STUDY DESIGN

This study is a multi-center, open label uncontrolled, non randomized study assessing the safety and efficacy, of 0.1mmol/kg Optimark and 0.2mmol/kg Optimark (Gadoversetamide Injection), as MRI contrast agents in patients with known or highly suspected liver pathology.

Protocol: Agents: Optimark is a sterile nonpyrogenic 0.5 mmol/aqueous solution of gadoversetamide. Optimark is provided in single dose rubber stoppered glass vials, each containing 20 ml of solution Magnevist is a commercially marketed product provided in 20 ml vials of 0.5 mmol/ml Gd-DTPA

Subjects, Randomization and Dosing: A total of 227 patients with highly suspected liver pathology previously detected with contrast enhanced computed tomography were enrolled in this study at 10 study centers in the US and 2 study centers in Germany (2 of the 10 US sites did not enroll any patients). The study was not randomized. Patients received either 0.1mmol/kg Optimark (99 patients) or 0.2mmol/kg Optimark (121 patients) at the discretion of the investigator. Seven patients dropped out of the study before dosing The criteria used by the investigators to decide whether to give either 0.1mmol/kg Optimark or 0.2mmol/kg Optimark were not specified

nclusion Criteria:

ge 2 years or greater

Patients must be highly suspected of having liver pathology at the time of the qualifying contrast enhanced computed tomography (CECT) evaluation

Patients must have had a CECT with an approved contrast agent within 3 weeks prior to the this contrast enhanced MR imaging examination

Signed informed consent

Reviewer's Comment: *The reason for this "qualifying CECT" (contrast enhanced CT) and it's role in this study is not entirely clear. As this is an inclusion criterion, presumably, in most cases, the CT scan was part of the patient's clinical diagnostic workup and was not part of this study itself Presumably the results of this CT scan were available to the investigator before the patient was enrolled and could have influenced the decision to enroll the patient in the study. The results of the qualifying CT are not specifically listed in the report and it appears that the CT scans were not compared directly to the MRI studies which were part of this protocol. In clinical practice, if the patient had already had a contrast enhanced CT, an MRI would only be ordered if the CT did not determine the diagnosis or did not provide sufficient diagnostic information. The fact that patients must be highly suspected of having liver pathology does not rule out the possibility of the patient having confirmed liver pathology at the time of CT, and having the CT does not rule out the possibility of the patient so having had a diagnostic MRI.*

Exclusion criteria

Pregnant or Nursing Female

.ypersensitivity reaction to any gadolinium based contrast material

Any contrast study within 48 hours

Any contraindication to MRI scan

History of any hemoglobinopathies

Patient's clinical status has changed in the time interval between the CT and the study MRI (for example due to surgery, biopsy etc.)

Safety Monitoring

The following evaluations for safety monitoring were obtained

History and Physical: A complete history (including list of current medications) and physical was obtained within 24 hours prior to injection. Physical examination was repeated at 24 hours after injection

Vital Signs: Vital signs were obtained immediately before injection, immediately after injection, 2 hours after injection, and 24 hours and 3 days after injection. Vital signs to be monitored are: heart rate, blood pressure, and spiration rate. Changes in vital signs greater than specified values were noted;

Systolic blood pressure > ± 20 mmHg
Diastolic blood pressure > ± 20 mmHg
Radial pulse > ± 20 bbm
Respiratory rate > ± 10 bpm

Clinical Laboratory: Serum laboratory assays were obtained at 24 hours prior to injection and 2 hours, 24 hours and 3 days after injection. These include CBC, chem-screen panel, electrolytes, LFTs and routine urinalysis. All laboratory values were reviewed by the investigator and any changes found by the investigator to be remarkable were entered on the case report forms. Any values falling outside the normal range were assessed by the investigators for clinical significance and relationship to study drug

***Reviewer's comment**: The investigators determined whether change in laboratory values were "clinically significant, and the criteria for doing so were not specified in the protocol. Since each investigator was using his own clinical judgment, "clinical significance" could vary widely from investigator to investigator*

EKG: 12 lead EKGs were obtained within 24 hours prior to injection and at 1hour±10 minutes post injection.

