Minimum-4.0*	*Maximum-3.36*

- The Principal Investigator and the medical professional that prepared the syringes and performed the injections were responsible for compliance. Each site maintained a drug accountability log. The listing of injection dates and times, including volume of drug administered and the sites of injection has been provided (Appendix 16.2.5-1, Vol. 2.63).
- There were 'calculation errors' made in the dosing of OptiMARK™ on two patients. One patient received the study drug at a dose of 0.125mmol/kg (more than the recommended dose of 0.1mmol/kg) and the other received a dose of 0.067 mmol/kg (Vol. 2.57, p 13.0043).

Appendix C [pp.13.0571-13.0579, Vol. 2.59] provides a dose schedule based on body weight. The maximum weight listed is 117.9 kgs (260 pounds) which gives a volume of 23.6mL (0.1 mmol/kg). In this study the following three patients (all from sites within the US) received a dose volume greater than the maximum stated/planned maximum volume (for the given body weight) of 23.6mL, thereby constituting a protocol violation/variation/non-compliance (exceeding volume):

a) B-006-27-M received 23.8mL (R forearm, body weight 119 kgs)
b) F-009-32-F received 25.4mL (L antecubital, body weight 127 kgs)- this was also the largest volume administered during this study
c) J-002-34-M received 25.0mL (R antecubital, body weight 126.8 kgs)

Note that these volumes however, are appropriate for the respective patients' given body weight in kilograms.

Treatment compliance was not maintained (and therefore constituting study variation/violation/non-compliance) in two patients, both of who received OptiMARK™: patient E-011 exceeded the recommended dose and patient J-011 received a dose of 0.067mmol/kg (lesser than the recommended dose). The Sponsor has indicated that these were due to "Calculation Errors".

STUDY PATIENTS-DISPOSITION:

Figure: Patient Disposition: 525 /Phase 3 (Pivotal)

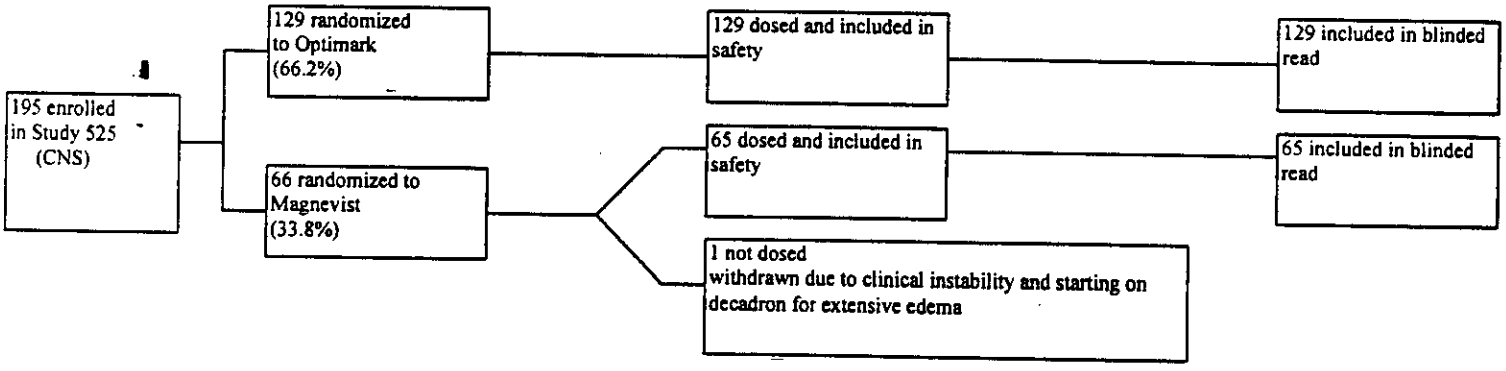

Table: Patient Disposition: 525 /Phase 3 (Pivotal)

Total enrolled:	195
Total randomized:	195 (not randomized = 2)
OptiMARK™:	129 (66.2%)
Magnevist®:	66 (33.8%)
Discontinued before dosing:	1 (0 OptiMARK™, 1 Magnevist®)
Discontinued after dosing:	0
Known Baseline Diagnoses:	192 (2 patients in the OptiMARK™ group were missing referral diagnosis information)
Safety analysis/Dosed patients:	194
OptiMARK™:	129 (66.5%)
Magnevist®:	65 (33.5%)
Efficacy analysis:	194
OptiMARK™:	129 (66.5%)
Magnevist®:	65 (33.5%)
Protocol Deviations:	14
OptiMARK™:	9
Magnevist®:	5

DEMOGRAPHICS AND CHARACTERISTICS:

1. All patients except for one were adults (>18 years).

2. The table below summarizes some of the characteristics.

Demographics & Characteristics: Report # 525 /Phase 3 (Pivotal) Protocol # 1177-95-03.03			
Parameters	OptiMARK™ N=129	Magnevist® N=66	*~ Comments*
Number exposed	129	65	*Enrolled (129 and 66)*
MR Exam N (%)			*A ratio of 4:1 was proposed- brain:spine (?rationale)*
Brain	99 (76.7)	52 (80)	
Spine	30 (23.3)	14 (21.5)	
Age (years)			*Mean age for both groups is ~44 years. 16 (12.4%) were >65 years in the study drug group*
Mean ± SD	45.1±15.3	44.3±14.9	
Range	12-78	23-77	
Sex N (%)			*A ~ 1:1 ratio is noted*
Male	72 (56)	30 (45)	
Female	57 (44)	36 (55)	
Race N (%)			*Majority is white*
White	112 (87)	57 (86)	
Black	10 (8)	5 (8)	
Asian	2 (2)	0 (0)	
Weight (kg)			*Dosage and volume is weight based*
Mean ± SD	77.7±15.4	74.8±15.2	
Range	44-127	53-125	
Height (cm)			
Mean ± SD	172.1±10.4	169.8±10.3	
Range	132-196	152-191	

MEASUREMENTS OF COMPLIANCE-SCANNER:

Refer to the study review section for additional details on imaging parameters. Appendix 16.2.5-9, Vol. 2.63, lists additional information on scanners.

- The majority of patients (78.4%) were scanned on the 1.5 Tesla MRI scanner.

EFFICACY RESULTS:

Efficacy analysis: 194
OptiMARK™: 129 (66.5%)
Magnevist®: 65 (33.5%)

The chart below summarizes patient disposition information related to efficacy.

Total enrolled:	195
Total randomized:	195 (not randomized = 2)
OptiMARK™:	129 (66.2%)
Magnevist®:	66 (33.8%)
Discontinued before dosing:	1 (0 OptiMARK™, 1 Magnevist®)
Discontinued after dosing:	0
Known Baseline Diagnoses:	192 (2 patients in the OptiMARK™ group were missing referral diagnosis information)
Safety analysis/Dosed patients:	194
OptiMARK™:	129 (66.5%)
Magnevist®:	65 (33.5%)
Efficacy analysis:	194
OptiMARK™:	129 (66.5%)
Magnevist®:	65 (33.5%)

GENERAL COMMENTS/CONCERNS:

Enrollment:

A. 12 sites were selected (of which two were outside the US); patients were enrolled in all the 12 sites. There is no homogeneity (in numbers) in the distribution between the sites.
B. The basis for choosing the ratio 2:1 between brain and spine is arbitrary.

C. Baseline/Referral Diagnosis and Baseline Qualifying Radiologic Examination

1. It is noted in the medical and surgical history section, (Vol. 2.63, Appendix 16.2.4-5) and in the qualifying radiologic examination section, (Vol. 2.63, Appendix 16.2.4-4) that, ~32 patients in the OptiMARK™ group **(32/129, ~ =24.8%)** and ~16 patients in the Magnevist® group **(16/65, ~ =24.6%)** had a therapeutic **(total ~ 48/194 = ~24.7%)** intervention/s (surgery or biopsy or radiation therapy or chemotherapy or a combination).
2. These numbers are not as high as they were noted in study #488 (the other pivotal CNS study), but still comprises of ~25% (48/194) of the study group. In study #488, ~ 83/201 (=~ 41.29%) patients had a similar history, and clearly made a significant statistical difference in driving the overall efficacy findings. Combined, it is noted in the studies (#488 and #525) that **~131/395 (83/201 + 48/194)=~33.16%** of the enrolled patients had a similar treatment history.
3. This constitutes an over representation of samples for these combined pivotal phase three studies. The reviewer will defer with further analysis of these post-treatment and non-post-treatment cases for this study (as performed and documented in the study #488), at this time. If further analysis is deemed appropriate, in consultation with the statistician, these will be provided. The conglomeration of these post-treatment cases has been a significant driving force to cause a statistical significance in the overall group. Refer to Statistical review for additional comments.

Protocol violations:

Parameters that would affect safety and efficacy data were not obtained at some of the stated time points due to: – patient failure to follow up, incomplete set of images, 6 lead v/s 12 lead EKG, etc., on 14 subjects. These were the protocol deviations/violations/non-compliance) constituting an incomplete database in those sections as applicable (Appendix 16.2.6-14, pp. 13.2460-67).

BLINDED READER METHODOLOGY

See report #488

PRIMARY EFFICACY ANALYSIS FOR BLINDED READERS: INTENT-TO-TREAT

The CNS Blinded Reading Methodology Report [pp.13.0745-54, Vol. 2.59] is part of protocol no. 1177-95-03.02 (rest of this review is on protocol no 1177-95-03-03). In original Protocol, there were 2 readers who reviewed all patient sets; First Amendment increased readers to 3; in the Second Amendment each of the 3 readers, review only 1/3rd of images. All these are similar and identical to the study #488 (the other CNS pivotal phase 3 study)

- Refer to the review section (# 488) for additional comments.

PRIMARY EFFICACY ENDPOINTS: [p. 13.0551, Vol. 2.59]

The three primary efficacy endpoints were:

1. "the score for the degree of ***confidence in the diagnosis***(es) indicated pre-contrast plus post-contrast compared to pre-contrast;"
2. "the image score for the ***level of conspicuity*** for all lesions visualized pre-contrast plus post-contrast compared to pre-contrast; and"
3. "the score for the ability to ***delineate lesion borders*** from parenchyma/structures pre-contrast plus post-contrast compared to pre-contrast."

- Details pertaining to the image acquisition, capture, display, blinded reader case report forms randomization, etc., have been reviewed and commented in the study #488 review section.

1. CONFIDENCE IN DIAGNOSIS

Note: The reviewer will use the word 'pre' *to refer to the* pre-contrast images *and* 'pair' *to refer to the* pre- plus post-contrast images *for further discussions.*

- Refer to the study #488 review section for additional comments and to the statistician's review for detailed comments.
- The blinded readers were given to use an 'ordinal (rank order)' 10 point scale (1 to 10, with 10 being the highest confidence level) to score their level of confidence in the diagnosis for each set of images (pre and pair).
  A score of 1 was assigned to any image that was non-diagnostic.
  Analysis of variance (ANOVA) was used to assess the treatment effect (OptiMARK™ and Magnevist®, the blinded reader effect, and treatment-by-reader interaction effect).
- Appendix 16.2.6-5 (Vol.2.64, pp. 13.2335-13.2352) contains individual patient listings for this primary efficacy end point, and table 14.2.1-1 (Vol. 2.57, p. 13.0090) lists the proportion of patients who had an increase, decrease, or no change from the pre to the pair for this end point.
- The tables below project the diagnostic confidence score (pre and pair) for both OptiMARK™ and Magnevist®.
- The score on the diagonal represents the same/no change, the score below the diagonal represents the decrease and the score above the diagonal represents the increase.

