DIAGNOSIS/INCLUSION CRITERIA: (Vol. 2.97, pp. 17.0486-87)

- Males and females 18 years or older suspected of having brain pathology who have been referred for a contrast-enhanced MRI examination.

~ Reviewer's comments: There are several other inclusion and exclusion criteria that are mentioned in this study. Some are similar and common to other studies. Detailed comments have been made in other studies in this review regarding these issues.

DOSE/ROUTE: (Vol. 2.97, p. 17.0489)

- OptiMARK™ doses of 0.1, 0.3, and 0.5 mmol/kg administered intravenously.

~ Reviewer's comments: The rate of administration and the methods are similar to the other studies.

DURATION OF TREATMENT:

- Each patient received two doses separated by 1 to 7 days.

REFERENCE TREATMENT:

- No reference treatments were employed in this study.

CRITERIA FOR EVALUATION:

Efficacy:

- 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".

- All images were evaluated by the principal investigator and the three blinded readers reviewed images from 77 patients. Efficacy was assessed through pre- and post-contrast MR image sets obtained after injection of two different doses in each patient. The ability of post-contrast images to provide additional diagnostic information was assessed by:

a) Improvement in border visualization
b) In edematous tissue visualization
c) In confidence of diagnosis
d) Increased sensitivity and specificity.

~ Reviewer's comments: Only brief and abbreviated comments are made as detailed comments have been made for the pivotal Phase 3 CNS studies (488 and 525).

Safety:

- Safety was monitored with pre- and post-contrast vital signs, hematology, clinical chemistry, and urinalysis.
- Tolerance was assessed through the patient's grading of heat, cold, and/or occurrence of pain at the injection site.
- Adverse events were collected through 24 hours following each administration.

STATISTICAL METHODS:

"Continuous variables were summarized using number, mean , median, standard deviation, minimum, and maximum calculations. Categorical variables were summarized using number and percent calculations. Changes from baseline were analyzed using analysis of variance. Transitions were examined using the Stuart-Maxwell test. Refer to the Statistician review for additional details."

SUMMARY- CONCLUSIONS:

Efficacy Results:

- The following end points were assessed and analyzed and the observations are summarized as follows:

  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.
- Given the study design and objectives of this study, the impact and significance that the patients with 'known' pathology had on the end points is of a lesser concern (see

detailed comments in the pivotal phase 3 studies-and comments below regarding medical history).

- Medical History: (appendix 16.2.4-2, Vol. 2.1000)
  31/83 (37.34%) of the enrolled patients had a "therapeutic history" (surgery or biopsy or radiation or chemotherapy or a combination thereof preceding the study over a variable period of time). The reviewer has grouped these as post-treatment patients and extensive comments have been made in the pivotal phase 3 CNS studies (see report 488, 525 and efficacy summary). The concerns, comments and analysis of the data made in these phase 3 studies are applicable. Analysis of such depth has been deferred for the following reasons:
  1. This is not a phase 3 pivotal study
  2. Efficacy data analysis made by the Sponsor (see above) for the primary efficacy end points revealed that statistically significant observations were not seen in a majority of the endpoints except increased border visualization with increasing doses (the Sponsor again is seeking a dose of 0.1mmol/kg for approval), and increased sensitivity- these again were noted despite a *highly selective population.*

Safety Results:

PATIENTS: ENROLLMENT & DISPOSITION:

- See table below:

STUDY # 464:PHASE 2: PATIENT ENROLLMENT: OptiMARK™								
		Treatment Group -OptiMARK™ dose pair (mmol/kg)						
Number of patients		0.1/0.3	0.3/0.1	0.1/0.5	0.5/0.1	0.3/0.5	0.5/0.3	Combined
Entered		12	16	12	14	15	14	83
Exposed		12	16	12	14	15	14	83
Completed		11	14	11	14	15	14	83
Evaluated for Safety		12	16	12	14	15	13	78
Evaluated for Efficacy		11	14	14	14	15	14	83
Dropped pre-dosing		0	0	0	0	15	13	78
Dropped after first dose		1	2	1	0	0	0	0
Dropped for adverse event		0	1	0	0	0	1	5
Demographics								2
Age (years)	N	12	16	12	14	15	14	83
	mean	42.1	39.6	45.4	45.2	49.3	49.4	45.2
	range	20-82	19-65	26-70	23-83	22-69	20-82	19-83
Drug Volume								
Total volume (ml)	N	11	14	11	14	15	13	78
	mean	61.7	56.7	84.6	91.9	120.7	118.6	90.3
	range	43.6-78.5	28.4-74.5	57.8-132	68.2-18.9	91.9-180.4	87.2-160.0	28.4-180.4

- The following conclusions are drawn:

1. The Sponsor chosen parameters for designation as abnormals/extremes for PE, Vital signs, and Labs are similar to those as in other studies and are acceptable.
2. The number of events occurring during/between the two sessions of the study were about equal.
3. There is suggestion that the number and the severity of these adverse events were greater with increasing doses.

4. The statistically significant changes noted in some of the lab parameters (see overall safety review section) were not clinically significant.
5. The statistically significant changes noted in some of the vital sign parameters (see overall safety review section) were not clinically significant.
6. Headache (9.6%) and taste perversion (6.0%) was noted to be the most common among adverse events.
7. The other adverse events thought to be related to OptiMARK™ (by the principal investigators) were vasodilation, injection site reaction, nausea, parosmia, chest pain, dizziness, pruritus and rash.
8. Concomitant Medications: (Vol. 2.95, p. 17.0038)
   ~20/83 (~24%) patients in this study were either on steroids and or antihistamines as concomitant medications during the study period.
   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 and therefore its interpretation. Given that this is not a pivotal efficacy study, consideration has been given on the impact (if any) on efficacy aspects.
   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 overview safety section for additional comments.
9. History of Allergy:
   This information has not been provided in the application for this study. However, the comments, concerns and recommendations (*labeling*) that have been made else where and in the overall safety section are applicable. The reviewer will defer to request for this information from the Sponsor at this time.

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10. The adverse events/reactions are summarized in the table below:

SAFETY : STUDY # 464:PHASE 2:OptiMARK™			
ADVERSE EVENTS:			
PATEINTS (N) EXPOSED = 83 (two doses for each patient) **DEATHS (N) = 0** **PATIENT (N) WITH SERIOUS ADVERSE EVENTS = 1** **DROPPED (N) DUE TO ADVERSE EVENTS = 2**		**PATIENTS (N) WITH ADVERSE EVENTS = 23** **TOTAL (N) ADVERSE EVENTS = 40** **POST-DOSING NON-AE WITHDRAWAL = 0**	
Treatment Group	**OptiMARK™ (mmol/kg)**		
Dose	**0.1**	**0.3**	**0.5**
N (RECEIVED DOSE)	52	55	54
N (EXPERIENCED AE)	6 (11.5%)	14 (25.5%)	12 (22.2%)
N (ADVERSE EVENTS)	6	18	16
INTENSITY OF AE	+ Dose related increasing occurrence and severity		
MILD (N)	6	13	11
MODERATE (N)	0	5	5
SEVERE (N)	0	1	0
LABORATORY EVENTS:			
Parameters affected	See overview of safety		
Dose relationship	?		
Time relationship	?		
Clinically significant (symptomatic)	No		
Duration (how long)	Sponsor states transient		
Statistically significant	yes		
Resolution (time to return to baseline)			
VITAL SIGNS:			
Parameters affected	See overview of safety		
Dose related	?		
Clinically significant (symptomatic)	No		
Duration (how long lasted)	Transitory		
Resolution (time to return to baseline)	Not mentioned		
Statistically significant	yes		
EKG			
NOT PERFORMED FOR THIS STUDY			

SERIOUS ADVERSE EVENT:

- Patient 464-C-015 developed a serious (listed as serious in the integrated summary of safety – p. 26.0091, Vol. 2.147) adverse event. Sponsor has used the terminology of severe and serious interchangeably, in other studies. Additionally, and more importantly, the description (including typographical and reporting) is different for the same event in Vol. 2.95, p. 17.0050.

  This is one of the few instances in this application where there is:

  1. **Inconsistency/difference** between different sections in the information submitted on the same matter/s.
  2. Definition of serious and severe needs clarification.

These make interpretation difficult and at times even confusing that one rises questions on the validity of entire data that is presented in this application. Given that these stem from a single application and that the difference/s is attributable to a single issue, it is meaningless to believe one and ignore the other. Clarifications are further needed on these issues from the Sponsor. Determination on whether these constitute innocent editorial mistakes or over-looked modifications and manipulations, is something that the reviewer feels is outside the scope of this review. See also comments made on the same issues in other parts of the review and in the overall safety review.

- Description of the patient with the serious adverse event:

SAFETY STUDY # 464 - PHASE 2:OptiMARK™ SERIOUS ADVERSE EVENT (N = 1)	
Parameters	**Patient**
	464-C-015
History	34, M with 3-year hx of medulloblastoma, s/p debulking, chemo, XRT with worsening ataxia, headache, intermittent nausea and hydrocepahlus (not clear if hydrocephalus was pre-existing)
Dose received	0.3mmol/kg
Immediate Events	None
Onset of symptoms	~ 3 hours post drug exposure
Presenting symptoms	Moderate nausea and vomiting
When evaluated	Next day as onset-1 day post-drug exposure
Findings	Suspicion of medulloblastoma recurrence with hydrocephalus Continued nausea and vomiting
Actions, treatment, investigations, disposition	Admission for shunt placement ~ 1 day post exposure Received second OptiMark™ dose (0.1mmol/kg) ~ 48 hours after the first dose Underwent shunt procedure ~36 hours after first dose and ~ 24 hours after second dose Discharged post surgery 7 days later
Resolution of symptoms/Outcome	Improved-cleared Discharged
Reviewer's Comments: Cannot fully exclude drug association, although there were a few symptoms to suggest increased intracranial pressure/hydrocephalus secondary to tumor. Listed description of other symptoms & signs is not pathognomonic to hydrocephalus. Exposure may have triggered these events. Onset of events or worsening occurred within three hours of exposure. Therefore one cannot attribute the events solely to the underlying pathology. Whether the drug makes pre-existing conditions worse is another strong possibility.	