TABLE 2.1 SAFETY MONITORING SCHEDULE

ı est	pre-dose		post-dose					
	baseline	immed.	immed.	0-2hr	2hr	24 hr	48hr	3days

Adverse Event Monitoring			x	x	x	x	x	x
CBC, dif, plts.	x				x	x		x
rum Gd concentration					x	x		x
hemistries	x				x	x		x
Urinalysis	x				x	x		x
Vital Signs		x	x		x	x		x
EKG		x				x		
Physical Examination	x					x		

Adverse Events

All events involving appearance or worsening of illnesses, signs or symptoms after implementation of study procedures were reported. Adverse events were classified as serious if they were life threatening or permanently disabling, require hospitalization or a prolongation of hospitalization or result in death, cancer, congenital abnormality, or overdose. Non serious adverse events were classified as moderate if they require medication or other treatment by a physician, and were classified as mild if they were self resolving without treatment. "Tolerability" was assessed by monitoring patient's complaints of feelings of warmth or discomfort

Efficacy

Imaging

Patients received either 0.1 mmol/kg /kg or 0.2mmol/kg Optimark at the investigator's discretion. Scans were performed on a commercially available MRI scanner. Each patient had a pre-dose T1 weighted and T2 weighted series covering the entire liver. All required sequences were obtained in the axial plane with parameters determined by the principal investigator at each institution. The same imaging plane and imaging parameters were used for both the pre dose and post dose images. Post contrast images (T1 only) were obtained at 15-25 sec. (arterial phase), 55-65 sec. (portal venous phase) and 5 minutes (equilibrium phase). The images from all three time points constituted the post dose image set.

Image Interpretation

Image sets were interpreted by 2 blinded readers. Because this study was terminated, efficacy data was not analyzed by the sponsor. The methodology of image interpretation, outcome variables etc. were not discussed in the sponsor's study report. No efficacy data is presented or discussed in the sponsor's study report

.2 RESULTS

atient disposition

227 patients with highly suspected liver pathology were enrolled in this study. 99 patients received a single intravenous dose of 0.1 mmol/kg Optimark 121 patients received 0.2 mmol/kg Optimark. 7 patients dropped it before dosing.

220 patients were dosed (99 patients 0.1 mmol/kg and 121 patients 0.2 mmol/kg) Seven patients dropped out before dosing for refusal to have MRI scan due to reasons such as claustrophobia. The majority of patients were white, and the male : female ratio was approximately 1:1 There were no statistically significant differences between the two groups in height, weight , sex, or race.

Demographics: N=220

age 56.2 ± 13.13 range 21-85

***Reviewer's Comment**: although the age requirement was only that age be greater than 2 years, no pediatric patients were entered in this study*

Sex : Male 119 (54%) Female 101 (46%)

Race: White 179 (82%), Black 21 (10%) Asian 12 (5%) Other 7 (3%)

Safety

Overall 40/220 patients who received Optimark (18.2%) experienced 154 adverse events
0.1mmol/kg , 15/99 patients (15.2%) experienced 23 adverse events
0.2 mmol/kg , 25/121 patients (20.7%) experienced 37 adverse events

***Reviewer's comment:** The incidence of adverse events in the 0.1 mmol/kg OptiMARK group appears lower than seen in the pivotal trials. This may be the result of patient selection*

Deaths 1
Patient 486-A-027 was a 45 year old male with end stage AIDS with severe neutropenia and intestinal obstruction, who died 3 days after receiving 0.1 mmol/kg Optimark. At autopsy he was found to have obstruction, transmural hemorrhage and necrosis of the terminal ileum. This death was attributed by the investigator to end stage disease.

***Reviewer's Comment:** Although it is clear that this death is not attributable to Optimark, one wonders why a moribund patient was entered into the study at all*

Four additional patients died after participation in the 3 day study at 29 days, 7 weeks, 3 months and 8 months after receiving 0.1 mmol/kg (3 patients) or 0.2mmol/kg (1 patient) Optimark. All patients had advanced primary or metastatic liver disease and all deaths were attributed to disease progression

Withdrawals due to adverse events 0

Serious adverse events other than death 0

Severe adverse events 0.1mmol/kg...1, 0.2mmol/kg...2

One 0.1mmol/kg Optimark patient (486-A-027) experienced severe bowel obstruction, hemorrhage and necrosis. This is the same patient listed above who died
One 0.2mmol/kg experienced severe headache and 1 patient experienced severe Asthenia

The most common adverse event was vasodilation (4/99 0.1mmol/kg, 10/121 0.2mmol/kg). No other adverse event had an incidence of greater than or equal to 5%, Other adverse events attributed to the drug by the investigators were taste perversion (7 patients), paresthesia (2 patients), headache (7 patients) parosmia (2 patients) and pharyngitis, facial edema, hypercalcemia increased saliva and increased creatinine (1 patient each)