Note: In looking at the frequency tables below, please note:

1. *number of subjects who fall on the diagonal - i.e., the pre and pair scores are the same.*
2. *number of subjects who fall above the diagonal - i.e., the pair is doing better than the pre.*
3. *number of subjects who fall below the diagonal - i.e., the pre is doing better than the pair.*

Primary Efficacy Analysis: Report # 525 /Phase 3 (Pivotal) Protocol # 1177-95-03.03

Cross Tabulation of Diagnostic Confidence Score Recorded* by Blinded Readers on "Pre" and "Pair" - OptiMARK™ (n = 129)

Diagnostic Confidence Score - "Pre"	Diagnostic Confidence Score - "Pair" 1	2	3	4	5	6	7	8	9	10
1	3						1		5	
2										
3								1		
4									1	
5	3				3	1	2		3	1
6				1			1	2		
7					1		1	2	6	5
8					1		3	4	12	11
9	1							1	13	10
10	1					1	1	7	4	16

*Empty cells are cells where the frequency is zero. Table prepared by FDA Statistician.

Primary Efficacy Analysis: Report # 525/Phase 3 (Pivotal) Protocol # 1177-95-03.03

Cross Tabulation of Diagnostic Confidence Score Recorded* by Blinded Readers on "Pre" and "Pair" - Magnevist® (n=65)

Diagnostic Confidence Score - "Pre"	Diagnostic Confidence Score - "Pair" 1	2	3	4	5	6	7	8	9	10
1	1				1					
2										
3										
4									2	
5					1		1	1	1	
6							2	1	2	
7							1	2	2	3
8							1	6	4	10
9				1	1	1		1	3	5
10								2	1	8

*Empty cells are cells where the frequency is zero. Table prepared by FDA Statistician.

- The table below summarizes the information from the frequency tables.

Primary Efficacy Analysis
Blinded Readers: Confidence in Diagnosis : Report # 525 /Phase 3 (Pivotal)

	Decrease	No change	Increase	Total (194)
OptiMARK™				
N	25	40	64	129
%	19.38	31.01	49.61	
Magnevist®				
N	8	20	37	65
%	12.31	30.77	56.92	

2. *LEVEL OF CONSPICUITY*

Note: The reviewer will use the word 'pre' *to refer to the* pre-contrast images *and* 'pair' *to refer to the* pre- plus post-contrast images *for further discussions.*

- Refer to the study review section for additional comments and to the statistician's review for detailed comments.
- The blinded readers were given to use an 'ordinal (rank order)' 10 point scale (1 to 10, with 10 being the highest confidence level) to score their level of confidence in the diagnosis for each set of images (pre and pair).
  A score of 1 was assigned to any image that was non-diagnostic.
  Analysis of variance (ANOVA) was used to assess the treatment effect (OptiMARK™ and Magnevist®, the blinded reader effect, and treatment-by-reader interaction effect).
- Appendix 16.2.6-4 (Vol.2.64, pp. 13.2323-12.2334) contains individual patient listings for this primary efficacy end point, and table 14.2.1-2 (Vol. 2.57, p. 13.0091) lists the proportion of patients who had an increase, decrease, or no change from the pre to the pair for this end point.
- The tables below project the conspicuity score (pre and pair) for both OptiMARK™ and Magnevist®.
- The score on the diagonal represents the same/no change, the score below the diagonal represents the decrease and the score above the diagonal represents the increase.

Note: In looking at the frequency tables below, please note:

1. *number of subjects who fall on the diagonal - i.e., the pre and pair scores are the same.*
2. *number of subjects who fall above the diagonal - i.e., the pair is doing better than the pre.*
3. *number of subjects who fall below the diagonal - i.e., the pre is doing better than the pair.*

Primary Efficacy Analysis: Report # 525 /Phase 3 (Pivotal) Protocol # 1177-95-03.03

Cross Tabulation of Conspicuity Score Recorded* by Blinded Readers on "Pre" and "Pair" - OptiMARK™ (n = 129)

Conspicuity Score - "Pre"	Conspicuity Score - "Pair" 1	2	3	4	5	6	7	8	9	10
1	28					1		1	3	4
2										1
3								1		1
4								1		
5						1		1		1
6								1	2	
7	2	1			2		1	1	6	5
8	2				1	1	2	4	9	7
9	1						1	2	4	6
10	2				1			2	4	15

*Empty cells are cells where the frequency is zero. Table prepared by FDA Statistician.

Primary Efficacy Analysis: Report # 525 /Phase 3 (Pivotal) Protocol # 1177-95-03.03

Cross Tabulation of Conspicuity Score Recorded* by Blinded Readers on "Pre" and "Pair" - Magnevist® (n = 65)

Conspicuity Score - "Pre"	Conspicuity Score - "Pair" 1	2	3	4	5	6	7	8	9	10
1	18							1	1	2
2		1								1
3										
4										2
5	1								1	
6									2	1
7									3	2
8						1		1	4	3
9	2						2	1	2	5
10	1								1	6

*Empty cells are cells where the frequency is zero. Table prepared by FDA Statistician.

- The table below summarizes the information from the frequency tables.

Primary Efficacy Analysis
Blinded Readers: Level of Conspicuity: Report # 525 /Phase 3 (Pivotal)

		Decrease	No change	Increase	Total (194)
OptiMARK™	N	24	52	53	129
	%	18.60	40.31	41.09	
Magnevist®	N	9	27	29	65
	%	13.85	41.54	44.62	

3. *BORDER DELINEATION*

Note: The reviewer will use the word 'pre' *to refer to the* pre-contrast images *and* 'pair' *to refer to the* pre- plus post-contrast images *for further discussions.*

- Refer to the study review section for additional comments and to the statistician's review for detailed comments.
- The blinded readers were given to use an 'ordinal (rank order)' 10 point scale (1 to 10, with 10 being the highest confidence level) to score their level of confidence in the diagnosis for each set of images (pre and pair).
  A score of 1 was assigned to any image that was non-diagnostic.
  Analysis of variance (ANOVA) was used to assess the treatment effect (OptiMARK™ and Magnevist®, the blinded reader effect, and treatment-by-reader interaction effect).
- Appendix 16.2.6-4 (Vol.2.64, pp. 13.2323-13.2334) contains individual patient listings for this primary efficacy end point, and table 14.2.1-3 (Vol. 2.57, p. 13.0092) lists the proportion of patients who had an increase, decrease, or no change from the pre to the pair for this end point.
- The tables below project the border delineation score (pre and pair) for both OptiMARK™ and Magnevist®.
- The score on the diagonal represents the same/no change, the score below the diagonal represents the decrease and the score above the diagonal represents the increase.

Note: In looking at the frequency tables below, please note:

1. *number of subjects who fall on the diagonal - i.e., the pre and pair scores are the same.*
2. *number of subjects who fall above the diagonal - i.e., the pair is doing better than the pre.*
3. *number of subjects who fall below the diagonal - i.e., the pre is doing better than the pair.*

Primary Efficacy Analysis: Report # 525 /Phase 3 (Pivotal) Protocol # 1177-95-03.03

Cross Tabulation of Border Delineation Score Recorded* by Blinded Readers on "Pre" and "Pair" - OptiMARK™ (n = 129)

Border Delineation Score - "Pre"	Border Delineation Score - "Pair" 1	2	3	4	5	6	7	8	9	10
1	28					1		1	3	4
2										2
3								1	2	
4							1			
5		1			2	1		1	1	4
6					1	1			4	2
7	2	1			2		1	2	5	3
8	1				1		2	7	5	6
9	1						1		4	4
10	3							3	6	8

*Empty cells are cells where the frequency is zero. Table prepared by FDA Statistician.

Primary Efficacy Analysis: Report # 525 /Phase 3 (Pivotal) Protocol # 1177-95-03.03

Cross Tabulation of Border Delineation Score Recorded* by Blinded Readers on "Pre" and "Pair" - Magnevist® (n =65)

Border Delineation Score - "Pre"	Border Delineation Score - "Pair" 1	2	3	4	5	6	7	8	9	10
1	18									4
2		1							1	2
3										2
4										
5									2	
6	1				1			1	4	1
7						1			2	1
8	1						3		1	4
9							2			3
10	2									7

*Empty cells are cells where the frequency is zero. Table prepared by FDA Statistician.

- The table below summarizes the information from the frequency tables.

Primary Efficacy Analysis
Blinded Readers: Border Delineation: Report # 525 /Phase 3 (Pivotal)

		Decrease	No change	Increase	Total (194)
OptiMARK™	N	25	51	53	129
	%	19.38	39.53	41.09	
Magnevist®	N	7	29	29	68
	%	10.77	44.62	44.62	

SECONDARY EFFICACY ANALYSIS FOR BLINDED READERS: INTENT-TO-TREAT

- **Secondary Endpoints:** [p. 13.0551 - 13.0552, Vol. 2.59]

The secondary end points were:

a) "the proportion of patients for whom the final clinical diagnosis agreed with the diagnosis from the pre-contrast plus post-contrast images (i.e., sensitivity and specificity);"
b) "the image score for the ability to distinguish edematous tissue from pathology pre-contrast plus post-contrast compared to pre-contrast;"
c) "the score for the degree of confidence that the total number of lesion(s) exist pre-contrast plus post-contrast compared to pre-contrast;"
d) "the number of lesions per patient pre-contrast plus post-contrast compared to pre-contrast;"
e) "the proportion of patients for whom the next anticipated management choice suggested for the patient was altered pre-contrast plus post-contrast compared to pre-contrast; and"
f) "the proportion of patients for whom the contrast agent impaired the ability to visualize lesion(s) or pathology."

- An additional independent reader compared the final clinical diagnosis -**(a)** and the number of lesions -**(b)** as determined/provided by the principal site investigator to the masked readers' diagnosis. This independent reader subsequently determined an agreement between the two- ***Agreement with Final Diagnosis***. These (a and c above) are the secondary end points that the Sponsor has pursued in the efficacy analysis.

- The table below (incorporated from the application) provides these results. Pseudo Sensitivity and Specificity results were also be derived by combining the Not Evaluable, No Agreement, and Partial Agreement into a Do Not Agree category (in the shaded area in the table) and the Basic Agreement and Absolute Agreement categories into an Agree category.

Secondary Efficacy Analysis: Report # 525/Phase 3 (Pivotal) Protocol # 1177-95-03.03
Table: Agreement with Final Diagnosis – Blinded Readers

Optimark	Not Evaluable	No Agreement	Partial Agreement	Basic Agreement	Absolute Agreement
	Pre-Contrast Diagnosis N(%)				
Disease	5 (4.5)	42 (37.5)	18 (16.1)	17 (15.2)	30 (26.8)
No Disease	1 (5.9)	5 (29.4)			11 (64.7)
	Pre- plus Post-Contrast Diagnosis N(%)				
Disease	3 (2.7)	42 (37.5)	22 (19.6)	17 (15.2)	28 (25.0)
No Disease	1 (5.9)	7 (41.2)			9 (52.9)
Magnevist	Pre-Contrast Diagnosis N(%)				
Disease	1 (1.9)	22 (40.7)	10 (18.5)	11 (20.4)	10 (18.5)
No Disease		6 (54.5)			5 (45.5)
	Pre- plus Post-Contrast Diagnosis N(%)				
Disease	1 (1.9)	22 (40.7)	12 (22.2)	8 (14.8)	11 (20.4)
No Disease		6 (54.5)			5 (45.5)

~ Table 11.4.1.5-3 (Vol. 2.57, p. 13.0052) provides the data on the Agreement with Final Diagnosis (see modified table above). Here again, although the Sponsor has demonstrated that the proportion of patients with disease that had agreement on the post-contrast diagnosis with the final diagnosis was similar for both OptiMARK™(40%) and Magnevist®(35%); the majority falls into the Do Not Agree category.