DISCONTINUATION:

- 2 patients described below discontinued due to adverse events:

SAFETY:STUDY # 464 - PHASE 2:OptiMARK™		
ADVERSE EVENT=DISCONTINUATION (N=2)		
	Patients	
Parameters	464-C-001	464-C-005
History	37, F with meningioma and seizure disoreder (type) on Dilantin and Neurontin	34, M with L temporal lobe tumor
Dose received	0.3mmol/kg	0.5mmol/kg
Immediate Events	None	Moderate cold discomfort
Onset of symptoms	Not mentioned (when prior to second dose?)	5 hours post-dosing
Presenting symptoms	Seizure disorder (type?; any different from usual seizures?)	Whole body rash and itching
When evaluated	Prior to second dose (when?)	Same time as AE
Findings	None mentioned	Generalized whole body rash (type?) with priritus that lasted 48 hours
Actions, treatment, investigations, disposition	Termination from study participation Presumed due to sub-therapeutic Dilantin levels	IV/PO Diphenhydramine Termination from study participation Presumed drug reaction
Resolution of symptoms	None mentioned	Yes, 48 hours with treatment
Reviewer's Comments:	The description provided (Vol. 2.147, p.26.0094) is lacking the details with respect to the timings of onset, termination of symptoms, etc. Sub-therapeutic dilantin levels may have been coincidental. Drug association might still exist*.	Rash is very poorly described Agree that this is most suggestive of a drug reaction**and attributable to the study drug

**Reviewer's comment: Some gadolinium agents can increase the risk of seizures in patients who are pre-disposed or known to have seizures. Labeling reflects this in some of the already approved agent/s (Magnevist®). See overall safety review for further comments.*

*** Labeling should reflect these concerns (seizures and rash)*

FINAL CONCLUSIONS

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 the study 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 be 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, this study was 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 for the Sponsor in that the study 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.
9. There were no deaths
   One patient had a serious adverse event in whom the possibility that OptiMARK™ could have worsened a pre-existing condition (nausea and vomiting in a patient with a brain stem tumor) cannot be fully ruled out as the symptom onset was sudden and within three hours post-dosing.
   There were two patients in this study who discontinued due to an adverse event: one patient experienced increasing seizures and the second patient developed whole body itchy rash. The latter is unequivocally drug related. In the former, the possibility that OptiMARK™ could have made the pre-existing seizures worse cannot be ruled out.
10. The concern of the EKG methodology, readings, etc are less of a concern in this study because there were no EKGs performed on any of the patients- which is a bigger concern.
11. There were ~ 24% of patients on steroids and or antihistamines as concomitant medications during the study. Therefore the observed adverse events (in terms of number and severity) could potentially be more.
12. There were transient lab and vital sign changes that were not clinically significant. These have been commented in the safety overview.
13. The minor lab deficiencies noted in the phase one studies were also noted here (urinalysis, etc).
14. Regulatory concerns regarding serious adverse event description that are typograghically different and descriptively different between the study volumes and the integrated summary volumes is noted. Additionally, incompleteness by not providing history of allergy in the medical history section is noted.

END OF STUDY REPORT 464

NDA # 20 937 **OptiMARK™** **Report # 465 /Phase 2**
IND# **Protocol # 1101-03**

- 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: 2.102-2.109

The comments on efficacy and safety for this non-pivotal phase 2 study/report is abbreviated (detailed comments have been made in pivotal phase 3 sections – study reports #488 and 525). Detailed comments on safety have been made in the over-all safety review section.

OVERVIEW: 465- PHASE 2 STUDY: OptiMARK™ : NDA # 20937					
Phase Start * End @	**Study # Protocol #**	**Title**	**Study Design**	**Objective**	**Population Exposed (N)=89**
2 01/18/94 03/13/95	465 1101-03	"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"	Double-blind, Randomized, Multi-center, Pseudo-crossover (1-7 days between first and second dose)	Safety, Tolerance, Efficacy + Imaging	Adults with known or suspected Spine pathology
Centers = 7 US = 4 Outside US = 3					

TITLE:

- 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".

STUDY PERIOD:

- First patient dosed January 18, 1994. Last patient dosed March 13, 1995.

OBJECTIVES: (Vol. 2.103, p. 18.0405)

- The main objectives of this study was:
  "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)".

METHODLOGY: (Vol. 2.103, p. 18.0406)

- This was a multicenter, double-blind, multidose within-patient clinical trial.
- 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.
- Safety evaluations included changes in laboratory parameters, vital signs and the incidence of adverse events.
- 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.
  6. Sensitivity, specificity, and agreement/disagreement of MRI diagnosis versus final diagnosis.

- Safety data were collected as indicated in the time events table below (these were identical to the phase 2 study 464):

SAFETY: TIMINGS OF EVENTS: PHASE 2: STUDY 465 – OptiMARK™							
Times	Pre-Dose	0 to < 2 hrs	2 hrs to < 4 hrs	4 hrs to 8 hrs	24 hrs to 48 hrs	72 hrs	>72hrs
LABS	X				X		
EKG	NONE						
PE	NONE						
VITALS	X	X	. X		X		

- The comments on values to designate the normal ranges and the abnormal ranges for these parameters have been made in the over-all safety review and in the pivotal phase 3 CNS reviews. The Sponsor set criteria to designate extreme values and significant changes etc. for vitals, labs, physical exam, adverse events are similar to the other studies. Refer to comments made in the overall safety section. The case report forms are noted.

DIAGNOSIS/INCLUSION CRITERIA: (Vol. 2.103, p. 18.0406)

- Males and females 18 years or older suspected of having spine pathology and/or structural abnormalities who were referred for a contrast-enhanced MRI.

~ Reviewer's comments: There are several other inclusion and exclusion criteria that are mentioned in this study. Some are similar and common to other studies. Detailed comments have been made in other studies in this review regarding these issues.

DOSE/ROUTE: (Vol. 2.102, p. 18.0018)

- OptiMARK™ doses of 0.1, 0.3, 0.5 mmol/kg administered intravenously.

DURATION OF TREATMENT:

- Patients received two different doses of OptiMARK™ separated by 1 to 7 days.

REFERENCE TREATMENT:

- No reference treatments were employed in this study.

CRITERIA FOR EVALUATION:

Efficacy:

- All images were evaluated by the principal investigator and images from 83 patients were reviewed by 3 blinded readers.

- Efficacy was assessed through pre- and post-contrast MR image sets obtained after injection of two different doses of OptiMARK™ in each patient. Each patient had two sets of images.
- The ability of post-contrast images to provide additional diagnostic information was assessed by improvement in border visualization, in edematous tissue visualization, in confidence of diagnosis, increased sensitivity and specificity.

Safety:

- Safety was monitored in terms of pre- and post-contrast vital signs, hematology, clinical chemistry, and urinalysis.
- Tolerance was assessed through the patient's grading of heat, cold, and/or occurrence of pain at the injection site.
- Adverse events were collected through 24 hours following each drug administration.
- See table of time events and enrolment above.

STATISTICAL METHODS:

- "Continuous variables were summarized using number, mean, median, standard deviation, minimum, and maximum calculations. Categorical variables were summarized using number and percent calculations. Changes from baseline were analyzed using repeated measure analysis of variance. Transitions were examined using the McNemar or Stuart-Maxwell test".

~ *Refer to Statistician's comments.*

SUMMARY-CONCLUSIONS:

Efficacy Results:

- The following end points were assessed and analyzed and the observations are summarized as follows:

  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 slightly 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.

- Medical History: (See appendix in the study volumes mentioned above)
  Concerns regarding patient enrichment ('post-treatment' patients) noted in studies 464, 525 and 488 and the effect that such post-treatment patients had on the efficacy data has been completely analyzed and commented in the pivotal studies and in the overall efficacy section. It is noted in this study that:
  31/88 **(35.2%)** of the enrolled patients had a "therapeutic history" (surgery or biopsy or radiation or chemotherapy or a combination thereof preceding the study over a variable period of time). Analysis of such depth has been deferred for the following reasons:
  1. This study is not a pivotal study.
  2. Efficacy data analyses made by the Sponsor (see above) for the primary efficacy end points revealed that statistically significant observations were not seen in a majority of the endpoints except in the sensitivity and specificity (see above)- despite involvement with a *highly selective population*.

SAFETY:

PATIENTS: ENROLLMENT & DISPOSITION: (Vol. 2.102, p. 18.0033)

- See table below:

SAFETY: STUDY # 465:PHASE 2: PATIENT ENROLLMENT/DISPOSITION/: OptiMARK™

		Treatment Group						
		OptiMARK™ dose pair (mmol/kg)						
Number of patients		0.1/0.3	0.3/0.1	0.1/0.5	0.5/0.1	0.3/0.5	0.5/0.3	Combined
Entered		18	19	13	14	13	15	92
Exposed		18	15	13	14	13	15	88
Completed		17	15	13	14	12	15	86
Evaluated for Safety		18	15	13	14	13	15	88
Evaluated for Efficacy		17	15	13	14	12	15	86
Dropped pre-dosing		0	4	0	0	0	0	4
Dropped after first dose		1	0	0	0	1	0	2
Dropped for adverse event		0	0	0	0	0	0	0
Demography								
Age (Years)	N	18	19	13	14	13	15	92
	mean	47.6	50.9	43.2	40.3	47.6	45.7	46.2
	range	26-73	18-74	19-68	18-59	37-74	20-81	18-81
Drug Volume								
Total volume (ml)	N	17	15	13	14	12	15	86
	mean	61.5	67.0	88.7	88.0	119.5	109.0	87.3
	range	28.3-106	42.4-98.8	65.4-141.1	57.5-136.0	71.4-49.1	87.2-128.0	28.3-149.1

- General comments/concerns:

1. The Sponsor chosen parameters for designation as abnormals/extremes for PE, Vital signs, and Labs are similar to those as in other studies and are acceptable.
2. The number of events occurring during/between the two sessions of the study were 27 events in 17 patients during the first scanning session, and 20 events in 16 patients during the second scanning event.

3. There is suggestion that the number and the severity of these adverse events were greater with increasing doses (similar to study 464-phase2).
4. The statistically significant changes noted in some of the lab parameters (see overall safety review section) were not clinically significant (similar to study 464-phase2).
5. The statistically significant changes noted in some of the vital sign parameters (see overall safety review section) were not clinically significant (similar to study 464-phase2).
6. Headache (6.5%) and taste perversion (6.5%) was noted to be the most common among adverse events. The other adverse events thought to be related to OptiMARK™ (by the principal investigators) were vasodilation, injection site reaction, nausea, taste perversion, dry mouth, palpitations, parosmia, dizziness, and rash.
7. Medical History: Concomitant Medications: (Vol. 2.95, p. 17.0038)
   - It is noted in this study that ~20/88(~22.72%) of the patients were either on steroids on antihistamines as concomitant medications during the study period.
   - 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 and therefore its interpretation. Given that this is not a pivotal efficacy study, consideration has been given on the impact (if any) on efficacy aspects.
   - 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 overview safety section for additional comments.
8. History of Allergy:
   - This information has not been provided in the application for this study. However, the comments, concerns and recommendations (*labeling*) that have been made else where and in the overall safety section are applicable. The reviewer will defer to request for this information from the Sponsor at this time.