PRIMARY & SECONDARY EFFICACY ANALYSIS FOR PRINCIPAL INVESTIGATORS

- The primary efficacy end points were also evaluated and analyzed for the principal investigators for each site. Using similar methodology as for the blinded read data, equivalency between OptiMARK™ and Magnevist® was established. As anticipated, (due to the fact that the principal investigators were not blinded to the patient's history and other pertinent information) there was ~91% in Absolute Agreement.
- Additional comments are made in the study review section of study 488.

SAFETY SUMMARY:

GENERAL COMMENTS/CONCERNS:

- See report #488 for more details

Medical history:

Concomitant medications

1. Sponsor's table 11.2-3 (Vol. 2.57 p13.0043) and Appendix 16.2.4-7 (Vol. 2.63, pp.13.2122-12.2147) lists the summary and the details of concomitant medications.
2. ~40 (**~20.6%**) patients (out of 194, includes both groups) received either steroids or antihistamines (for various reasons) amongst other medications during the study

period (24 hours prior through 48-72 hours post) as concomitant medication/s. Steroids, by various known and unknown mechanisms, can alter the various pathological sequelae associated many disease processes (e.g. edema, enhancement, etc.). This can result in changes in the images.

3. Both steroids and antihistamines can mask (or decrease or curb) some of the symptoms and signs of drug reactions. In fact, it is a well known and an accepted practice in clinical medicine to administer these drugs to treat allergic reactions to drugs. The observed adverse reactions in this study may therefore not reflect the true incidence or severity of the event/s. These projected values are probably lesser (in number and severity) than what might have been the actual occurrence. See safety section for additional comments.

Dosing:

- Sponsor does not state whether OptiMARK™ and Magnevist® are physically similar (color, viscosity, etc.) so that person injecting drug and assessing patient remains blinded to its identity.

Regulatory concerns-protocol violation:

1. Appendix C [pp.13.0571-13.0579, Vol. 2.59] provides a dose schedule based on body weight. The maximum weight listed is 117.9 kgs (260 pounds) which gives a volume of 23.6mL (0.1 mmol/kg). In this study the following three patients (all from sites within the US) received a dose volume greater than the maximum stated/planned maximum volume (for the given body weight) of 23.6mL, thereby constituting a protocol violation/variation/non-compliance (exceeding volume):
   B-006-27-M received 23.8mL (R forearm, body weight 119 kgs)
   F-009-32-F received 25.4mL (L antecubital, body weight 127 kgs)- this was aiso the largest volume administered during this study
   J-002-34-M received 25.0mL (R antecubital, body weight 126.8 kgs)
   Note that these volumes however, are appropriate for the respective patients' given body weight in kilograms.
2. Treatment compliance was not maintained (and therefore constituting study variation/violation/non-compliance) in two patients, both of who received OptiMARK™: patient E-011 exceeded the recommended dose and patient J-011 received a dose of 0.067mmol/kg (lesser than the recommended dose). The Sponsor has indicated that these were due to "Calculation Errors".
3. Parameters that would affect safety and efficacy data were not obtained at some of the stated time points due to: – patient failure to follow up, incomplete set of images, 6 lead v/s 12 lead EKG, etc., on 14 subjects. These were the protocol deviations/violations/non-compliance) constituting an incomplete database in those sections as applicable (Appendix 16.2.6-14, pp. 13.2460-67).
4. Label should specify and reflect appropriate ages in the drug indication (should not include less than 18 years). Patient J-012, was 12 years old and there were no reported adverse events on this patient. This age group is not part of the inclusion

criteria for this study application, and therefore constitutes protocol/study variation/violation/non-compliance.

EKG:

1. The concerns are similar as noted in study 488- reader inappropriateness, frequency and timing is inadequate, chosen parameters are wide, etc.
2. ~69/194 (35%) of the records were incomplete (absence of QT measurements and other deficiencies).
3. The Sponsor reported 7 patients in the OptiMARK™ group and 4 patients in the Magnevist® group with changes in the EKG from baseline at 24 hours; but none with clinically significant changes. These changes included sinus tachycardia, SVT, PVCs, BBB, prolonged QRS, Twave changes, QT prologation.

Enrollment/Exposure/Disposition:

The table below summarizes the demography, disposition, AE and dosing information for both the drugs:

SAFETY: Enrollment/Disposition/Dose/AE: Number 525 Phase 3 – Pivotal CNS OptiMARK™ NDA # 20937			
		Treatment Group	
		OptiMARK™ (0.1 mmol/kg)	Magnevist® (0.1 mmol/kg)
Number of Patients		0.1	0.1
Entered study		129	66
Exposed to drug		129	65
Completed study		129	65
Evaluable for Safety		129	65
Evaluable for Efficacy		129	65
Dropped pre-dosing		0	1
Dropped for adverse event		0	0
Demography			
Age(Years)	N	129	65
	Mean	45.1	43.8
	range	12-78	23-72
Drug Volume			
TotalVolume (mL)	N	129	65
	mean	15.6	15.1
	range	8.8-25.4	10.5-25.0

- Safety data was collected at various time points as shown in the table below:

SAFETY: 525-PHASE 3-PIVOTAL: TIME EVENTS: OptiMARK™ NDA # 20937								
Time	Med Hx	Meds	Physical	Vitals [1]	EKG [2]	Labs [3]	AE	Tolerability
within 14 days pre	X							
within 24 hrs pre		X	X		X	X		
immed pre		X		X				
MRI - non-contrast		X						
DOSE		X					X	
MRI - post-contrast		X						
immed post image		X		X			X	X
2 hrs post		X		X		X	X	
24 hrs post		X	X	X	X	X	X	
48 hrs post (phone)		X					X	
3 days post		X		X		X	X	

1 includes systolic and diastolic blood pressure, pulse, and respiratory rate (no temperature)
2 12-lead EKG
3 includes hematology, chemistry (note: serum Ca^{+2} measured using atomic absorption assay as Sponsor states that OptiMARK™ interferes with colorimetric assay) serum Gd, and urinalysis: all labs in USA and Canada shipped to NDA; all labs in Europe shipped to [redacted]
AE = adverse event monitoring for two hours post-dose, then at discrete times as indicated
Tolerability: patient will be asked about sensations of heat, cold, or pain at injection site and whether it was mild, moderate, or severe

Other comments/concerns:

- OptiMARK™ and Magnevist® were well tolerated in this comparative study at 0.1mmol/kg dose.
- There were no statistically significant differences between the treatment groups with respect to adverse event frequency; intensity; or demographic subgroups.
- There were common adverse events for both the groups (paresthesia and taste perversion).
- Injection associated events were comparable between the two groups (10 events for OptiMARK™ group and 9 events for the Magnevist® group). Sensation of feeling cold was the most commonly reported symptom.
- There were no serious or unexpected changes in labs, vitals, EKGs, or physical examinations.
- The table above summarizes the demography, disposition, AE and dosing information for both the drugs:
- There were no deaths, serious adverse events, dropouts due to adverse events or post-dosing dropouts.
- 4 patients (5 events) in the OptiMARK™ and 1 patient (2 events) in the Magnevist® group experienced severe adverse events (see comments in other studies and in the overall safety review section regarding the issues on the terminology of serious and severe adverse events and the implementation of these in the application) in this study.

SEVERE ADVERSE EVENT: (OptiMARK™ group)

525-F-019: 45-F; Headache; Recovered before study time ended (72 hours).
525-H-004: 58-F; Chest pain, leg cramps; Recovered before study time ended (72 hours).

525-I-002: 32-M; Headache; Recovered before study time ended (72 hours).
525-G-003: 52-M; Headache; On-going headaches even after completion of study-presumed to be secondary to continued CSF leakage abd meningitis.

- There were 22 patients who required medical treatment due to adverse events (15 in the OptiMARK™ group and 7 in the Magnevist® group). 2 patients in the OptiMARK™ group (525-G-014 and 525-J-018 with treatment for headache) who received treatment were considered drug related.
- Most AEs (69.6% in the OptiMARK™ group and 82.8% in the Magnevist® group) occurred within 24 hours after dosing.
- The table below summarizes some of the safety findings:

SAFETY: STUDY 525: PHASE 3: PIVOTAL: OptiMARK™ NDA # 20937

ADVERSE EVENTS:

OptiMARK™	Magnevist®
PATEINTS (N) EXPOSED = 129	PATEINTS (N) EXPOSED = 65
DEATHS (N) = 0	DEATHS (N) = 0
PATIENT (N) WITH SERIOUS ADVERSE EVENTS = 0	PATIENT (N) WITH SERIOUS ADVERSE EVENTS = 0
DROPPED (N) DUE TO ADVERSE EVENTS = 0	DROPPED (N) DUE TO ADVERSE EVENTS = 0
POST-DOSING NON-AE WITHDRAWAL (N)= 0	POST-DOSING NON-AE WITHDRAWAL = 0
PATIENTS (N) WITH ADVERSE EVENTS= 33	PATIENTS (N) WITH ADVERSE EVENTS= 16
TOTAL (N) ADVERSE EVENTS = 56	TOTAL (N) ADVERSE EVENTS = 29
PATIENTS WITH SEVERE ADVERSE EVENTS= 4	PATIENTS WITH SEVERE ADVERSE EVENTS = 1

	Dose (0.1mmol/kg) Treatment Group		
	OptiMARK™	Magnevist®	
N (RECEIVED DOSE)	129	65	Comments for OptiMARK™
N (PATIENTS WITH AE)	33 (25.6%)	16 (24.6%)	• Most frequent: headaches (10.1%); dizziness (3.9%), paresthesia (3.1%), taste perversion (2.3%)
N (ADVERSE EVENTS)	56	29	
INTENSITY OF AE			• Onset within 2 hours of dosing, lasted ~ 2.05 (± 4.31)
MILD (N)	40 (71%)	23 (79%)	
MODERATE (N)	11 (20%)	4 (14%)	• Others : nausea
SEVERE (N)	5 (9%)	2 (7%)	

EKG & PE

No clinically significant changes between the two groups

VITAL SIGNS

No clinically significant or meaningful changes for either group. Small statistically significant changes for OptiMARK™ were decrease in pulse rate (immediately post injection) and decrease in DBP at ~ 72 hours post-injection.

LABORATORY EVENTS

	Statistically significant	Clinically significant
Parameters affected	Total Iron (>80% ↑ from baseline in 5%)	No
Dose related	Diurnal variation	
Time related		
Resolution time		

OTHER LABS

Several small insignificant changes at 2 hours post, 24 hrs post and 72 hours post- not meaningful clinically (see overall safety review section for complete details.

DEATH:

- The death of one patient was reported who had participated in the study, the details of which is shown below:

SAFETY: 525-PHASE 3 PIVOTAL: DEATH: OptiMARK™ NDA # 20937	
Patient	525-E-015
History	58 yr old WF with metastatic breast disease (liver, brain), R hemiparesis, seizure disorder, hypothyroidism, s/p XRT
Dose	0.1mmol/kg
Death Date	15 days post dose
Immediate events	None reported
Events during 72 hour mointoring	No new events reported; but seizures continued
Subsequent events/course	Continued seizures Hypotension New quadriparesis (MRI spine negative for mets; MRI brain-↑mets in number and new multiple water shed infarcts)
Presumed cause of death/contributing causes	PE Sepsis due to pneumonia
Autopsy	None performed
Reviewer's Comments:	It is unlikely that OptiMARK™ contributed to the death of this patient with multiple problems, including terminal malignancy, and end organ failure. The possibility that OptiMARK™ could have been an other precipitating factor that increased/worsened the pre-existing seizure disorder cannot be ruled out. Similar situations have been noted and commented on in other sections of this review; and other gadolinium agents have shown to exhibit a similar behavior (see Magnevist® package insert). Labeling to appropriately reflect this concern is recommended.

FINAL CONCLUSIONS:

1. This study 525-a pivotal phase 3 CNS study was identical in study design, end points, and several other aspects-including the protocol. Extensive comments have been made in study 488 on the study design and efficacy analysis and findings. Similar comments are applicable to this study. In fact, these have been combined as a separate review-overview of efficacy. Repetitions in comments are avoided. The breakdown on the efficacy data for this study shows similar analyses and for #488. The concerns of the qualifying MRI, patient enrichment, the Sponsor set equivalence interval, blinded reader methodology- were all noted in this trial as well. The impressions are similar- which is the Sponsor has not proven or established equivalence without an equivalence interval.
2. The safety profile of OptiMARK™ is similar to Magnevist® as noted in the study 488, and from this aspect, equivalence is probably proven. There were no deaths attributable to OptiMARK™; but in the patient (525-E-015) who died 15 days post-dosing, there could be associated morbidity in that the pre-existing seizures probably worsened.
3. Further efficacy comments and safety comments are made in the overall efficacy and safety review sections respectively.

END OF STUDY REPORT 525

OVER VIEW OF EFFICACY

Gadolinium is a diagnostic agent that might be helpful in gaining additional information when used appropriately to manage patients better.
There are already three other approved gadolinium diagnostic agents in the market (see comparators in the safety review section) subservient to the needs of imaging and diagnosis when a MR imaging modality with a contrast agent is necessary or called for in indicated patients including patients with brain tumors and terminal cancer.
OptiMARK™ is neither claiming superiority nor has been shown to be superior to Magnevist® or placebo. OptiMARK™ blends well with the other comparable agents in the 'over-all' picture and 'appears' to be made of the same fabric on a gross level on the following profiles: physio-chemical properties, chemical properties, PK profile, and in the safety profile as well, to a large extent. This reviewer will be commenting only on the CNS efficacy claim and emphasis will therefore be given to those trials in this program that involved the Brain or the Spine. There were no Phase 1 imaging studies. Two of the six phase 2 studies were CNS trials- study 464 and 465 for the brain and spine respectively. These have also been reviewed separately. The non-pivotal phase three studies were terminated prior to completion and efficacy data were not submitted. Two pivotal Phase 3 CNS studies (488 and 525), identical in design, and with similar end points were carried out to demonstrate equivalence between OptiMARK™ and Magnevist®. These pivotal phase 3 trials are the center of focus and complete review of the respective protocols and the trials have also been made separately. A brief description of these efficacy related trials will follow.

Phase 2 Results:

Two studies for CNS (464-Brain-N=78 for efficacy, and 465-Spine-N=86 for efficacy) were carried out in this program as phase 2 studies.

Study 464 (N=78 for efficacy):

- This was Multicenter, Double-Blind, Multidose, Within-Patient Study to Evaluate the Safety, Tolerance, Efficacy of MP-1177/10 Injection in MRI of the Brain.
- The main objectives were: to determine the dose-related safety, tolerance, and efficacy of intravenously administered OptiMARK™ (gadoversetamide injection) in patients with known or suspected brain pathology (previously detected by computed tomography or ultrasound).
- The patients were randomly assigned to one of three pairs of OptiMARK™ doses (0.1, 0.3 mmol/kg; 0.1, 0.5 mmol/kg; and 0.3, 0.5 mmol/kg) as one of two dosing sequences (low dose followed by high dose or vice versa). Each patient received two sets of images during two sessions.
- The primary efficacy endpoints were:
  a) "Contrast-to-noise ratio for the selected region of interest (ROI)
  b) The proportion of patients for whom contrast-enhanced MRI altered patient management according to the principal investigator

c) The proportion of patients for whom contrast-enhanced MRI provided additional diagnostic information according to the blinded readers and the principal investigator
d) The proportion of patients for whom the higher (or lower) dose was selected as the better dose by the blinded readers for each pair of doses within patients
e) The number of lesions detected pre- and post-contrast and
f) Sensitivity".

- The following were the efficacy results which included ~37.34% of post-treatment patients (status post biopsy and or surgery and or post chemo and or post radiotherapy).

  Border Visualization: No statistically significant changes by blinded readers at any dose between pre- and post-contrast images, but improved border visualization with increasing dose.
  Edematous Tissue: No statistically significant changes by blinded readers at any dose between pre- and post-contrast images.
  Confidence in Diagnosis: No statistically significant changes from base line by blinded readers at any dose.
  Number of lesions: Remained the same from pre to post-contrast images.
  Sensitivity: Increased for blinded readers from pre-contrast to post-contrast images.
  As anticipated (due to the fact that the principal investigators had additional information about the patients), the scores on some of these endpoints were higher for the principal investigators.

Study 465 (N=86 for efficacy):

- This was "A Multicenter, Double-Blind, Multidose, Within-Patient Study to Evaluate the Safety, Tolerance, and Efficacy of MP-1177/10 Injection in MRI of the Spine and/or Associated Tissue".
- The main objectives were: "To determine the dose-related safety, tolerance, and efficacy of OptiMARK™ (gadoversetamide injection) in patients with known or suspected spine pathology and/or structural abnormality (previously detected by computed tomography or ultrasound)".
- The patients were randomized to one of three OptiMARK™ dose pairs (0.1, 0.3 mmol/kg; 0.1, 0.5 mmol/kg; 0.3, 0.5 mmol/kg) as one of two dosing sequences (low dose followed by high dose or vice versa). Each patient was evaluated at each of two imaging sessions.
- The primary efficacy endpoints were:
  1. Contrast-to-noise ratio for the selected region of interest.
  2. The proportion of patients for whom contrast-enhanced MRI altered patient management according to the principal investigator.
  3. The proportion of patients for whom contrast-enhanced MRI provided additional diagnostic information according to the blinded readers and the principal investigator.
  4. The proportion or patients for whom the higher (or lower) dose was selected as the better dose by the blinded readers for each pair of doses within patients.

5. The number of lesions detected pre- and post-contrast.

- Sensitivity, specificity, and agreement/disagreement of MRI diagnosis versus final diagnosis.
- The following were the efficacy results which included a **~35.2%** post-treatment patients:

Border Visualization: There were no statistically significant changes by the blinded readers or principal investigators in the pre- to post-contrast images at any dose.
Edematous Tissue: There were no significant change between pre and post-contrast images by the blinded readers or the principal investigators at any dose for this end point.
Confidence in Diagnosis: There were no significant changes between the pre and post-contrast images (from baseline) for either the blinded readers or the principal investigators.
Sensitivity: As anticipated, the principal investigators had higher scores compared to the blinded readers; but there were no dose-related differences in the readings for the principal investigators.
Specificity: There was a slight increase in the scoring by the blinded readers between the pre and post-contrast images.
Number of Lesions: On an average, the number of lesions remained the same between the pre and the post-contrast images.

Efficacy: Phase 2-Impressions:

1. The phase 1 PK studies laid the foundation for these phase two studies in terms of safety and kinetics.
2. Appropriate dosage ranging selections were made to determine the set efficacy points.
3. Selection of these primary efficacy end points is inappropriate – for e.g. edematous tissue evaluation is more appropriately achieved using the technique of T1/T2 rather than with a contrast (also see confidence in diagnosis below).
4. Several of the primary end points in both the studies failed to show a clear change by the blinded readers in the pre- to post-contrast images at any dose.
5. Confidence in diagnosis (see also comments in phase 3 pivotal studies) was an inappropriate entity to have pursued given that a large percentage of patients were post-treatment cases, in whom it is not very difficult to identify post-operative changes, there by making such a diagnosis 'occur passively and automatically' with ease and confidence. This problem has been noted universally across the trials evaluated for CNS efficacy.
6. From an efficacy stand point, these studies were helpful in suggesting that perhaps there was increased sensitivity from pre to post-contrast and that border delineation was improved with increasing doses.
7. Possible capitalization (with a view to plan phase three studies) on the findings from these studies from an efficacy standpoint was not significant, if any dismal.
8. The safety data was helpful. These phase two studies suggested that the number and the severity of adverse events were greater with increasing doses. These findings and the fact that the other approved agents have proven efficacy at a 0.1mmol/kg dose

lead to the dose selection of 0.1mmol for the phase three studies and for the requested dosage for labeling.

Non-pivotal Phase 3 Studies:

- No efficacy data was generated from these studies.
- These studies were terminated prior to completion of enrollment in order to incorporate FDA suggested study design modifications, including a comparator group (like Magnevist®) and overall analysis plan to demonstrate equivalence to the approved comparator, therefore, these data were not statistically evaluated for efficacy. See regulatory history for additional comments.

Pivotal Phase 3 trials (488 and 525)

- These were multi centered, parallel group, randomized, single dose, double blind comparative studies (refer to respective Study Review Sections) in patients with known or highly suspected CNS pathology.
- The trial compared OptiMARK™ and Magnevist® with reference to safety, tolerability, and efficacy; and aimed to show: that OptiMARK™ was equivalent to Magnevist® in patients undergoing a MRI of the central nervous system.
- The three primary efficacy endpoints were:
  1. the score for the degree of **confidence in the diagnosis**(es) indicated pre-contrast plus post-contrast compared to pre-contrast
  2. the image score for the **level of conspicuity** for all lesions visualized pre-contrast plus post-contrast compared to pre-contrast; and
  3. the score for the ability to **delineate lesion borders** from parenchyma/structures pre-contrast plus post-contrast compared to pre-contrast.
- The following are results of the analysis for each of the primary efficacy endpoints for both the studies:

APPEARS THIS WAY
ON ORIGINAL

1. Confidence in Diagnosis:

Primary Efficacy Analysis Blinded Readers: Confidence in Diagnosis : Report # 488 /Phase 3 (Pivotal)					
		Decrease	No change	Increase	Total (200) for efficacy
OptiMARK™	N	28	51	53	132
	%	21.21	38.64	40.15	
Magnevist®	N	18	26	24	68
	%	26.47	38.24	35.29	

Primary Efficacy Analysis Blinded Readers: Confidence in Diagnosis : Report # 525 /Phase 3 (Pivotal)					
		Decrease	No change	Increase	Total (194) for efficacy
OptiMARK™	N	25	40	64	129
	%	19.38	31.01	49.61	
Magnevist®	N	8	20	37	65
	%	12.31	30.77	56.92	

2. Level of Conspicuity:

Primary Efficacy Analysis Blinded Readers: Level of Conspicuity: Report # 488 /Phase 3 (Pivotal)					
		Decrease	No change	Increase	Total (200) for efficacy
OptiMARK™	N	24	69	39	132
	%	18.18	52.27	29.55	
Magnevist®	N	5	37	26	68
	%	7.35	54.41	38.24	

Primary Efficacy Analysis Blinded Readers: Level of Conspicuity: Report # 525 /Phase 3 (Pivotal)					
		Decrease	No change	Increase	Total (194) for efficacy
OptiMARK™	N	24	52	53	129
	%	18.60	40.31	41.09	
Magnevist®	N	9	27	29	65
	%	13.85	41.54	44.62	

3. Border Delineation:

Primary Efficacy Analysis Blinded Readers: Border Delineation: Report # 488 /Phase 3 (Pivotal)					
		Decrease	No change	Increase	Total (200) for efficacy
OptiMARK™	N	23	56	54	132
	%	17.42	41.67	40.91	
Magnevist®	N	11	28	29	68
	%	16.18	41.18	42.65	

Primary Efficacy Analysis Blinded Readers: Border Delineation: Report # 525 /Phase 3 (Pivotal)					
		Decrease	No change	Increase	Total (194) for efficacy
OptiMARK™	N	25	51	53	129
	%	19.38	39.53	41.09	
Magnevist®	N	7	29	29	68
	%	10.77	44.62	44.62	

- Some of the comments and concerns already expressed in the study review section are mentioned here briefly for completeness and thoroughness.