APPEARS THIS WAY
ON ORIGINAL

9. The adverse events are summarized in the table below:

SAFETY : STUDY # 465: PHASE 2:OptiMARK™			
ADVERSE EVENTS:			
PATEINTS (N) EXPOSED = 88 (two doses for each patient) DEATHS (N) = 0 PATIENT (N) WITH SERIOUS ADVERSE EVENTS = 1 DROPPED (N) DUE TO ADVERSE EVENTS = 0		PATIENTS (N) WITH ADVERSE EVENTS = 23 TOTAL (N) ADVERSE EVENTS = 47 POST-DOSING NON-AE WITHDRAWAL = 3	
Treatment Group	OptiMARK™ (mmol/kg)		
Dose	0.1	0.3	0.5
N (RECEIVED DOSE)	60	61	54
N (EXPERIENCED AE)	7 (11.7%)	14 (23.0%)	12 (22.2%)
N (ADVERSE EVENTS)	9	22	16
INTENSITY OF AE	+ Dose related increasing occurrence and severity		
MILD (N)	6	15	14
MODERATE (N)	3	5	1
SEVERE (N)	0	2	1
LABORATORY EVENTS:			
Parameters affected	(see overall safety review section)		
Dose relationship	Probably not		
Time relationship	None mentioned		
Clinically significant (symptomatic)	No		
Duration (how long lasted)	None mentioned		
Statistically significant	yes		
Resolution (time to return to baseline)			
VITAL SIGNS:			
Parameters affected	See overall safety review section		
Dose related	Probably not		
Clinically significant (symptomatic)	No		
Duration (how long lasted)	Transitory		
Resolution (time to return to baseline)	None mentioned		
Statistically significant	yes		
EKG			
NOT PERFORMED FOR THIS STUDY			

SERIOUS ADVERSE EVENT:

- Patient 465-B-008 developed a serious (listed as serious in the integrated summary of safety – p. 26.0091, Vol. 2.147) adverse event. Sponsor has used the terminology of severe and serious interchangeably, in other studies. Additionally, and more importantly, the description (including typographical and reporting) is different for the same event in the study volumes in different sections (between the actual study volumes and the ISS volumes). This is one of the few instances in this application where there is:
  1. Inconsistency/difference between different sections in the information submitted on the same matter/s.
  2. Definition of serious and severe needs clarification.

  These make interpretation difficult and at times even confusing that one rises questions on the validity of entire data that is presented in this application. Given that

these stem from a single application and that the difference/s is attributable to a single issue, it is meaningless to believe one and ignore the other. Clarifications are further needed on these issues from the Sponsor. Determination on whether these constitute innocent editorial mistakes or over-looked modifications and manipulations, is something that the reviewer feels is outside the scope of this review. See also comments made on the same issues in other parts of the review and in the overall safety review.

- Description of the patient with the serious adverse event:

SAFETY STUDY # 465 - PHASE 2:OptiMARK™ SERIOUS ADVERSE EVENT* (N=1)	
Parameters	**Patient**
	465-B-008
History	20 year, M, hx of progressive loss of strength and sensation in the R shoulder to finger tips (?duration)
Dose received	0.3mmol/kg followed 24 hours later by 0.5mmol/kg
Immediate Events	None reported
Onset of symptoms	~ 10 hours post second dose exposure (~34 hours from first)
Presenting symptoms	Sudden headache, severe burning pain from head to toe
When evaluated	Same day as symptoms
Findings	Suspicion of seizure ?exam findings (none listed)
Actions, treatment, investigations, disposition	Admission Head CT (? Contrast)-reported normal Lumbar puncture-reported normal Discharged 2 days later Re-admitted the next day (~3 days from second dose) for headache (?exam, ?findings, ?disposition) Re-evaluation ~8 days from second dose-full strength in arm, same sensory loss as initial exam
Resolution of symptoms/Outcome	Improved motor deficits, continued sensory loss, presume not related to the drug
Reviewer's Comments: Cannot exclude drug association. Exposure may have triggered these events. Onset of events or worsening occurred within ten hours of exposure to a total dose of 0.8mmol/kg. There are no other pre-existing attributable condition/s mentioned. Therefore, one cannot rule out the possibility if this indeed was an ictal phenomenon and the continued sensory loss seen ~8 days later is/was a Todd's phenomenon (seen post-ictally). Whether the drug makes pre-existing (not mentioned) conditions worse is another possibility. The work- up should have included amongst others an EEG.	

**Reviewer's comment: Some gadolinium agents can increase the risk of seizures in patients who are pre-disposed or known to have seizures. The possibility of non-convulsive status or other seizure phenomenon cannot be fully ruled out in this case. See overall safety review for further comments. Labeling should reflect these concerns (risk for seizures)*

POST DOSING WITHDRAWAL OR DROPOUTS PRESUMED NOT DUE TO AE:

- There were three patients in this study who received the drug, but later were withdrawn from further continuation not due to adverse reactions/events. These were:

1. 465-B-003: Received 0.3mmol/kg dose
   Developed uncontrollable spasms prior to MRI, thought to be secondary to underlying disease (timing onset not mentioned, but should probably be minutes from dosing as patient was waiting for scanning after the dosing)

Cannot exclude possibility of drug association. Were these spasms? Were these seizures? In any event, exacerbation and worsening of underlying disease due to the drug is a possibility.

2. 465-C-010: Received 0.1mmol/kg dose
   Too ill to continue, presumed due to underlying condition.

What was the illness? Did this underlying illness worsen so rapidly following drug administration (most scans were done within minutes after dosing)? If the patient was so ill to begin with, why enroll and expose such a patient to a 'study with an investigational' drug?

3. 465-E-001: Received 0.3mmol/kg dose
   Withdrew consent (reasons?)

FINAL CONCLUSIONS

1. Several observations were similar as noted in study 464 for efficacy and safety.
2. The adverse event/reaction profile was also similar on several aspects-intensity, number, systems affected, dose relationship, vital sign changes, lab changes. ~22.72% of the exposed patients were on steroids/antihistamines in this study. This needs to be factored in the equation in the interpretation of the noted adverse reactions.
3. There were no deaths. One patient developed a serious adverse event in whom a seizure with a post-ictal Todd's phenomenon cannot be ruled out. There were three drop outs post-dosing, in whom data is inadequate to fully rule out (or rule in) drug association.
4. EKGs were not performed at all on any of the 88 exposed patients.
5. Minor lab deficiencies as noted in the phase one studies and study 464, are observed in this study.
6. Efficacy data did not show a significant difference between the pre and the post contrast on several of the efficacy end points according to the Sponsor. Detailed comments on these (as made for the pivotal studies 488 and 525) have been deferred (also by the FDA statistician). Additionally, ~35.2% of the enrolled patients were 'post treatment' patients.
7. Regulatory concerns comprised issues as noted in study 464- incomplete medical history (history of allergies) and data (missing patient information in line listings), typographical and reporting differences between two sections of the application on the patients (serious adverse reactions), inadequate information (patients who were dropped post-dosing).

END OF STUDY REPORT 465

NDA # 20 937 **OptiMARK™** **Report # 484 & 485/Phase 3: Open-Label**
IND# **Protocol # 1177-95-02.01**

- 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: 2.110-2.117

Regulatory note:

These studies were terminated prior to completion in order to incorporate FDA suggested study design modifications, including a comparator group (i.e., Magnevist®) and overall analysis plan to demonstrate equivalence to the approved comparator. Therefore, these studies were not statistically evaluated for efficacy. See regulatory history for additional comments.

Studies 484 and 485 followed the same clinical trial protocol, only the study number was different. Therefore, the data generated during the studies were combined and the report was written as one report.

These studies are non-pivotal and the comments are brief. Comments made in the pivotal phase three studies 488, 525, and in the overall safety review are applicable.

OVERVIEW: 484 & 485 PHASE 3 OPEN-LABEL STUDIES: OptiMARK™ : NDA # 20937					
Phase Start End	**Study # Protocol #**	**Title**	**Study Design**	**Objective**	**Population Exposed (N=15+39=54)**
3 Sep 29, 1995 Feb 23 1996	484 & 485 1177-95-02.01	"A Multicenter, Open-label Study to evaluate theSafety, Tolerability, and Efficacy of OptiMARK™ (Gadoversetamide Injection) in MRI of the Central Nervous System"	Open-label, Single-dose, Multi-center	Safety, Tolerance, Efficacy + Imaging*- but no data	>2 years with known or suspected lesions of brain or spine (none enrolled less than 18 years of age.
Centers Total = 15 US centers = 12 (7 without patients) Outside US = 3 (2 without patients)					

*** These studies were terminated and were not analyzed for efficacy by the Sponsor. There is no efficacy data in this application for these studies.**

TITLE:

- "A Multi-center, Open-Label Study to Evaluate the Safety, Tolerability, and Efficacy of OptiMARK™ (Gadoversetamide Injection) in MRI of the Central Nervous System"

STUDY PERIOD:

- First patient dosed September 29, 1995. Last patient dosed February 23, 1996.

OBJECTIVES: (Vol. 2.111, p.19.0360)

- The objective of this study was to evaluate the safety, tolerability, and efficacy of intravenously administered OptiMARK™ as an MRI contrast agent in patients with known or highly suspected CNS pathology including brain and associated structures as well as spine and associated tissue abnormalities. Specifically, the objectives were:

  To determine the **safety** profile of OptiMARK™ utilizing a dose of 0.1 mmol/kg or 0.3 mmol/kg. Safety was assessed in a broad patient population in terms of clinical signs and symptoms including physical examinations, monitoring of vital signs and electrocardiograms, incidence and nature of adverse events, and clinical laboratory measurement.

  To determine the **tolerability** of OptiMARK™ by evaluating the incidence of heat, cold and pain at the injection site during and immediately following intravenous administration.

  To determine the **efficacy** profiles of OptiMARK™ in patients undergoing MR imaging of the CNS. Specifically, unenhanced dual echo images (T1-weighted, T2-weighted, and proton density) were evaluated for detection/classification of CNS pathology and compared to enhanced T1-weighted images for each patient. Final clinical diagnosis was used to determine sensitivity and specificity, pre- and post-contrast enhancement.