1. Concerns on Data Acquisition Methodology:

a) The responses expected of the blinded readers to questions were recorded on scales that were ordinal, artificial, and subjective.

b) Each reader read only 1/3rd of the images. Inter-reader variability made a statistical difference when the raw data is analyzed. However, the probability that it made any significant statistical difference when the mean difference in the scores were analyzed was low as discussed with the Statistician and by the review of the ANOVA data analysis provided in the application.

c) The contrast images and the non-contrast images were not read separately. As much as they are usually reviewed together in clinical practice, for purposes of a "study", these probably should have been read separately.

d) The common code numbers also appeared on the monitor each time any of the images were recalled using the codes, along with the images themselves. Memory of these numbers would facilitate matching of the pre images with the corresponding post/pair causing a memory bias. Memory of the images themselves (even without the numbers appearing) can also cause a memory bias.

e) The question regarding final diagnosis and the list provided to categorize diseases is inappropriate (this affects the secondary efficacy endpoint).

2. Concerns on data analysis and methodology:

a) In concurrence with the Statistician, the reviewer acknowledges that the designation of the primary and secondary endpoints was consistent with the protocol (as in the NDA submission), but the statistical methods used to analyze

these endpoints were not (that is, the Sponsor introduced a new methodology after the data was acquired).

b) The efficacy results contained in the NDA were derived using ANOVA for calculating confidence intervals, and an equivalence region defined as –1.5 to +1.5. The protocol calls for the use of t-tests and standard confidence interval methods, but does not define an equivalence region.

c) The Sponsor has chosen the equivalence interval of (-1.5,1.5). This is a wide interval based on which (and in the opinion of the Statistician); the Sponsor has been able to prove equivalence between OptiMARK™ and Magnevist®. If a narrower interval is chosen, the data then suggests no equivalence. The overall data by itself (for both the agents) does not suggest that the pair (pre contrast + post contrast) is clearly and very strongly superior to the pre. It is beyond the scope of this review to further comment on this aspect and additionally, the Sponsor is not claiming superiority over the comparator. This "wide equivalence" region that the Sponsor has chosen, calls for further careful clinical and statistical relevance and validity. If this region is statistically acceptable, the reviewer concurs that the Sponsor has demonstrated equivalence. Refer to the Statistician's review for additional comments.

3. Comments on the data/findings:

a) The various frequency scores for OptiMARK™ and Magnevist® are probably statistically similar (proving no significant statistical difference between the two, and thereby establishing equivalence **if** the equivalence interval of –1.5 to +1.5 is acceptable).

b) It is worthy to note from the above illustrations, that the majority of the cases in both the groups (for both studies) had no change or actually a decrease (when combined) in all the three primary efficacy end points. This is probably due to the fact that the cases were largely selective (e.g. a pre contrast scan easily shows a post-operative defect even without contrast) and enriched (the out come was known when the qualifying MRI was performed). Discussion on findings and data is a derivative of what was evaluated that was the 'root' or the "mother" for the subsequent findings. One should bear in mind, that these observations (the results) are the "effects" and not the "cause". It is only appropriate to discuss these concerns at this time.

4. Concerns on patient selection and enrollment:

a) **Qualifying MRI:**

- The concerns of the 'qualifying MRI examination' have been discussed in the study review sections. This probably resulted in study samples containing an over-representation of patients with obvious disease. The information so obtained when used for patient management, is ethical, fair, appropriate, and actually a very thoughtful clinical decision. The Sponsor has stated (refer to correspondence) that the number of patients that were disqualified based on

the qualifying MRI were not tracked and therefore, the total number of patients who were 'screened' prior to enrollment is unknown. This may have potential underlying significant statistical concerns (such as bias, enrichment, non-representative sample, etc.) that is not answerable at this time, nonetheless, too important to be discarded or ignored as the entire study is based on the data collected from these cases. By obtaining this qualifying MRI prior to enrolment into the study, the category of patients in whom pathology is "suspected" is erased and one is totally left with patients with "known" pathology. This has a direct impact on the proposed labeling and indication.

b) **Non representative patient selection:**

- It has been noted throughout these trials that there has been a large group of patients with history of surgery and or biopsy and or radiation therapy and or chemotherapy that were enrolled in this clinical program. These are the approximate percentages by study for 488 and 525:

  Study 488 pivotal phase 3: 55/133 (41.35%) in the OptiMARK™ group
  28/68 (41.17%) in the Magnevist® group

  Study 525 pivotal phase 3: 32/129 (24.8%) in the OptiMARK™ group
  16/65 (24.6%) in the Magnevist® group.

- This is a largely selective population (non-representative sample) in whom one can expect predictable (pathological and radiological) abnormalities that can be residual or static or on-going, including iatrogenic causes of break down in the blood brain barrier. Such postoperative changes and defects are easily recognizable, particularly in the brain studies, making interpretation very easy even to the blinded reader (who was not provided with any additional information). Additionally, break down in the blood barrier occurs more frequently in post therapeutic cases (surgery or chemotherapy or radiation therapy or combination); resulting in contrast enhancement and therefore in better visualization, etc.
- This has resulted in statistically significant greater scores in the blinded "pair" reading when compared to the blinded "pre" reading as demonstrated in the frequency table (see below) for post-treatment patients and not for the rest of the patients (who are not part of the former group, that is, those patients who did not have any therapeutic intervention which can or might cause such changes as described above). **The mean change (from pre to pair) in the primary endpoints was statistically different from zero among post-treatment patients. However, this relationship was not maintained in the non-post-treatment patients. Therefore, the statistical significance of this relationship observed in the overall group is being driven by the results of the post-treatment patients.**

- The table below shows the frequency between these post treatment and non-post-treatment patients:

EFFICACY: POST/NON-POST-TREATMENT: Report # 488 /Phase 3 (Pivotal) OptiMARK™Protocol # 1177-95-03.03				
	OptiMARK™		Magnevist®	
Parameters	Post-Treatment	Non-Post-Treatment	Post-Treatment	Non-Post-Treatment
Conspicuity Score	36% (20/55)	24.6% (19/77)	64% (18/28)	22.5% (9/40)
Confidence Score	51% (28/55)	32.4% (25/77)	46% (13/28)	27.5% (11/40)
Border Delineation Score	60% (33/55)	27% (21/77)	50% (13/28)	37.5% (15/40)

Note: A similar analysis for the pivotal phase 3 study 525 has been deferred at this time as the outcome of such an analysis is expected to be no different than study 488.

- It therefore becomes extremely important and crucial to critically weigh some of the issues discussed in the study review section and in other parts of this report in determining the validity of these results (which seems acceptable for equivalence claim on a face value if the equivalence interval chosen by the Sponsor is acceptable).
- If, in the review team's opinion it is determined that these concerns are significant and meritorious, no credit should be given for this claim/indication (non approvable).
- If the equivalence interval is acceptable by the team looking past the concerns of the qualifying MRI and the selective patient group, then appropriate changes in the claim or labeling should be made to reflect these observations such as: "OptiMARK™ is indicated for use in patients who have known CNS pathology (specifically post treatment patients) as opposed to those in whom it is suspected with a high degree... and ...OptiMARK™ is indicated for use after appropriate imaging studies have been obtained with another approved gadolinium agent.....".

IN SUMMARY

The Sponsor chose to prove equivalence to another approved gadolinium agent. For the same reasons mentioned earlier, the review process should therefore be more critical of the methodology and in the analysis of the information so obtained. The data and the images are "after effects". The way and the methods of acquiring this data and the images are crucial. The means and the 'yard stick' so used to measure this data is exceptionally important for an equivalence trial. As discussed above: the Sponsor's efficacy claim for the CNS (Brain and Spine) indication (particularly based on the pivotal phase 3 studies 488 and 525 encompassing 132 + 129 = 260 patients) based on equivalence to Magnevist® is to a large extent driven by or influenced by the following:

1. Efficacy data from the phase 2 studies 465 and 464, were unable to re-inforce the primary phase 3 pivotal endpoints. In fact, the data and findings show no statistical

significance according to the Sponsor or several endpoints. These studies were also 'contaminated' by a large proportion of post-treatment patients. The reviewer has chosen not to comment extensively on these studies (as for the pivotal studies), particularly on the statistical aspects, as the FDA statistician has deferred to make comments on these non-pivotal studies.

2. Potentially favorable and reinforcing data could have possibly stemmed from the non-pivotal phase 3 CNS studies (484/485), but these were terminated prior to completion.
3. The entire efficacy data for the CNS indication therefore dwells within the two studies 488 and 525.
4. The possibility that a selection bias might exist in the qualifying MRI (which could easily have been a screening MRI). Patient enrichment is a serious possibility. The patients so enrolled after this qualifying MRI were highly selective and therefore non-representative. These comprised (83/201+ 48/194 = 131/395 for both studies for both drugs) 33.16% with a therapeutic history (referred to as the post-treatment cases by the reviewer). In concurrence with the FDA Statistician, the reviewer has provided analysis in these pivotal 3 CNS studies and shown that the data so derived was largely driven by these post-treatment cases. In fact, the reviewer has demonstrated that there were statistically significant differences between the post treatment and the non-post-treatment patients.
   When the 'qualifying MRI' and the 'highly selective post treatment cases' are factored in together, the resultant is a single scenario of 'cases with known disease/pathology'. Sponsor's claim of utility in patients in whom CNS pathology is highly suspected is completely in valid, because there were no suspicions at the time of enrollment. One cannot make a claim on non-existent matters. The randomization between OptiMARK™ and Magnevist® had no effect in reality and essentially was nullified due the similarity in the spectrum of the patient population. Studies with 'known pathology and radiological abnormalities' were duplicated with OptiMARK™ and Magnevist®. Despite these advantages (qualifying MRI and enrichment), the Sponsor could prove equivalence between the two drugs only when a "wide" equivalence interval of + 1.5 to – 1.5 was chosen (not proposed in the protocol, but instituted later by the Sponsor). The FDA statistician has demonstrated that the data would not prove equivalence if any narrower interval other than the + 1.5 to –1.5 is chosen for the set primary efficacy end points. This is probably due to inappropriate selection of the primary efficacy end points, and the distribution of these post-treatment cases homogeneously between the two drugs, thereby, generating scores that are near equal (as shown above).
6. The Sponsor has therefore not been able to demonstrate or establish:
   a) The proposed indication of patients with suspicion of CNS pathology- there were no patients in whom CNS pathology was 'suspected'- they were all known even before enrollment. Enrollment bias cannot be ruled out.
   b) 'Suspicion or known' CNS pathology: implies a reasonably wide variety of patients with different pathology (known and unknown). These patients were non-representative and comprising predominantly of post-treatment patients, in whom the known pathology led to very predictable results → easy interpretation of the images with confidence → predictable MR changes due to the iatrogenic causes of break down in the blood brain barrier → easier visibility (conspicuity)

and greater enhancement (affecting all the three primary efficacy endpoints). Patient enrichment cannot be ruled out.

c) If one considers the equivalency claim to Magnevist®: the subsequent results could be easily predicted at the time of the qualifying MRI examination itself. Comparison between gadolinium agents (given their similarities in many profiles) is not going to reveal significant differences (to a large extent). Therefore, to establish equivalency (may have been ok for safety) for efficacy between these agents is in a way a 'cloning/re-duplicating' process. Such being the case, an equivalency trial should show 'equality'. The Sponsor has established equivalency only when an interval of +1.5 to – 1.5 is used. Besides the fact that there was no equivalency without such an interval, this Sponsor chosen interval (not proposed before the trial) is the only way that equivalence can be established. Equivalence is proven only with an equivalence interval, and with one that is "wide".

CONCLUSION

1. Non Approval for CNS Efficacy or

2. Conditional Approval for CNS Efficacy (if the equivalence interval is acceptable and ignoring selection bias & non-representative patient population/patient enrichment), to incorporate the following (that is only scientifically fair and ethical):

   a) OptiMARK™ is indicated in patients with known CNS pathology (particularly post treatment patients) and exclusion of 'highly suspected' from proposed indication and labeling; and or
   b) Contrast MRI with another approved agent is required when OptiMARK™ is used.

RECOMMENDATION

See Page 13 in Regulatory Section

END OF EFFICACY (CNS) REPORT

NDA # 20 937
IND#

OptiMARK™ SAFETY OVERVIEW

- Volumes Reviewed: NDA # 20 937 Volumes # 2.1 - 2.168 and additional information provided by Sponsor related to Safety (dated 4-28-98, 7-9-98)
- Primary Volumes for this review: 2.147 – 2.165

FOREIGN MARKETING SAFETY:

- The Sponsor has no history of marketing in any foreign country/ies (Vol. 2.2, p. 1.0242).

CHEMISTRY, MANUFACTURING & CONTROLS:

- Refer to the Chemistry review section for complete details.
- A brief summary of some of the chemical properties of OptiMARK™ is mentioned below:

General:

- The "active ingredient" in OptiMARK™ is a complex consisting of gadolinium (+3) and the chelating agent versetamide. Gadolinium is a paramagnetic ion that enhances the relaxation rates of immediately surrounding water when placed in a magnetic field thereby increasing brightness when T1-weighted magnetic resonance imaging is performed. OptiMARK™ does not cross the intact blood-brain barrier.
- Trade Name: OptiMARK™
- Generic Name: Gadoversetamide Injection
- Code Name: MP-1177/10
- Chemical Name: [8,11-bis(carboxymethyl)-14-[2-[(2-methoxyethyl)amino]-2-oxoethyl]-6-oxo-2-oxa-5,8,11,14-tetraazahexadecan-16-oato(3-)]gadolinium
- Empirical Formula: $C_{20}H_{34}N_5O_{10}Gd$
- Description: non-ionic gadolinium chelate of diethylenetriamine pentaacetic acid bismethoxyethylamide (gadoversetamide).
- Contents & Physico-Chemical Properties are summarized in the table below:

SAFETY: PHYSICO-CHEMICAL PROPERTIES: NDA # 20 937-OptiMARK™	
Component	**Concentration (mg/ml)**
gadoversetamide versetamide calcium hydroxide calcium chloride dihydrate sodium hydroxide hydrochloric acid	330.9
Property	**Feature**
Appearance	clear, colorless to pale yellow solution
Sterility	sterile, nonpyrogenic
pH	5.5 - 7.5
Osmolality	1110mOsm/kg H_2O at 37°C (3.9 times that of plasma)
Viscosity	2.0cP at 37°C 3.1cP at 20°C
Density	1.160g/ml at 25°C
Concentration	0.5M [= 0.5 mmol/ml]

SIMILAR (CLASS) PRODUCT INFORMATION:

- Pharmacologic Category: gadolinium-containing intravenous contrast agent for magnetic resonance imaging.
- Information from Related IND's / NDA's: Below is a table which provides relevant information on OptiMARK™ and other approved agents (Magnevist, Omniscan, and ProHance) that belong to the same pharmacological category (in relationship to gadolinium compounds; source: respective labels/proposed labeling):

SAFETY: SIMILAR (CLASS) PRODUCT INFORMATION: NDA # 20 937-OptiMARK™				
Brand Name	**OptiMARK™**	**Magnevist®**	**Omniscan®**	**ProHance®**
Sponsor	Mallinckrodt	Berlex Labs	Nycomed	Bracco Diagnostics
IND / NDA #	41534/20-937	19-596	20-123	20-131
Generic Name	gadoversetamide	gadopentetate dimeglumine	gadodiamide	gadoteridol
Description	non-ionic gadolinium complex of diethylenetriamine pentaacetic acid bismethoxyethyl-amide (gadoversetamide)	a gadolinium complex of N-methylglucamine salt of diethylenetriamine pentaacetic acid	non-ionic gadolinium complex of diethylenetriamine pentaacetic acid bismethylamide	gadolinium complex of 10-(2-hydroxpropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid
Concentration of Active Drug	330.9 mg/ml	469.01 mg/ml	287 mg/ml	279.3 mg/ml
Recommended Dose	0.1 mmol/kg (0.2 mL/kg)	0.1 mmol/kg (0.2 mL/kg)	0.1 mmol/kg (0.2 mL/kg)	0.1 mmol/kg (0.2 mL/kg)
Volume Restrictions	[none specified by Sponsor]	20 ml	none specified in label	none specified in label
Maximum Volume Studied	118 ml	not mentioned in label	52 ml	not mentioned in label
Method of Administration	IV bolus	IV bolus not to exceed 10ml/15secs	IV bolus	IV bolus (>60mL/min) rapid infusion (10-60mL/min)
Repeat Dosing	not studied	not approved in label	approved in label	approved in label
pH	5.5 - 7.5	6.5 - 8.0	5.5 - 7.0	6.5 - 8.0
Viscosity	2.0 cP at 37°C 3.1 cP at 20°C	2.9 cP at 37°C 4.9 cP at 20°C	1.4 cP at 37°C 2.0 cP at 20°C	1.3 cP at 37°C 2.0 cP at 20°C
Density	1.160 g/ml at 25°C	1.195 g/ml at 25°C	1.14 g/ml at 25°C	1.137 g/ml at 25°C
Osmolality	1110mOsm/kg H_20 at 37°C (3.9 X plasma)	1960mOsm/kg H_20 at 37°C (6.9 X plasma)	789mOsm/kg H_20 at 37°C (2.8 X plasma)	630mOsm/kg H_20 at 37°C (2.2 X plasma)
Mean Distribution ±SD	13.3 ± 6.8 minutes	12 ± 7.8 minutes	3.7 ± 2.7 minutes	12 ± 2.4 minutes
Mean Elimination Half-Life ±SD	103.6 ± 19.5 minutes	96 ± 7.8 minutes	77.8 ± 16 minutes	94.2 ± 4.8 minutes
Mean Plasma Clearance Rate	72 ± 16.3 mL/hr/kg	1.94 ± 0.28 mL/min/kg	1.8 mL/min/kg	1.50 ± 0.35 mL/min/kg
LD_{50}-mice (mmol/kg)	28	6-10	15-34	12
Reference	NDA # 20-937	package insert November 1997	ONC-2E April 1996	Dec 94

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- Other safety information (including adverse events, etc.) for the comparable agents can be summarized as follows:

SAFETY: SIMILAR (CLASS) PRODUCT INFORMATION: NDA # 20 937-OptiMARK™

Brand Name	OptiMARK™	Magnevist®	Omniscan®	ProHance®
Sponsor	Mallinckrodt	Berlex Labs	Nycomed	Bracco Diagnostics
IND / NDA #	41534/20-937	19-596	20-123	20-131
Generic Name	Gadoversetamide	gadopentetate dimeglumine	Gadodiamide	Gadoteridol
Description	non-ionic gadolinium complex of diethylenetriamine pentaacetic acid bismethoxyethyl-amide (gadoversetamide)	a gadolinium complex of N-methylglucamine salt of diethylenetriamine pentaacetic acid	non-ionic gadolinium complex of diethylenetriamine pentaacetic acid bismethylamide	gadolinium complex of 10-(2-hydroxpropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid
Demographics				
Mean age >18	49.52 (yrs.)	46.4 (yrs.)	52	53
Mean Age ≤18	*	-	-	8.7
Age range	18-85* (yrs.)	1-93 (yrs.)	--2-88--	2-91
Age ≥65 yrs.	17%	18.3%	-	-
Sex	M≅F	M≅F	M≅F	M≅F
Race	~84% Caucasian	~82% Caucasian	~93% Caucasian	~83% Caucasian
Dose				
Total exposed	1663	~1113	~945	~1251
Recommended	0.1mmol/kg 0.2mL/kg	0.1mmol/kg 0.2mL/kg	0.1mmol/kg 0.2mL/kg	0.1mmol/kg 0.2mL/kg
Rate	1-2mL/sec	≤10mL/15secs	none mentioned	10mL-60mL/min (rapid IV infusion) or >60mL/min (IV bolus)
Administration	IV bolus (hand)	IV bolus	IV bolus	Rapid IV infusion or IV bolus
Repeat dosing	Not studied	None mentioned	Approved	Approved
Max. Volume Studied	118mL	Not to exceed 20mL	52mL	None mentioned
Pediatric use	Not studied*	Approved (2yrs & older)	Approved (2yrs & older)	Approved (2yrs & older)
Indications	Adult CNS & Spine and Liver	Adult CNS & Spine and Body (non-cardiac) Children CNS & Spine	Adult CNS & Spine and Body (non-cardiac) Children CNS & Spine	Adult CNS & Spine Children CNS & Spine
Contraindication	Mentioned (allergic to contents)	None	None	None
Warnings & Precautions**	Similar (when addressed) with reference to sickle cells, hemoglobinopathies, allergic/hypersensitive drug reactions, repeat dosing, renal impairment, labs interactions due to agent, fertility, pregnancy, carcinogenicity, lactation, physician supervision, image interpretation along with non-contrast studies, usage of drug immediately after drawing, drug interactions, etc.			
Adverse Reactions (most common)	Headache (8.4%) Taste perversion (4.4%) Dizziness (3.1%) Nausea (3%) Vasodilation (2.3%) Paresthesia (2.1%) Inj. site reaction (1.2%) Body as a whole & others (<1%)	Head ache (5.5%) Inj. site reaction (2.8%) Nausea (2.5%) Dizziness (<2%) Body as a whole & others (<1%)	Headache (<3%) Dizziness (<3%) Nausea (<3%) Inj. site reaction (<1%) Body as a whole & others (<1%)	Nausea (1.4%) Taste perversion (1.4%) Body as a whole & others (<1%)

one pediatric patient (12 years old) was enrolled in the entire clinical drug development program (in pivotal phase 3, #525) [p. 26.0025, Vol. 2.147]. * One Pediatric Phase I study (safety and pharmacokinetic) ** The package insert for Magnevist® lists seizures.