METHODLOGY/STUDY DESIGN: (Vol.2.111, p.19.0360)

- These studies were multicentered, open-labeled clinical trials to determine the safety, tolerability, and efficacy of intravenously administered OptiMARK in patients, 2 years of age or older, with known or suspected pathology of the brain or spine.
- The results of the contrast-enhanced MRI were compared to the results of the unenhanced MRI. Two masked readers independently assessed the unenhanced and contrast-enhanced MRI examinations and determined agreement with the site final diagnosis.
- The principal efficacy endpoints were:
  1. The proportion of patients for whom contrast-enhanced MRI provided additional diagnostic information.
  2. Changes in degree of confidence that lesion/pathology exist.

3. Changes in degree of confidence in the overall diagnosis.
4. The proportion of patients for whom the final clinical diagnosis agrees with the pre-contrast and the post-contrast diagnosis, according to both the blinded readers and the principal investigator.

- Safety evaluations included changes in physical examination, laboratory parameters, electrocardiograms and vital signs, and incidence of adverse events.
- Tolerability was assessed by the incidence of sensations/discomfort experienced by the patient at the injection site.

DIAGNOSIS/INCLUSION CRITERIA: (Vol.2.111, p.19.0361)

- Males and females
  2 years or older, suspected of having CNS pathology, for which a contrast-enhanced MRI evaluation was considered to be diagnostic tool.

DOSE/ROUTE: (Vol. 2.110, p.19.0018)

- OptiMARK doses of 0.1 or 0.3 mmol/kg administered intravenously.

REFERENCE TREATMENT:

- No reference treatments were employed in this study.

CRITERIA FOR EVALUATION:

Safety:

- Safety was monitored in terms of pre- and post-contrast physical examinations, vital signs, electrocardiograms (ECGs), and laboratory parameter changes (see table below).
- Adverse events were collected through 72 hours following each drug administration.
- Tolerance was determined through the patient's assessment of heat, cold, and/or occurrence of pain at the injection site.

SAFETY*: 484 & 485 Phase 3 – Open-Label Studies Timing of Safety Parameters: OptiMARK™ NDA # 20937							
Study Number	Pre-Dose	0 to < 2 hrs	2 hrs to < 4 hrs	4 hrs to 8 hrs	24 hrs to 48 hrs	72 hrs	>72hrs
Laboratory Safety Testing							
484	X		X		X	X	
485	X		X		X	X	
Vital Signs							
484	X	X	X		X		
485	X	X	X		X		
Electrocardiograms							
484	X				X		
485	X				X		
Physical Examinations							
484	X				X		
485	X				X		

Reviewer's Note: The CRFs pertaining to efficacy and safety have been noted (Vol. 2.114, pp. 19.1744-19.1827).

STATISTICAL METHODS:

- "Continuous variables were summarized using number, mean, standard deviation, minimum, and maximum calculations. Categorical variables were summarized using number and percent calculations. Changes from baseline were analyzed using analysis of variance".

SUMMARY:

Efficacy Results:

- **Terminated prior to completion. Data not submitted for evaluation/review efficacy.**
- Although not applicable it is worth while mentioning the following:
  Medical History: (Vol. 2.117)
  ~ 21/54 (38.8%) of the enrolled patients under these two studies, had a "therapeutic history" (surgery or biopsy or radiation or chemotherapy or a combination thereof preceding the study over a variable period of time). The reviewer has grouped these as post-treatment patients and extensive comments have been made in the pivotal phase 3 CNS studies (see report 488 and 525). The concerns, comments and analysis of the data made in these phase 3 studies are not directly applicable for these studies. Analysis has been deferred for the following reasons:
  1. This is not a phase 3 pivotal study
  2. Efficacy data analysis has not been provided by the Sponsor and the Sponsor is not pursuing this claim for these studies.

SAFETY RESULTS:

PATIENTS: ENROLLMENT & DISPOSITION: (Vol. 2.110, p.19.0032)

- See table below:

SAFETY: 484/485:PHASE 3 –OPEN LABEL: OptiMARK™ NDA # 20937 PATIENT ENROLLMENT/DISPOSITION				
		Treatment Group		
		OptiMARK™ dose pair (mmol/kg)		
Number of patients		**0.1**	**0.3**	**Combined**
Entered		50	5	55
Exposed		49	5	54
Completed		48	5	53
Evaluated for Safety		**49**	**5**	**54**
Evaluated for Efficacy		0	0	0
Dropped pre-dosing		1	0	1
Dropped postdosing (non-AE)		1	0	1
Serious AE		0	0	0
Dropped for adverse event		0	0	0
Demography				
Age (Years)	N	49	5	54
	mean	46.4	61.2	47.8
	range	20-76	49-71	20-76
Drug volume				
Total volume (ml)	N	49	5	54
	mean	14.8	53.1	18.4
	range	9.5-20.6	49.8-56.0	9.5-56.0

General safety comments/concerns

1. The Sponsor has used similar parameters to define values as extreme or of clinical significance, for: Vital signs, Physical Examination, EKGs, and Labs, as in most of the other trials in this application; commendable for uniformity. Comments have been made in the overall safety review section. The case report forms have been noted (Vol. 2.114, pp. 19.1744-19.1827). These are acceptable, except for EKGs.
2. Medical History:

a) History of hemoglobinopathies is an exclusion criterion and has been listed among the warnings in the proposed labeling. Besides medical history, the reviewers have not been able to determine how this diagnosis was made and there are no special tests (e.g., sickle cell screening, hemoglobin electrophoresis) that the Sponsor has provided in this study. Several of the hemoglobinopathies may be asymptomatic (mild) so the patients may not be aware of the condition.

b) History of Allergy:
It is noted in this study (484), that there were 2 patients who had a history of allergy to iodine or other contrast agents (amongst other allergies) and one of them experienced an adverse event during the study on exposure to OptiMARK™ (1/2=50%).
As discussed in other studies and in the overall safety section, 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...etc). See comments in the overall safety section.

c) Concomitant Medications: (Vol. 2.117)

- ~6/54 (~**11.11%**) of the patients in this study were either on steroids and or antihistamines as concomitant medications during the study period.
- 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 and therefore its interpretation. This concern is not applicable since no efficacy data is being analyzed.
- 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.

3. Vital signs did not include temperature recording. It is not clear if there was any monitoring (EKG or Vitals) during the drug injection/dosing.
4. Labs: (see Appendix for "Clinical Laboratory Extreme Values and in the CRF's for "Out-Of-Range Laboratory Instructions")

a) Urinalysis (microscopy) does not specify whether the analysis performed was on a centrifuged specimen.
In the urinalysis, the Sponsor allows for >10WBC/HPF and for >100RBC/HPF as extreme values without specifying the sex of the patient, both of these values are clearly abnormal in men and in certain women.
The Sponsor considers a positive urobilinogen in the urinalysis as an extreme value; but traces of urobilinogen can be excreted in urine in normal people.

5. EKG:
   a) As indicated in the overview of safety, the qualifications and background of the EKG readers is being verified. The Sponsor indicated that the majority of the EKGs were read by the site principal investigator/s. It was noted in the pivotal Phase 3 study (#488) and others, that all the site principal investigators had either a radiology and or a 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).
   d) The Sponsor chosen parameters (see above) are too wide for the PR and QRS complexes (QT intervals were not measured at all-see below).
   e) QT or QTc intervals were not measured in all of the patients (100% without QT measurements). QT interval measurements are probably the most important and clinically useful measure when one is evaluating the effects of drugs on the heart. To exclude this is meaningless and makes the entire EKG readings futile and non-informative. The importance of the lack of its recording is highlighted by the following: 1) there were EKG changes (including symptomatic) seen in the phase

1 trials, 2) there were no EKGs at all (not even partial readings) in the majority of the phase 2 trials. If anything, more importance should have been placed on securing these. The selected patient population (complicated case on multiple medications, etc.) by itself called for such precautions.

f) There were no EKG changes that were reported to have changes from baseline or that were clinically significant according to the Sponsor- this has absolutely no clinical significance.

7. Other safety comments:

- Adverse Events/Reactions:

a) There were no deaths; or serious adverse event, or dropped patients due to adverse reactions.

b) The number of patients reporting adverse events were 17/54 (31.84%).

c) The majority of adverse events in the Optimark™ group were in the mild category.

d) Headache was the most common adverse event occurring in 13.0% of cases, followed by taste perversion (5.6%).

e) The incidence and the severity of these adverse events were more with the 0.3 mmol/kg dose compared to the 0.1mmol/kg dose, suggesting a dose-related effect.

f) There were no clinically interpretable trends observed in labs, physical exams that could be attributable to OptiMark™.

g) There were 13 patients with 20 significant changes in vitals (see overall safety review section).

h) Hematology and lab abnormalities were noted that were transient and statistically significant (see overall safety review section).

i) The table below summarizes some of these observations:

SAFETY: STUDY 484 & 485: PHASE 3:OPEN-LABEL:OptiMARK™ NDA # 20937			
ADVERSE EVENTS:			
PATEINTS (N) EXPOSED = 54 DEATHS (N) = 0 PATIENT (N) WITH SERIOUS ADVERSE EVENTS = 0 DROPPED (N) DUE TO ADVERSE EVENTS = 0			PATIENTS (N) WITH ADVERSE EVENTS = 17 (31.48%) TOTAL (N) ADVERSE EVENTS = 19 POST-DOSING NON-AE WITHDRAWAL = 1
Treatment Group	OptiMARK™ (mmol/kg)		
Dose	0.1	0.3	
N (RECEIVED DOSE)	49	5	Comments
N (PATIENTS WITH AE)	14 (28.6%)	3 (60.6%)	• Most frequent: headaches (13.0%); taste perversion (5.6%)
N (ADVERSE EVENTS)	16	3	• All resolved by the end of the study
INTENSITY OF AE			• Others : nausea, dizziness
MILD (N)	12	0	
MODERATE (N)	4	2	
SEVERE (N)	0	1	
EKG & PE			
No clinically significant changes			
VITAL SIGNS			
13 patients with 20 clinically significant changes			
LABORATORY EVENTS			
	Statistically significant	Clinically significant	
Parameters affected	Hematology (6), Chemistry (11)	Iron saturation, LDH, Calcium	
Dose related	Probably not	Probably not	
Time related	See overall safety review section	See overall safety review section	
Resolution time	None mentioned	None mentioned	

FINAL CONCLUSIONS:

1. These studies were completely futile (from the Sponsor's point of view) for efficacy. Exceptionally valuable information could have potentially stemmed from these studies with a different design. Further analysis should have been carried out given that the phase 2 studies did not provide adequate data for a large part. The efficacy data thus far has not evolved in providing the anticipated results.
2. The dose related trends of adverse events were noted.
3. Minor lab abnormalities and vital sign changes were noted. There were no deaths or serious adverse events.
4. EKG concerns prevail in particular, the entire EKG information is futile because there were no QT measurements in all the enrolled patients – a big deficiency and over-sightedness. Various other entities in this clinical program has generated information (PK studies, dosing information, renal studies, etc.) that is helping the clinical program overall, but the foundation as for EKG data and information is concerned is still not stable and has not evolved to the expected level of providing adequate safety information.