~ Reviewer's comment: Some of the information presented above in the 'similar (class) product section' should be addressed in the labeling section for OptiMARK™.

MICROBIOLOGY:

- Refer to Microbiology review section for complete details.

PRE-CLINICAL/NON-CLINICAL ISSUES:

- In vitro and in vivo studies were carried out. These studies evaluated:
  a) Pharmacology, pharmacokinetic profile, distribution profile of the drug
  b) Acute Toxicity
  c) Subacute Toxicity
  d) Genetic Toxicity
  e) Special Toxicity
  f) Reproductive toxicity

- The table below summarizes some of these important findings. Additional and detailed information regarding pharmacology/toxicology/biopharmacology may be found in the appropriate review section. Additional information may be found in the application (Vol. 2.2, pp. 1.0282-1.0308).

SAFETY:PRE-CLINICAL STUDIES: NDA # 20 937-OptiMARK™					
	Study Type	Number of studies	Species	System/Organ Affected/Study	Results Comments
1	Pharmacology	4	Mice, rats, beagle dogs, rabbits	CNS	↓ motor activity prolonged anesthesia
				CVS	↓ mean BP ↓ left vent. systolic press
2	Acute Toxicity	5	Please see pharmtox review LD_{50}(mice)=28mmol/kg Intracisternal LD_{50} (rats)=0.166mmol/kg		
3	Sub Acute Toxicity	4	rats, beagle dogs	Skin	Reversible generalized hair loss & scabbing
				Proximal Convoluted Tubule	Micro-vacuolation- reversible, asymptomatic, nondysfunctional
				Chemistry	↑ PO_4 & Cl, ↓ Uri. Ca^{2+}
				Testes, Epididymides, Germinal epith.	+ toxicity signs in rats(- in single dose study) no toxicity in dogs
4	Special Toxicity	2	Rabbits	IV	Mild venous irritation
				IM, SC	Mild Inflammatory Reaction
5	Reproductive Toxicity	7	Rats, rabbits	Fertility	Impaired, degeneration of testicular germinal epithelium, ↓sperm count
				Fetal Malformations	Forelimb flexure Multiple cranio-facial defor.
6	Genetic Toxicity	4	Mice	Chromosomal	Negative by large, + in one study @ 5000µg/mL
7	Pharmacokinetic/Metabolism	18	Rats, beagle dogs	See pharmtox/biopharm review & table below No protein binding, No metabolism Rapid urinary excretion	
8	Comparative Studies	12	beagle dogs, rabbits, mice, rats	Magnevist® (comparator)	No differences in hemodynamic responses, enhancement, relaxivity, skin irritation, erythrocyte crenation, bioequivalence, etc.

- The following information has been provided and addressed in the "warnings" and "precautions" section, pertaining to the pre-clinical safety issues. *These should be appropriately reflected in the* ***labeling***. These are:

a) The Sponsor cites prior *in vitro* studies suggesting alignment of deoxygenated sickle RBC's in a magnetic field, which may result in vaso-occlusive complications *in vivo*. The Sponsor further states that OptiMARK™ Injection has not been studied in patients with sickle cell anemia or other hemoglobinopathies.

b) Patients with ***renal impairment*** should be evaluated with caution due to renal excretion of the drug.

c) The Sponsor proposes ***Pregnancy Category C*** precautions and caution in nursing mothers (it is not known whether the drug is excreted in human milk; a low but measurable lacteal transfer occurred in rats in a 24-hour period when ^{153}Gd-labeled gadoversetamide was administered intravenously to lactating rats at a dose of 0.1mmol/kg) [p. 1.0213, Vol. 2.1].

d) ***Carcinogenic potential*** has not been evaluated (with long-term studies in animals or humans).

e) The Sponsor states that ***irreversible loss of germinal epithelium*** was observed in reproductive toxicity studies in male rats receiving a dose of 2.0mmol/kg/day (7920 mg/m^2) for 50 days. This dose was 3.2 times the clinical dose of 2442 mg/ m^2 based on body surface area, 20 times the recommended human dose of 0.1mmol/kg. [pp. 1.0212 - 1.0213, Vol. 2.1].

f) The Sponsor states that OptiMARK™ interferes with the colorimetric assay for serum calcium and iron.

g) Not studied were: ***race or drug-drug interactions (label/concomitant medications)***

h) The safety of ***repeat doses*** (in humans) has not been evaluated ***(label/dosing)***

CLINICAL & HUMAN PHARMACOKINETIC & BIOAVAILABILITY SUMMARY

- Pharmacologic Category: gadolinium-containing intravenous contrast agent for magnetic resonance imaging.
- Please refer to the pharmacology and bio-pharmacology section of the review for additional and complete comments. Additional information is also available in the submitted application (pp. 1.0309-1.0341, Vol.2.2; pp. 1.0207 - 1.0208, Vol. 2.1].
- The table below provides a summary on these pharmacokinetic studies:

SAFETY:HUMAN PHARMACOKINETIC STUDIES: NDA # 20 937-OptiMARK™			
STUDY	DESIGN/PURPOSE	DEMOGRAPHICS	DOSE
#433 Phase 1 Site: US	Randomized, double-blind, placebo controlled PK, Safety, Tolerance First-in-human	Healthy Adult Male only Placebo = 4 **Drug = 16**	Ascending 0.1,0.3,0.5,0.7
#1177-01 Phase 1 Site: Japan	Randomized, double-blind, placebo controlled PK, Safety, Tolerance	Healthy Adult Male only Placebo=4 **Study Drug = 16**	Ascending 0.05,0.1,0.3,0.5,
#489 Phase 1 Site: US	Multicenter (10), Randomized, double-blind, placebo controlled PK, Safety, Tolerance Special population (CNS path, Liver path, RI)	Patients with CNS Path = Patients with Liver Path = Patients with Renal Impairment = 14 Placebo=42 **Study Drug=121** Male & Female <18>2 years = 0	Ascending 0.1,0.3,0.5
#538 Phase 1 Site: US	Open-label, Multicenter (6) PK, Safety, Tolerance Special population (CNS path, Liver path, Renal Insuffiency) Normals	Adults only Normals = Patients with CNS Path = Patients with Liver Path = Patients with Renal Impairment = 22 **Study Drug = 54**	Single dose 0.1
#543 Phase 1 Site: US	Open-label, Single center PK, Safety, Tolerance Dialysis Clearance	Adults with ESRD on hemodialysis **Study Drug = 8** Male & Female	Single dose 0.1

~ Reviewer's comment: The phase 1 study/ies mentioned here have been reviewed and commented by this reviewer separately else where in this review. Also see pre-clinical studies section above.

~ The conclusions drawn from the pharmacokinetic studies are follows:

a) *In all groups, OptiMARK™ was observed to distribute rapidly into the extracellular fluid volume following an intravenous bolus dose.*
b) *The PK and elimination were not affected by gender, age or disease state (CNS or Liver).*
c) *OptiMARK™ was not metabolized (no detectable biotransformation or decomposition in the body) and was completely eliminated in the urine.*
d) *In normal subjects, the mean terminal elimination half-life was 1.73 hours (see table below).*
e) *The pharmacokinetics appears to be linear.*
f) *Renal Impairment decreases the rate of OptiMARK™ excretion.*
g) *Extracorporeal Hemodialysis efficiently removes OptiMARK™ from the circulation.*
h) *No age effects on kinetics or elimination were noted*
i) *No protein binding in vitro*
j) *Primarily renal excretion by glomerular filtration; apparent linear elimination kinetics over dose range studied*
k) *The tables below provide additional information on clinical pharmacology:*

SAFETY: CLINICAL PHARMACOLOGY:NDA # 20 937-OptiMARK™*	
mean distribution (mean ± SD)	*13.3 ± 6.8 minutes*
elimination half-life (mean ± SD)	*103.6 ± 19.5 minutes*
volume of distribution at steady state	*162 ± 25 mL/kg (normal subjects; equivalent to that of extracellular water)*
renal clearance rate	*69 ± 15.4 mL/hr/kg*
plasma clearance rate	*72 ± 16.3 mL/hr/kg*

SAFETY: CLINICAL PHARMACOLOGY:NDA # 20 937-OptiMARK™*		
Population	*Elimination Half-Life (hours)*	
	Men	*Women*
healthy volunteers	*1.73 ± 0.31*	*1.73 ± 0.40*
normal patients	*1.90 ± 0.50*	*1.88 ± 0.47*
renally impaired	*8.74 ± 5.14*	*6.91 ± 2.46*
hepatically impaired	*2.09 ± 0.03*	*2.35 ± 1.09*

**From "Table 2: Elimination Profiles ..." [p. 1.0208, Vol. 2.1]*

SUBJECT/PATIENT DISPOSITION, DEMOGRAPHICS:

- There was a total of 1684 patients/subjects enrolled in all studies of which 1309 were given OptiMARK™ (total of 1663 injections as 354 patients received two doses), 329 were given Magnevist®, and 46 received placebo.
- Of the total 1684 patients/subjects, 870 (52%) were men and 814 (48%) were women; 1718 (84.3%) were White, 183 (9%) were Black, 48 (2.4%) were Asian, and 89 (4.4%) were Others.
- In the OptiMARK™ group, 680 (52%) were men and 629 (48%) were women; the average age was 49.4 years [p. 26.0057, Vol. 2.147]. In the Magnevist® group, 165 (50%) were men and 164 (50%) were women; the average age was 51.4 years. In the placebo group, 25 (53%) were men and 21 (47%) were women; the average age was 44.4 years. Additional information is provided in the "Demographic Overview Table" below.

SAFETY: DEMOGRAPHIC OVERVIEW: OptiMARK™			
Parameter	OptiMARK™	Magnevist®	Placebo
Total Number (%)	1309 (~78%)	329 (~19%)	46 (~3%)
Mean Age (years)±SD [Range]	49.52 ± 14.95 [12 - 85]*	51.4 ± 14.8 [20 - 86]	44.4 ± 13.0 [21 - 73]
Sex: number (%)			
- Male	680 (52%)	165 (50%)	25 (54%)
- Female	629 (48%)	164 (50%)	21 (46%)
Race: number (%)			
- White	1102 (84%)	268 (81%)	41 (89%)
- Black	116 (9%)	35 (11%)	5 (11%)
- Asian	33 (3%)	11 (3%)	0 (0%)
- Others	58 (4%)	15 (5%)	0 (0%)
Mean Height(cm)±SD [Range]	170.3 ± 10.1 [120 - 208]	170.4 ± 10.3 [140 - 196]	171.9 ± 8.9 [156 - 190]
Mean Weight(kg)±SD [Range]	75.35 ± 16.28 [38 - 145]	76.6 ± 17.3 [42 - 141]	81.4 ± 19.6 [52 - 153]
Mean BSA (m^2) ±SD [Range]	1.88 ± 0.23 [1.22 - 2.68]	1.90 ± 0.3 [1.4 - 2.7]	2.0 ± 0.2 [1.5 - 2.7]

[Data from pp. 26.0058 - 26.0059, Vol. 2.147]

~ Reviewers' Note: According to the Sponsor, "The results of the analysis of the demographic data for homogeneity across the clinical program indicated that there were no dose or treatment effects for age, weight, height, body surface area (BSA), or race" [p. 26.0057, Vol. 2.147]

~ One pediatric patient (12 years old) was enrolled in the entire clinical drug development program [p. 26.0025, Vol. 2.147]*

~ Reviewers' Comment: On p. 1.0348, Vol. 2.2 (and in the proposed labeling section), the Sponsor states, "A total of 2038 subjects or patients were exposed to study drug or placebo ..." The actual breakdown is:

1309 OptiMARK™ (number of patients = 1309, number of exposures = 1663 because 354 patients received two doses-phase 2, #s-464, 465, 466, 467, 468, 469) → these are the critical numbers

329 Magnevist®

46 placebo

→ 1684 subjects participating in studies and 2038 is total number of exposures to any agent (i.e. Magnevist® + placebo + Magnevist®).