END OF STUDY REPORT 484 & 485

NDA # 20 937 **OptiMARK™** **Report # 488 /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: 2.46-2.56

Regulatory note:

1. Study was initiated (date first patient received study drug) - 15 Jan 1996 (Protocol proposed Oct 95, Amendment #1 made in April 1996, Amendment #2 made in November 1996, Amendment #3 Made on May 30 1997)
2. Study ended (date last patient received study drug) - May 31 1997
3. 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.

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. 2.49, p 12.0948) provides a sample consent form.

~ Reviewer's comment: Some of the statement/s in the benefits section 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) in patients with known or highly suspected CNS pathology the aims of which is stated below.

- The trial aimed to compare OptiMARK™ and Magnevist® with reference to safety, tolerability, and efficacy -- [p. 12.0533, Vol. 2.48]
  "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."
- **Exclusion criteria:**
  Pregnancy and lactation, previous receipt of *investigational (?such as)* drug within 30 days of study, prior hypersensitivity reaction to gadolinium-containing contrast agents, change in clinical status between study MRI and qualifying MRI, standard MRI contraindications (e.g., aneurysm clips, pacemaker, cochlear implants, etc.), any contrast-enhanced examination within 48 hours before the baseline labs and history of hemoglobinopathies

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; p12.0550, Vol. 2.48).
- In a majority of the patients, the drug was administered via the antecubital vein (Appendix 16.2.5-1, Vol. 2.53)
- The maximum volume that was administered was 23.4 mL in patient H-006 in the R antecubital vein (Appendix 16.2.5-1, Vol. 2.53, p 12.2427)
- The table below summarizes some of the dosing information:

Dosing* Information:Report # 488 /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™	133 (66.2%)	15.1	17.9	1.13
Magnevist®	68 (33.8%)	15.9	19.9	1.11
Comments (OptiMARK™)	*Total exposed- 133*	*Maximum volume-23.4ml*	*Minimum-4.0*	*Maximum-3.53*

*Appendix C [pp. 12.0577-85, Vol. 2.48] 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)
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

- 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. 2.53).

SAFETY ASSESSMENTS:

The Sponsor collected the following data at various time points as indicated in the table below in the safety section.

1. Medical and Surgical History (Med Hx)
2. Concomitant Medications (Meds) - included all medications (including procedural medications) as well as over-the-counter medications taken within 24hours prior to drug administration through the completion of all follow-up following drug administration
3. Physical Examinations (Physical) - conducted by medically-certified individual (medical doctor, doctor-in-training, physician assistant, or nurse practitioner). The Sponsor defined a clinically significant change as "any variation in physical findings which has medical relevance resulting in alteration in medical care" [p. 12.0543, Vol. 2.48]
4. EKG - 12-lead electrocardiogram. The Sponsor defined the following changes as extreme and requiring additional comments on the Case Report Forms:

➢ PR interval < 60msec or >240msec
➢ QRS interval <40msec or >160msec
➢ QT interval <200msec or >500msec

The Sponsor used the same definition for clinically significant change as in the physical examination section (see #3 above)

5. Clinical Labs (Blood and Urine) -

Blood included hematology (hemoglobin, hematocrit, RBC count, WBC count and differential, platelet count, PT and PTT); chemistry (glucose, Na+, K+, Cl-, Ca+2, PO4, alkaline phosphatase, SGOT/AST, LDH, creatinine, uric acid, BUN, total iron, iron binding capacity, ferritin, total protein, total and direct bilirubin, uric acid).

The extreme values were flagged and expressed as X% above the upper limit or X% below the lower limit of normal-see Sponsor's listing [p.12.0546, Vol 2.48]. The Sponsor's normal reference range is also listed.

Out-of-range values at 2hrs, 24(±2) hours, and at approximately 3 days post-contrast agent adiministration were compared to the baseline values and the following etiology codes were designated (p12.0547, Vol 2.48)

1=No change or change not clinically significant from baseline; no follow-up required

2=Change from baseline clinically significant and attributable to disease; no follow- up required

3=Change from baseline clinically significant and attributable to procedure; no follow-up required

4=Change from baseline clinically significant and attributable to the study drug; FOLLOW-UP REQUIRED (these will be repeated as determined by the principal investigator until value(s) returns to baseline or until the principal investigator deems that further follow-up is no longer necessary)
5=Apparent lab error
6=Unevaluable; COMMENT REQUIRED
Baseline out-of-range values will be recorded. For values which are out-of-range and of clinical significance, further commentary will be provided and documented.

The Sponsor used the same definition for clinically significant change as in the physical examination section (see #3 above)

6. Vital Signs (Vitals) - included systolic and diastolic blood pressure, pulse, and respiratory rate. The Sponsor defined the following changes as extreme and requiring additional comments on the Case Report Forms:

- BP : systolic > 20mmHg, diastolic > 20mmHg
- radial pulse > 15 beats per minute
- respiratory rate > 10 breaths per minute

The Sponsor uses the same definition for clinically significant change as in the physical examination section (see #3 above)

7. Adverse Events (AE) - "An adverse event is defined as any undesirable experience occurring to the patient following drug administration, regardless of attribution" [p. 12.0548, Vol.2.48]. The Sponsor stated "serious adverse events are defined as those events which constitute a significant hazard to the patient and may include, but are not limited to the following: life threatening, persistent or significant disability/incapacity, requires hospitalization or extends inpatient hospitalization, events with the following outcomes: death, unusual or unexpected reactions, unusual frequency of reactions" [p.12.0549, Vol. 2.48]

8. Tolerability Assessments (Tol) - sensations or discomfort (heat, cold, and/or pain) that the patient experienced at the injection site were recorded on the Case Report Forms and were graded as: mild (slight sensation/discomfort), moderate (definite but tolerable sensation/discomfort), or severe (excruciating sensation/discomfort).

EFFICACY ASSESMENTS:

The Sponsor used the following imaging parameters (CNS):

Imaging Parameters and Sequences:

Intracranial Pre-dose:	Spinal Pre-dose:
T1-weighted (short TR, short TE)	T1-weighted
T2-weighted (long TR, long TE)	T2-weighted spin echo
Proton density (long TR, short TE)	

The plane and parameters were determined by the principal investigator for both intracranial and spinal studies. Post-dose plane and parameters were the same as the pre-dose studies.

IMAGE INTERPRETATION

(Reviewer's note: The case report forms pertaining to MR Imaging Record -technical details [p.12.0899, Vol 2.48]; MR Efficacy Record -pre-contrast [pp.12.0901-02, Vol 2.48]; MR Efficacy Record -pre- plus post-contrast [pp.12.0903-05, Vol 2.48]; MR Lesion Record -pre- and post-contrast brain and spine [pp. 12.0906-07, Vol 2.48]; Final Clinical Diagnosis [pp. 12.0913-14, Vol 2.48]; Extent of Agreement form [p. 12.0915, Vol 2.48]; Blinded Reader Case Report forms [pp. 12.0916-18, Vol 2.48] have been noted.)

PRINCIPAL INVESTIGATOR

- Principal Investigator reviewed non-contrast T1- and T2- weighted images (proton density, if appropriate) and recorded findings before adding the contrast-enhanced images to the analysis

  Non-Contrast Images Alone:

  a) technical adequacy
  b) normal or abnormal
  c) diffuse or focal disease
  d) number of lesions (">10" if applicable)
  e) confidence that lesions / pathology exist on a scale:
  1- low
  2 - modest
  3 - moderate
  4 - high
  5 - extreme
  f) patient course / management based on findings
  g) diagnosis
  h) confidence in diagnosis [per same scale as in part (e)]

- Non-Contrast and Contrast-Enhanced Images Together: [Note - items in italics are different or new compared to those assessed for the non-contrast images above]

  a) Technical adequacy
  b) Normal or abnormal
  c) Diffuse or focal disease
  d) Number of lesions (">10" if applicable) _
  e) Confidence that total number of lesions exist (per same scale as in part (e) above)
  f) Whether additional disease detected only on post-contrast images (not on pre-)
  g) Whether additional diagnostic information was provided relative to:
  1 . lesion conspicuousness
  2 . border delineation
  3 . improved distinction of edema from pathology
  4 . exclusion of pathology
  5 . alteration / clarification of diagnosis
  h) Whether contrast impaired recognition of lesion / pathology
  i) Patient course / management based on findings
  j) Diagnosis
  k) Confidence in diagnosis
  l) Evidence of recurrence

FINAL DIAGNOSIS:

Appendix D [pp. 12.0587-88, Vol 2.48] lists the diagnosis codes

- The Principal Investigator would follow each patient for up to 30 days to determine the final diagnosis. If at the completion of this interval a final diagnosis is 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

Principal Investigator performed extent of agreement assessment for the pre and post-contrast MRI diagnosis compared to the patient's clinical diagnosis, which the Sponsor defined as follows:

"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."

MASKED (BLINDED) READER EVALUATIONS:

~ Reviewer's note: The CNS Blinded Reading Methodology Report [pp.12.0875-84, Vol 2.48] 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 reviewed only 1/3rd of images.

- Three radiologists (masked readers) having no affiliation with the clinical trial sites and blinded to patient identity, history, and contrast agent used read the images and recorded in the case report form as follows:

1. Brain v/s spine
2. Technically adequate
3. Type of disease (diffuse only, focal only, diffuse and focal no evidence)
4. Number of lesions
5. Size of smallest lesion
6. Degree of confidence related to the number (primary efficacy indicator)
7. Level of conspicuity (primary efficacy indicator)
8. Delineation between lesion and parenchyma/structure (primary efficacy indicator)
9. Distinguish between pathology and edema
10. Diagnosis

- **CASE REPORT FORMS** [pp. 12.0916-12.0919, Vol. 2.48]

The case report forms that the blinded readers completed is listed completely for purposes of thoroughness given that this is a pivotal phase 3 trial.

1. "What type of MR scan was this examination?" (brain/spine)
2. "Is the technical quality of the MR images adequate for radiological diagnosis?" (yes/no) (if no → reasons for this - motion/signal void/positioning/other - please specify → then proceed to next patient) – multiple selections allowed
3. "Indicate which type of disease is present (diffuse only, focal only, diffuse disease and focal disease, or no evidence of disease)." -one selection only.
4. "Please indicate the number of lesions for this patient as indicated by the given set of images: If zero is answered, go to Question #6 and continue" (0 - >10) –one selection only
5. "Measure the size of the smallest lesion." Line drawn across largest diameter of smallest lesion on image, computer displays pixel size which is converted to mm by computer using look-up table (FOV and matrix size)
6. "Choose one number that best reflects your degree of confidence that the total number of lesions identified in Question #4 does exist." (1=no confidence, 10=extreme degree of confidence-scale 1 through 10)- one number to be circled
7. "Choose one number that best reflects the level of conspicuity for all lesions visualized." (1=no lesions, 10=clearly visualized-scale 1 through 10)-one number to be circled
8. "Choose one number that best reflects your ability to delineate lesion borders from parenchyma/structures." (1=no lesions, 10=clearly visualized-scale 1 through 10)-one number to be circled
9. "Choose one number that best reflects your ability to distinguish edematous tissue from pathology." (1=no edematous tissue, 10=clearly distinguishable-scale 1 through 10)-one number to be circled
10. "Indicate your diagnosis(es) for this patient based on the MR images provided. Check all that apply." (chosen from list-p. 12.0918)
11. "Select one number to that best reflects your degree of confidence in the diagnosis (es) selected in question #10. If your diagnosis is unknown, select (1) as the degree of confidence." (1=no confidence, 10=extreme degree of confidence-scale 1 through 10)-one number to be circled "Select one number that best reflects the level of

conspicuity for each lesion (or class of lesions) on a scale of 1 to 10." (1 = barely obvious)

12. "Did the administration of contrast impair your ability to visualize lesions or pathology?" (yes/no/not applicable; if yes → "type of impairment" selected from "flow artifact", "loss of signal due to T2 effects" or "other", if "other" selected, type must be specified by reader; "not applicable" should only be used for non-contrast image set)
13. "What would you suggest as the next anticipated management choice for this patient?" {selection from list including "Chemotherapy", "Radiation Therapy", "Surgery", "Biopsy", "Additional Imaging (Please specify)", "Other: (Please specify)", "Unable to Determine", and "None"

- Each blinded/masked reader would review 1/3rd of patients' image sets
- "Computer Assisted Masked Reading system (CAMR)" [p. 12.0875, Vol. 2.48] designed by [redacted] were used for viewing images
  2 separate Macintosh® computer systems - one for image display and one for data entry
  up to 4 high-resolution monitors were used
  display functions: "image brightness and contrast adjustment; magnification and panning; distance or area measurement" [p. 12.0876, Vol. 2.48]
- Information captured and displayed with images
- Data files grouped into sets for each patient: [p. 12.0877, Vol. 2.48]
  - "Group 1. Patient image sets consisted of the pre-contrast images plus a duplicate of the pre-contrast T1 images"-this set would have a random code number. Therefore, when this code was used, the images appeared as follows: T1 on monitor 1, T2 on monitor 2, proton density on monitor 3 and T1 on monitor 4
  - "Group 2. Patient image sets consisted of all the pre-contrast images and the post-contrast images"-this set would be given a different random code number. Therefore, when this code was used, the images appeared as follows: T1 on monitor 1, T2 on monitor 2, proton density on monitor 3 and contrast T1 on monitor 4
  - Randomization program used to assign random number to each image set – reader could select number for patient study and then number for each individual sequence.
  - Readers were given list of codes for pre-contrast and pre- plus post- contrast groups:
    order of reading determined by separate random ordering of patient images
    each patient's images read twice - once separately with the non enhanced images and once with all images combined (pre plus post-contrast)
- Training was provided to the three readers on lesion identification, measurement of size with electronic calipers, diagnostic codes, and use of system; 10-12 image sets from Phase 2 trials were used for training (same images for all readers)
- The efficacy evaluations would be similar to the evaluations of the principal investigator.
- An additional independent reader would compare the final clinical diagnosis provided by the site to the masked readers' diagnosis. This independent reader would subsequently determine an agreement between the two.

STATISTICAL ANALYSIS:

[See page 124 for discussion and comments]

- Analysis on both evaluable patients and intent-to-treat (failure imputed for drop-outs and for missing or un-evaluable images); analysis of both blinded reader data as well as Principal Investigator data
- $\alpha = 0.05$
- Primary Endpoints: [p. 14.0833, Vol. 2.69]

  "the score for the degree of confidence in the diagnosis(es) indicated pre-contrast plus post-contrast compared to pre-contrast;"
  "the image score for the level of conspicuity for all lesions visualized pre-contrast plus post-contrast compared to pre-contrast; and"
  "the score for the ability to delineate lesion borders from parenchyma/structures pre-contrast plus post-contrast compared to pre-contrast."
  each primary endpoint measured on scale (1-10); two one-sided confidence interval methodology to be used

→ μ_O = mean score of change from pre-contrast to pre-contrast plus post-contrast for OptiMARK™

→ μ_M = mean score of change from pre-contrast to pre-contrast plus post-contrast for Magnevist®

→ s_O = standard deviation of scores for OptiMARK™

→ s_M = standard deviation of scores for Magnevist®

→ n_O = sample size for OptiMARK™

→ n_M = sample size for Magnevist®

→ $t_{(1-\alpha, \nu)} = 1-\alpha^{th}$ percentile of t distribution with ν degrees of freedom

→ consider OptiMARK™ and Magnevist® equivalent if "100(1-2α) confidence interval for $\mu_O - \mu_M$ given by

→ \|- - [sic]

→ ... is contained in the interval (δ_L, δ_U)" [p. 14.0835, Vol. 2.69]

→ {Note: according to the Second Amendment,

$$\mu_O - \mu_M = \bar{x}_O - \bar{x}_M \pm t_{(1-\alpha, \nu)} \sqrt{\frac{s_O^2}{n_O} + \frac{s_M^2}{n_M}}$$

[p. 14.0762, Vol. 2.69]}

- in addition, the hypothesis that μ_M and μ_O are different from zero was tested using a t-test

in original Protocol, safety parameters were used to calculate sample size and statistical tests planned were:

- ♦ χ^2 test for assessing equality of proportions of patients with adverse events and with significant EKG, laboratory, or vital sign changes in each group; ANOVA with pre-test measures as co-variate for continuous values (lab test, vital signs)

- χ^2 test for distribution of grades of heat, cold, and pain for tolerability of OptiMARK™ and Magnevist®
- χ^2 test for efficacy indicators measured as proportion; ANOVA for number of lesions and confidence scores

in First Amendment, degree of confidence in diagnosis was used to calculate sample size; planned tests were:

- for endpoints with scores per lesion (degree of confidence that lesion exists, conspicuity, border delineation, and confidence in diagnosis for each lesion pre- plus post- contrast compared to pre-contrast), "aggregate score" calculated for patient by taking sum of scores for each indicator and dividing by product of number of lesions and 10 (number of levels in scale) = (sum) / (10)(# lesions)
- for each score and for aggregate score, difference of score pre- plus post-contrast minus pre-contrast calculated and categorized as "improved" if >0 or not improved if not equal to 0 [sic] [p. 14.0686, Vol. 2.69]
- Fisher's exact test used for testing equality of proportions in each group with improvement in scores for pre- plus post- contrast compared to pre-contrast alone for: degree of confidence in overall diagnosis, degree of confidence in existence of lesion (aggregate score), conspicuity (aggregate score), border delineation (aggregate score), degree of confidence in diagnosis of lesion (aggregate score), and change in next anticipated management choice; Fisher's exact test also used to test proportion of patients in each group in whom contrast impaired visualization
- agreement with final diagnosis categorized as "in agreement" (if 'basic' or 'absolute') or "not in agreement" (if 'partial', 'no agreement', or 'not evaluable') – proportions in each group tested using Fisher's exact test
- ANOVA used to test equality of means for each group for mean difference in scores pre- plus post- contrast compared to pre-contrast for: degree of confidence in diagnosis, aggregate score for confidence in existence of lesion, aggregate score for conspicuity, aggregate score for border delineation, and aggregate score for confidence in lesion diagnosis
- paired t-test within groups to test mean difference in confidence or aggregate score pre- plus post- contrast compared to pre-contrast as well as for difference in number of lesions per patient pre- plus post- contrast compared to pre-contrast; ANOVA used to test hypothesis of equal means for both groups
- kappa statistic was used to measure inter-reader variability

- **SECONDARY ENDPOINTS:** [p. 14.0833 - 14.0834, Vol. 2.69]

→ "the proportion of patients for whom the final clinical diagnosis agrees with the diagnosis from the pre-contrast plus post-contrast images (i.e., sensitivity and specificity);"

→ "the image score for the ability to distinguish edematous tissue from pathology pre-contrast plus post-contrast compared to pre-contrast;"

→ "the score for the degree of confidence that the total number of lesion(s) exist pre-contrast plus post-contrast compared to pre-contrast;"
→ "the number of lesions per patient pre-contrast plus post-contrast compared to pre-contrast;"
→ "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"
→ "the proportion of patients for whom the contrast agent impaired the ability to visualize lesion(s) or pathology."
→ 95% confidence intervals will be generated:
→ if endpoint has a score(1-10) or is continuous, t-distribution will be used
→ if endpoint measured as proportion, methodology of Clopper-Pearson will be used

- Sample Size Rationale: [see Sponsor's Table 1, p. 14.0836, Vol. 2.69]

→ Sponsor assumed that coefficient of variance is 40% (per Phase 2 studies).
→ Sponsor sought "equivalence criteria of 20% of the mean" [p. 14.0836, Vol. 2.69].
→ Sponsor sought 90% power for study.
→ In original Protocol, sample size calculation based on comparison of safety of OptiMARK™ compared to Magnevist® yielded 70 patients in each arm for a power of 80% to detect a 10% difference between the means (2-sided with $\alpha = 0.05$).
→ In First Amendment, sample size calculation based on degree of confidence in diagnosis pre-contrast plus post-contrast compared to pre-contrast categorized as difference > 0 (improved) or difference ≤ 0 (not improved) yielded need for ≥ 100 patients in OptiMARK™ arm and ≥ 50 patients in Magnevist® arm; Sponsor assumed that OptiMARK™ provided improvement in 58% (per "previous experience") and that Magnevist® provided improvement in 50% (no basis provided for this assumption); sought power of 80% to detect difference of 10%.