Further clarity is required in the labeling section to reflect these numbers appropriately.

- The table below summarizes the overall exposed patient disposition by treatment: (OptiMARK™, Magnevist® or Placebo)

SAFETY: OVERALL-EXPOSED/DISPOSITION/DOSE/AE: NDA # 20 937-OptiMARK™									
	OptiMARK™ mmol/Kg							Magnevist® mmol/kg	Placebo
	0.1	0.2	0.3	0.4	0.5	0.7	Combined	0.1	
Entered	986	214	229	24	263	0	1711	337	46
Dropped pre-dose	27	4	8	2	7	0	48	8	0
Exposed/Safety evaluation	959	210	221	22	256	4	1663*	329	46
Serious Adverse events	5	See Serious adverse events below and comments in individual trials					8	2	0
Deaths	1	0	0	0	0	0	1	0	0
Patients with one or more adverse events	281 (29.3%)	See Adverse events below and comments in individual trials					510 (30.7%)	114 (34.7%)	22 (47.8%)
Patients with no events	678 (70.7%)	No comments					1153 (69.3%)	215 (65.3%)	24 (52.2%)
Dropped post-dose	3	0	5	0	4	0	12	0	0
Dropped for Adverse Event	0	0	2	0	2	0	4	0	0
Actual subjects/patients							1309*	337	46

* See comments above

- The table below summarizes the information on demographics/enrollment/disposition by trials (phase studies).

~ Reviewer's comment: The table below does not include all the studies. These studies are included here for safety review only. As mentioned in the regulatory review, these studies are:

1. *The ones Sponsor is not pursing, however, has been included for safety*
2. *The liver studies have not been reviewed by this reviewer; these were reviewed in detail by another medical reviewer*

The rest of the studies have been reviewed by this reviewer, in which is contained information on enrollment/demographics, etc. These are else where in the review. Refer to the respective study reports for additional information.

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SAFETY: COMBINED PATIENT ENROLLMENT**/DISPOSITION BY PHASES: OptiMARK™							
		Treatment Group					
		OptimMARK™ (mmol/kg)					
Study/Trial number Phase/Area of Study Number of Patients		467 2/Liver	468 2/MRA	469 2/MSK	486/487 3/Liver	490 3/Liver	526 3/Liver
Entered/Enrolled		88	6	81	227	100	102
Exposed to drug		86	5	76	220	98	100
Completed study		85	5	68	220	98	100
Evaluable for Safety		86	5	76	220	99	100
Evaluable for Efficacy		85	0	68	0	99	100
Dropped pre-dosing		2	1	5	7	1	2
Dropped after first dose		1	0	6	0	0	0
Dropped for adverse event		0	0	2	0	0	0
Deaths		0	0	0	1	0	0
Serious adverse events		0	0	0	0	0	2
Demography							
Age (Years)	N	88	6	81	220	99	102
	mean	56.5	61.5	45.2	56.2	54.6	57.2
	range	31-80	48-71	19-84	21-85	18-80	23-86
Drug Volume							
Total Volume (ml)	N	85	5	68	220	98	102
	mean	74.1	62.7	93.4	22.6	15.4	15.1
	range	26.3-141.0	50.9-75.2	36.7-185.0	7.8-44.0	8.1-25.4	8.6-28.0

** This is not the complete listing. The reviewer has not incorporated those studies that have been reviewed elsewhere in this table. These listed here are the ones that either the Sponsor is not pursuing or that were assigned to another clinical reviewer. These have been included here for purposes of completeness.

DEATHS: [see appendix A page 219 for details]

There was one death (468A027) in a patient during the study period, who died ~ 72 hours after drug exposure (probably not attributable to OptiMARK™ ; + autopsy). There were deaths in seven others who had participated in one of these trials at some point, but outside the study period. These were:

486B004- died 29 days later; probably not attributable to OptiMARK™ (? autopsy)
486E016- died seven weeks later; probably not attributable to OptiMARK™ (+ autopsy)
487E020- died six months later; probably not attributable to OptiMARK™ (? autopsy)
487E023- died eight months later; probably not attributable to OptiMARK™ (? autopsy)
490C001- died one week later; probably not attributable to OptiMARK™ (? autopsy)
525E015- died 15 days later; probably not attributable to OptiMARK™ (no autopsy); but developed serious adverse event when alive and had intractable seizures (see report 525 for complete details)
526A026- died 19 days later; probably not attributable to OptiMARK™.
None of these deaths are attributable to OpitMARK™. If any, there may be associated morbidity with patient 525E015, in whom one cannot completely rule out the possibility if OptiMARK™ made the seizures worse.

SERIOUS ADVERSE EVENTS: [see corresponding study review sections for details]

8 patients experienced serious adverse events while enrolled in this clinical OptiMARK™ program. These were:

465B008- [see page 84]	Sponsor's impression: No relationship to OptiMARK™. Reviewer's impression: An ictal phenomenon with post-ictal Todd's paralysis cannot be ruled out.
464C015- [see page 75]	Sponsor's impression: due to underlying condition Reviewer's impression: Nausea and vomiting may have worsened due to OpitMARK™.
543A003- [see page 51]	Sponsor's impression: coincidental dizziness, palpitations, diaphoresis and dyspnea with arrhythmia Reviewer's impression: probably coincidental; but in this patient with ESRD, the association is still a possibility although 48 hours post exposure
538C010- [see page 41]	Sponsor's impression: not stated Reviewer's impression: Unlikely to be associated with OptiMARK™.
538G010- [see page 41]	Sponsor's impression: not stated Reviewer's impression: cannot rule out ictal phenomenon or TIA
489D012- [see page 65]	Sponsor's impression: not associated with OptiMARK™ Reviewer's impression: probably not associated
526E037-	Sponsor's impression: orthostatic hypotension 24 hours post secondary to GI bleeding Reviewer's impression: same as Sponsor's
526J001-	Sponsor's impression: coincidental Reviewer's comment: as Sponsors

DISCONTINUATION FOR ADVERSE EVENTS:

4 patients discontinued after exposure due to adverse events. These were:

464C001-	Sponsor's impression: seizures due to sub therapeutic anticonvulsant levels Reviewer's impression: OptiMARK™ could have also contributed to seizures
464C005-	Sponsor's impression: rash most likely due to OptiMARK™ Reviewer's impression: as Sponsor's
469G008-	Sponsor's impression: rash and hive probably drug related Reviewer's comments: as Sponsor's
469G012-	Sponsor's impression: hives and itching due to OptiMARK™ reviewer's impression: as Sponsor's.

DOSING INFORMATION:

REPEAT DOSING:

- **Not Evaluated by the Sponsor**

*~ Reviewer's comment: **Labeling** should appropriately reflect this (e.g. repeat dosing not evaluated/indicated)*

DRUG-DRUG INTERACTION:

- **Not studied by Sponsor**

*~ Reviewer's comment: **Labeling** should appropriately reflect this (e.g. drug-drug interaction not studied; therefore caution, etc; caution when allergic to other contrast agents, etc.)*

HISTORY OF ALLERGY:

- It is worthy to mention this observation made by the reviewer during the review (of the assigned indications and others for safety) process. It has been noted that in those patients who had a history of an allergic reaction to an iodinated agent or other iv contrast agent, there was a high incidence of an adverse event (any, including rash) when exposed to either OptiMARK™ or Magnevist®. These have been commented in the individual clinical trial reports.
- In particular, the following studies showed the extent of this correlation:

Study 489:	100% (that is all those patients who had a history of allergy to iodinated or like agents developed an adverse event)
Study 543:	50%
Study 538:	66.6%
Studies 484/485:	50%
Study 488:	40%
Study 464:	Not determinable (not submitted)
Study 465:	Not determinable (not submitted)

- This information on patients' allergy history was not obtained for studies 465 and 464. The reviewer has deferred to seek this information from the Sponsor at this time.
- In clinical practice (when indicated), it is customary to obtain a contrast enhanced MRI either when the contrast CT fails to provide the necessary information or when patients give a history of allergic reaction to iodinated agents (or shell fish, eggs, sea food, etc) or when CT is contraindicated. This particular group (although not large when compared to the general population) is definitely a targeted one. It is only safe to mention this as a warning or precaution.
- ***Labeling*** should appropriately indicate this, because although the total number is not large, there is a high degree of correlation and may be important when this particular population is considered.

CONCOMITANT MEDICATIONS:

- The Sponsor has not studied the effects of other drugs (drug to drug interaction).
- This reviewer notes, that there were a significant number of patients in this clinical program across the different clinical trials that were on steroids and/or anti-histamines during the study period (amongst other medications). These have been commented in the individual review sections. In particular, the patients enrolled in the CNS trials were on large doses at times. Their medical condition (tumors, post-surgical, post-radiation, post-chemo, etc.) dictated the need. As discussed in the efficacy section, this 'selective population' of patients also comprised a large part of the patients who were on steroids as concomitant medication.
- Steroids, by various known and unknown mechanisms, can alter the various pathological sequelae associated with many disease processes (e.g. edema, enhancement, etc.). This can result in changes in the images. Further comments are deferred on this issue in this section.
- Both steroids and antihistamines can mask (or decrease or curb) some of the symptoms and signs of drug reactions. In fact, it is a well known and an accepted practice in clinical medicine to administer these drugs to treat allergic reactions to drugs. The observed adverse reactions in this clinical program may therefore not reflect the true incidence or occurrence or severity of the event/s. These present projected values are probably lesser (in number and severity) than what might have been the actual occurrence.
- This observation is listed below:

Study	Patients (~% of exposed patients) on steroids or antihistamines or both
Study 464 Phase 2:	24%
Study 465 Phase 2:	22.72%
Study 525 Phase 3 pivotal:	20.6%
Study 538 Phase 1:	16.6%
Study 488 Phase 3 pivotal:	13.9%
Study 484/485 Phase 3:	11.11%
Study 489 Phase 1:	6.6%

- This observation is very critical in assessing the overall safety of OptiMARK™ especially in terms of incidence/occurrence/severity adverse events.

DRUG OVERDOSEAGE

- Sponsor's experience with overdosage may be limited with respect to the clinical consequences, as there have been no reported overdoses (p. 10215A, Vol. 2.1).
- Nonetheless, PK studies indicated that the drug is dialyzable, and that in vitro studies indicate no protein binding.