RESULTS

The tables below indicate the demographics and disposition of the patients enrolled that would form the basis for efficacy and safety analysis:

APPEARS THIS WAY
ON ORIGINAL

STUDY PATIENTS-DISPOSITION:

Figure: Patient Disposition: 488 /Phase 3 (Pivotal)

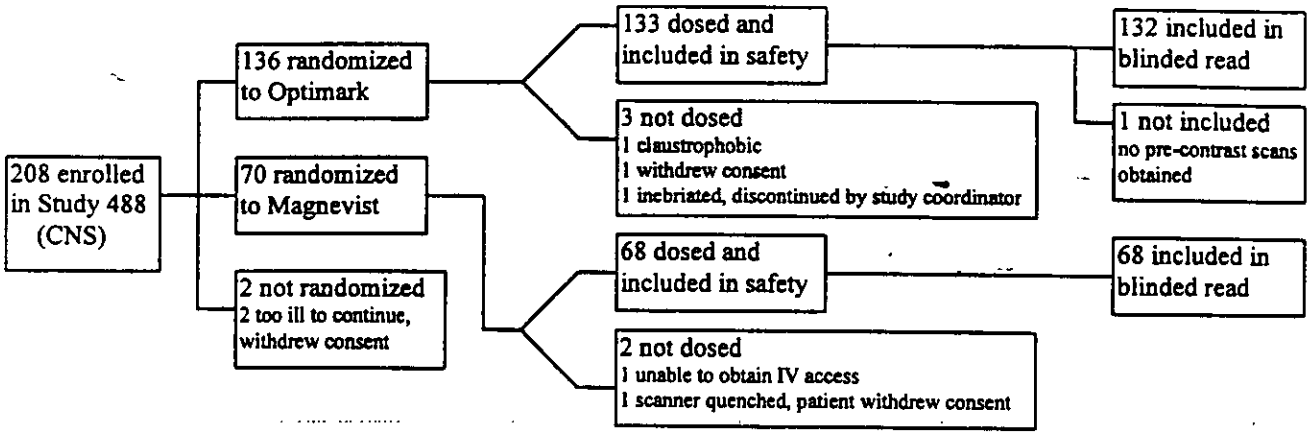

Table: Patient Disposition: 488 /Phase 3 (Pivotal)

Total enrolled:	208
Total randomized:	206 (not randomized = 2)
OptiMARK™:	136 (66.0%)
Magnevist®:	70 (34.0%)
Discontinued before dosing:	5 (3 OptiMARK™, 2 Magnevist®)
Discontinued after dosing:	0
Known Baseline Diagnoses:	198 (2 patients in the OptiMARK™ group and 1 in the Magnevist® group were missing referral diagnosis information)
Safety analysis/Dosed patients:	201
OptiMARK™:	133 (66.2%)
Magnevist®:	68 (33.8%)
Efficacy analysis:	200 (one patient did not have pre-contrast studies, but received study drug)
OptiMARK™:	132 (66%)
Magnevist®:	68 (34%)
Protocol Deviations:	7
OptiMARK™:	5
Magnevist®:	2

The table below summarizes some of the patient characteristics.

Demographics & Characteristics: Report # 488 /Phase 3 (Pivotal) Protocol # 1177-95-03.03			
Parameter	OptiMARK™ N=136	Magnevist® N=70	*–Comments*
Number exposed	133	68	
MR Exam N (%)			
Brain	94 (69.1)	48 (68.6)	*A ratio of 4:1 was proposed-brain:spine (?rationale)*
Spine	42 (30.9)	22 (31.4)	
Age (years)			
Mean ± SD	44.9±14.3	45.5±13.9	*Mean age for both groups is ~45 years. 15 (11%) were >65 years in the study drug group*
Range	18-80	20-73	
Sex N (%)			*Majority is male*
Male	84 (62)	41 (59)	
Female	52 (38)	29 (41)	
Race N (%)			*Majority is white*
White	115 (85)	58 (83)	
Black	11 (8)	7 (10)	
Asian	3 (2)	3 (4)	
Weight (kg)			*Dosage and volume is weight based*
Mean ± SD	76.0±17.4	80.2±17.4	
Range	45-117	44-129	
Height (cm)			
Mean ± SD	171.0±10.6	173.0±9.4	
Range	120-191	152-193	

EFFICACY RESULTS

Efficacy Number

Efficacy analysis: 200 (one patient did not have pre-contrast studies, but received study drug)

OptiMARK™: 132 (66%)

Magnevist®: 68 (34%)

The chart below summarizes patient disposition information related to efficacy:

Total enrolled:	*208*
Total randomized:	*206 (not randomized = 2)*
OptiMARK™:	*136 (66.0%)*
Magnevist®:	*70 (34.0%)*
Discontinued before dosing:	*5*
Discontinued after dosing:	*0*
Known Baseline Diagnoses:	*198 (2 patients in the OptiMARK™ group and 1 in the Magnevist® group were missing referral diagnosis information*

Measurement of compliance- scanner:
Refer to the study review section for additional details on imaging parameters. Site D used 1.0 Tesla unit on ten subjects to obtain the images; and Site K used 0.5 Tesla unit on 26 patients.

- The majority of patients (82.1%) were scanned on the 1.5 Tesla MRI scanner.

COMMENTS/CONCERNS

The case report forms pertaining to MR Imaging Record -technical details [p.12.0899, Vol 2.48]; MR Efficacy Record -pre-contrast [pp.12.0901-02, Vol 2.48]; MR Efficacy Record -pre- plus post-contrast [pp.12.0903-05, Vol 2.48]; MR Lesion Record -pre- and post-contrast brain and spine [pp. 12.0906-07, Vol 2.48]; Final Clinical Diagnosis [pp. 12.0913-14, Vol 2.48]; Extent of Agreement form [p. 12.0915, Vol 2.48]; Blinded Reader Case Report forms [pp. 12.0916-18, Vol 2.48] have been noted.

ENROLLMENT:

A. There is no homogeneity in numbers in the distribution of patients amongst the different centers.

B. The basis for choosing the ratio 2:1 between brain and spine is arbitrary.

C. **Baseline/Referral Diagnosis and Baseline Qualifying Radiologic Examination**

- The Qualifying MRI was obtained in all the patients prior to study enrollment - "Qualifying MRI" – required to have had a contrast-enhanced MRI (with approved agent) within eight weeks prior to study (but at least 72 hours earlier for patients with congestive heart failure or renal insufficiency – serum creatinine $\geq$ 1.5 mg/dl)
- The table below lists the diagnoses at the time of referral, which subsequently formed the basis for:
  a) the qualifying radiologic examination
  b) the Final Diagnosis (standard of truth)
  c) the collected and analyzed efficacy data to arrive at the various primary and secondary end points including the extent of agreement

Baseline Diagnoses: Report # 488 /Phase 3 (Pivotal) Protocol # 1177-95-03.03			
Diagnosis (N=198)	OptiMARK™ N=131(%)	Magnevist® N=67(%)	*–Comments/Note*
Degenerative or Demyelinating	44 (33.6)	25 (37.3)	*2 patients in the OptiMARK™ group and 1 in the Magnevist® group were missing referral diagnosis information. The numbers exposed were 133 and 68 respectively. See additional comments below*
Tumor	37 (28.2)	21 (31.3)	
Other	22 (16.8)	12 (17.9)	
Unknown	8 (6.1)	4 (6.0)	
Normal	6 (4.6)	1 (1.5)	
Infection/ Inflammation	6 (4.6)	-	
Trauma	4 (3.1)	-	
Vascular/ Collagen	4 (3.1)	4 (6.0)	

- The table below lists the sites of disease/pathology for these patients

Site pathology: Report # 488 /Phase 3 (Pivotal) Protocol # 1177-95-03.03				
Number		133 (%)	68 (%)	*~Comments*
N (%)	**Brain**	94 (69.1)	48 (68.6)	*A ratio of 80:20 was proposed- brain:spine*
	Spine	42 (30.9)	22 (31.4)	

- The qualifying MRI preceded and determined patient enrollment. It was obvious (given that these were performed using another approved gadolinium agent) that the pathology and the radiological findings were known prior to enrollment. The information obtained from a baseline MRI when utilized 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 these cases. By obtaining this qualifying MRI prior to enrolment into the study, the category of patients in whom pathology is "suspected" was erased and is completely left with patients with "known" pathology. This has a direct impact on the proposed labeling and indication.

D. **Patient enrichment-"post-treatment" patients**:

- It is noted in the medical and surgical history section, (Vol. 2.53, Appendix 16.2.4-5) and in the qualifying radiologic examination section, (Vol. 2.53, Appendix 16.2.4-4) that, ~55 patients in the OptiMARK™ group, (55/133, ~ =**41.35%**) and ~28 patients in the Magnevist® (28/68, ~ =41.17%) group had a therapeutic intervention/s (surgery or biopsy or radiation therapy or chemotherapy or a combination). 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 (therefore greater enhancement and better border delineation). Such postoperative changes and defects are easily recognizable (easier diagnosis and confidence in diagnosis), 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 tables (see below) for post-treatment patients. This is not the case 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).

Note: The reviewer would like to designate the former group as "Post-Treatment" patients and the latter group as "Non-Post-Treatment" patients.

- The data analysis with frequency tables for this highly selective population is shown below:

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.*

Study #488: Post-Treatment Patients

Cross Tabulation of Conspicuity Score Recorded* by Blinded Readers on "Pre" and "Pair" - OptiMARK™ (n = 55)

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

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

Study #488: Post-Treatment Patients

Cross Tabulation of Conspicuity Score Recorded* by Blinded Readers on "Pre" and "Pair" - Magnevist® (n = 28)

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

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

- Note that in the conspicuity score, ~20/55 (36%) post treatment patients in the OptiMARK™ group and ~18/28 (64%) patients in the Magnevist® group had a better pair score.

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.*

Study #488: Post-Treatment Patients

Cross Tabulation of Diagnostic Confidence Score Recorded* by Blinded Readers on "Pre" and "Pair" - OptiMARK™ (n = 55)

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

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

Study #488: Post-Treatment Patients

Cross Tabulation of Diagnostic Confidence Recorded* by Blinded Readers on "Pre" and "Pair" - Magnevist® (n = 28)

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

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

- Note the better pair diagnostic confidence score: ~28/55(51%) for post-treatment patients in the OptiMARK™ group and ~ 13/28(46%) for post-treatment patients in the Magnevist® group.

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.*

Study #488: Post-Treatment Patients

Cross Tabulation of Border Delineation Recorded* by Blinded Readers on "Pre" and "Pair" - OptiMARK™ (n = 55)

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

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

Study #488: Post-Treatment Patients

Cross Tabulation of Border Delineation Recorded* by Blinded Readers on "Pre" and "Pair" - Magnevist® (n = 28)

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

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

- Note the better pair border delineation score: ~33/55(**60%**) for post-treatment patients in the OptiMARK™ group and ~14/28(**50%**) for post-treatment patients in the Magnevist® group.

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.*

Study #488: CNS Study - Non-Post-Treatment Patients

Cross Tabulation of Conspicuity Score Recorded* by Blinded Readers on "Pre" and "Pair" - OptiMARK™ (n = 77)

Conspicuity Score - "Pre"	Conspicuity Score - "Pair"									
	1	2	3	4	5	6	7	8	9	10
1	19					2		1	1	
2										
3			1							
4	2					1				
5				1					1	1
6			1	2	2					1
7				1	2	5			1	1
8	1			1		2		1	1	2
9					1			1	3	5
10								1	1	12

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

Cross Tabulation of Conspicuity Score Recorded* by Blinded Readers on "Pre" and "Pair" - Magnevist® (n = 40)

Conspicuity Score - "Pre"	Conspicuity Score - "Pair"									
	1	2	3	4	5	6	7	8	9	10
1	10					1	1			1
2										
3										
4					1					
5						1				1
6				1					1	1
7	1		1							
8							1	2	1	
9									1	2
10										12

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

- Note the conspicuity score of: ~19/77(**24.67%**) for non-post-treatment patients in the OptiMARK™ group and ~9/40(**22.5%**) for non-post-treatment patients in the Magnevist® group.

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.*

Study #488: CNS Study - Non-Post-Treatment Patients

Cross Tabulation of Diagnostic Confidence Score Recorded* by Blinded Readers on "Pre" and "Pair" - OptiMARK™ (n = 77)

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

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

Cross Tabulation of Diagnostic Confidence Recorded* by Blinded Readers on "Pre" and "Pair" - Magnevist® (n = 40)

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

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

- Note the diagnostic confidence score: ~25/77(**32.4%**) for non-post-treatment patients in the OptiMARK™ group and ~ 11/40(**27.5%**) for non-post-treatment patients in the Magnevist® group.

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.*

Study #488: CNS Study - Non-Post-Treatment Patients

Cross Tabulation of Border Delineation Recorded* by Blinded Readers on "Pre" and "Pair" - OptiMARK™ (n = 77)

Border Delineation Score - "Pre"	Border Delineation Score - "Pair" 1	2	3	4	5	6	7	8	9	10
1	19				1			3		
2							1			
3				1						
4	1			1						
5					1	1				2
6	1		1	1	4		1	2		1
7	1					1	1	1	1	1
8						2		1	1	1
9							1	1	3	3
10								1	1	14

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

Cross Tabulation of Border Delineation Recorded* by Blinded Readers on "Pre" and "Pair" - Magnevist® (n = 40)

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

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

- Note the border delineation score: ~21/77(**27%**) for non-post-treatment patients in the OptiMARK™ group and ~ 15/40(**37.5%**) for non-post-treatment patients in the Magnevist® group.

- The table below summarizes the data on the post-treatment and the non-post-treatment patients for both OptiMARK™ and Magnevist®:

EFFICACY: POST/NON-POST-TREATMENT: Report # 488 /Phase 3 (Pivotal) 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% (14/28)	37.5% (15/40)

Note: A similar analysis for the pivotal phase 3 study 525 has not been carried out at this time as the outcome of such an analysis is expected to be no different than study 488.

- As stated above, this combination of the qualifying MRI and the highly selective population affects the study and the outcomes in several ways such as:

a) Patient selection bias (non-representative sample)
b) Easier diagnosis and confidence in diagnosis, easier visualization and border delineation (affecting all primary efficacy end point/s and the agreement in diagnosis)
c) Greater scores in the extent of agreement (see below for further comments)

- The subsequent data collection, analysis, interpretation and conclusions are all "passive" and are secondary derivatives. The basis and the foundation upon which further efficacy data was built are biased, easily predictable, and anticipatory to a large extent. The qualifying MRI was performed using an approved gadolinium agent, and Magnevist® (also an approved agent) was used as a comparator. Studying these cases with OptiMARK™ only further 'cloned/duplicated' these known findings; and in a larger sense, these patients were not only "re-studied" with OptiMARK™ but also were a largely selective group.
- **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.**

BLINDED READER METHODOLOGY:

The CNS Blinded Reading Methodology Report [pp.12.0875-84, Vol. 2.48] 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.

A. Case Report Forms/Evaluation:

- In the Blinded Reader evaluation, the question related to the type of disease-diffuse v/s diffuse and focal is confusing. Commenting on border delineation between the lesion and parenchyma/structures and edematous tissue from pathology if the lesion or pathology is non-enhancing would be difficult. This delineation is still possible

based on the MR sequence used (eg: T1 v/s T2 v/s proton density) in the pre-contrast studies, which is *independent of the drug.* 'Confidence in diagnosis' scale is artificial (as are scales for conspicuity, border delineation, etc.) – care necessary in interpretation of meaning.

- The responses expected of the blinded readers to questions are recorded on scales that are ordinal, artificial, and subjective.
- It is not appropriate to expect the blinded reader Radiologists to guess at whether "Chemotherapy" or "Radiation Therapy" or "Surgery" happen to be the next management step: with no knowledge of the patient's clinical status and history and with necessarily limited knowledge of changes in Oncology and Surgery practice there is no way this will reflect actual clinical practice. For a Radiologist, the decision about whether or not "Additional Imaging" is necessary is entirely appropriate and another option such as 'Oncologic/Surgical Consult' would be more logical than those provided. Radiologists perform and interpret imaging studies; they do not generally administer chemotherapy and the decision about the appropriateness of these options lies with those specialists who do (just as decisions about the appropriateness of imaging studies and imaging-guided therapy lie with Radiologists and not with other physicians).
- It is not clear whether the blinded reader would be completing one case report form for the pre-dose images and an other for the pre-dose plus post-dose images. The application includes a single case report form [pp.12.0916-17, Vol 2.48]. This case report form is of the earlier version of the protocol.

B. **Inter-reader variability**:

- Images from one third of the total population studied were read by each reader. This included pre-dose images (T1, T2 and proton images) and pre-dose plus post-dose images. This does not allow for inter reader variability correction.
- Inter-reader variability making a statistical difference exists 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 is low as discussed with the Statistician and by the review of the ANOVA data analysis provided in the application.

C. **Final diagnosis**:

- The basis for categorizing and grouping some of the diseases in this fashion is too broad and does not reflect the actual diagnosis/es, e.g., degenerative or demyelinating is inappropriate to be grouped together and has no diagnostic meaning (and therefore no therapeutic or clinical use).
- The question regarding final diagnosis and the list so provided to categorize diseases is inappropriate (this affects the secondary efficacy endpoint).
- The Blinded Readers are required to indicate diagnosis from the list provided from the Sponsor. It would be difficult to assign patients into some of these categories (note that the blinded readers are blinded to the history and patient information) because some of these listed either do not have pathognomonic MR features (eg.:

GBM, Lymphoma, benign v/s malignant) or may not be possible to make the diagnosis with MR alone (eg. arteritis, benign v/s malignant).

- The un-enhanced images from this study were used in arriving at the final diagnosis amongst other entities. The truth and the final diagnosis cannot rest in any clinical trial of this nature when a contrast agent is being evaluated, where the non-contrast images are a part of the standard of the truth.

D. **Reading of Images**:

- The contrast images and the non-contrast images are not read separately. As much as they are usually reviewed together in clinical practice, for purposes of a "study", these should have been read separately.
- As noted in the efficacy methodology section above, 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. This latter situation is probably universal and is attributable to any reader.

E. **Primary efficacy analysis for blinded readers: intent-to-treat**

- **Primary Efficacy Endpoints**: [p. 12.0, Vol. 2.48]

- 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 were the data for each of these primary efficacy end points.

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 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.2.54, pp. 12.2601-12.2620) contains individual patient listings for this primary efficacy end point, and table 14.2.1-1 (Vol. 2.46, p. 12.0091) 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 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 # 488 /Phase 3 (Pivotal) Protocol # 1177-95-03.03

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

Diagnostic Confidence Score - "Pre"	Diagnostic Confidence Score - "Pair" 1	2	3	4	5	6	7	8	9	10
1	1									
2			1			1	1			
3						2	1		3	
4				1						
5					1					
6		1			2	1	4	1	3	4
7			1			3	6	11	2	4
8			1		1	1	5	10	6	7
9						1	0	3	7	2
10			1			1	2	1	4	25

*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 Diagnostic Confidence Score Recorded* by Blinded Readers on "Pre" and "Pair" - Magnevist® (n=68)

Diagnostic Confidence Score - "Pre"	Diagnostic Confidence Score - "Pair" 1	2	3	4	5	6	7	8	9	10
1						1				
2			1							
3				1			1	1		
4					1	2				
5					2			5	2	1
6			1			2	4	3	7	1
7							2	1	4	2
8								2	4	17
9										
10										

*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 # 488 /Phase 3 (Pivotal)

		Decrease	No change	Increase	Total
OptiMARK™	N	28	51	53	132
	%	21.21	38.64	40.15	
Magnevist®	N	18	26	24	68
	%	26.47	38.24	35.29	

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 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.2.54, pp. 12.2588-12.2600) contains individual patient listings for this primary efficacy end point, and table 14.2.1-2 (Vol. 2.46, p. 12.0092) 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 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 # 488 /Phase 3 (Pivotal) Protocol # 1177-95-03.03

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

Conspicuity Score - "Pre"	Conspicuity Score - "Pair"										
	1	2	3	4	5	6	7	8	9	10	
1	22					2		1	1		
2				1						1	
3						1	1				
4	2				1	1			1	1	
5				1	2	2	1	1	2	4	
6					1	2	7		1	3	
7					1		4	2	5	6	
8	1					1		2	3	5	
9								1	3	32	
10			1		1	1					

*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 Conspicuity Score Recorded* by Blinded Readers on "Pre" and "Pair" - Magnevist® (n = 68)

Conspicuity Score - "Pre"	Conspicuity Score - "Pair"										
	1	2	3	4	5	6	7	8	9	10	
1	13					1	1		1	1	
2									1		
3						1		1	1	2	
4				1	1	1	1	2	2	2	
5	1		1					1	2	2	
6							2	2	1	2	
7									2	3	
8										18	
9											
10											

*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 # 488 /Phase 3 (Pivotal)

		Decrease	No change	Increase	Total
OptiMARK™	N	24	69	39	132
	%	18.18	52.27	29.55	
Magnevist®	N	5	37	26	68
	%	7.35	54.41	38.24	

2. *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 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.2.54, pp. 12.2588-12.2600) contains individual patient listings for this primary efficacy end point, and table 14.2.1-3 (Vol. 2.46, p. 12.0093) 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.