31 adverse events in 22 patients were attributed to the drug (at either dose) by the investigator. These included vasodilation (15 patients), taste perversion (6 patients), parosmia (2 patients), paresthesia (2 patients) and facial edema, increased saliva, increased creatinine hypercalcemia headache and pharyngitis (1 patient each)

Vital signs

Using the sponsor's guidelines 59 patients experienced notable changes in vital signs. One patient experienced a 44 mm hg increase in systolic BP and a 31 mm increase in diastolic BP during a liver biopsy procedure 2 hours after dosing. No others were considered to be clinically significant

Table 2.2 NUMBER OF PATIENTS WITH NOTABLE POST DOSE CHANGES IN VITAL SIGNS

Change	0.1 mmol/kg			0.2 mmol/kg		
	0 hr	2hr	24 hr	0 hr	2hr	24 hr
Systolic BP ± > 20 mm	6	4	4	6	9	13
Diastolic BP ± > 20 mm	0	5	0	1	2	3
Pulse rate ± > 15 bpm	5	7	4	5	7	8
respiration rate ± > 10 bpm	0	0	1	0	0	0

Clinical and Laboratory Monitoring

CBC, Serum Chemistry and Urinalysis results were analyzed by evaluating the " standardized result " defined as;

standard result = (result -lower normal range) / (upper normal range - lower normal range)

Reviewer's Comment: *Results presented in this way are clinically meaningless, particularly if results are combined from different laboratories with different reference ranges. One can not look at results presented in this way and tell if a particular lab result presented a clinically significant risk to the patient. For some parameters, (e.g. serum potassium) even a relatively small deviation from normal could be life threatening, whereas, on the other hand, even very high values for glucose or SGOT pose no immediate threat. Of much more concern would be values that are outside of the laboratory's "panic values", that is values where laboratory policy requires immediate notification of the ordering physician. Such "panic values are not discussed in this submission. The determination of whether a particular laboratory value was "clinically significant" was left up to the investigators who were radiologists, not internists. Using the "standard results"*

a value between 0 and 1 would be within the normal range, a negative value would be below the normal range and a value3 greater than 1 would be above the normal range.

patients had changes in serum calcium that were considered by the investigators to be both clinically significant and attributable to Optimark

Scatter plots of result vs. baseline value were plotted for all parameters (presumably for the values for 2 hours after dosing although this is not explicitly stated) (Pages 20.0354 to 20.0396 vol. 2.118)
The only clinically significant trend in the data was a fall in serum calcium in a large number of patients who received 0.2 mmol/kg (This is seen in the scatter plot on page 20.0358 vol.2.118. This is the only clinically significant trend in the data found in the scatter plots by this reviewer.)
LFTs were high for most patients both baseline and post dose with .few large changes. This is what would be expected in patients with liver pathology.
The large changes relative to the normal range seen in serum glucose, in a large number of patients was probably due to the fact that these glucose values were random rather than fasting levels.

Three patients had clinically significant changes in hematology parameters according to the investigators. These included a decrease in hematocrit at 2 hours which returned to normal at 24 hours. A decrease in WBC RBC Hct and Hgb at 2 hours that returned to normal at 24 hours and a clinically significant decrease in RBC hct and Hgb at 2 hours that returned to baseline at 24 hours

***Reviewer's Comment**: This reviewer can not conceive of what the investigators were thinking. The only possible cause for a clinically significant fall in Hct in 2 hours would be severe bleeding or a severe hemolytic anemia, and in either case there would be other signs and symptoms that would point to the cause. In neither case would values be expected to return ton normal in 24 hours. This reviewer would attribute these above changes to lab. error.*

EKG
According to the investigators , no patient experienced clinically significant EKG changes. And there were no statistically significant changes in EKG .

***Reviewer's Comment**: EKGs were **not** obtained immediately before and immediately after dosing, but at baseline (up to 24 hours pre dose) and at 24 hours post dose. These results do not rule out the possibility of clinically significant, or even potentially life threatening EKG changes immediately at the time of dosing. The EKGs were read by the investigators who were radiologists, not cardiologists. QT intervals were not given in the patient data listings*

"Tolerance"
35/99 Optimark patients (35.4%), and 21/94 Magnevist reported injection associated discomfort. The most common sensation was cold in 20% of Optimark patients and in 14 percent of Magnevist patients

Reviewer's Comment: What the sponsor refers to as "tolerance" involves only mild to moderate transient patient discomfort which probably has no implications for patient safety

Efficacy
There was no analysis or presentation of efficacy data in the sponsor's report for these studies

2.3 REVIEWER'S ANALYSIS

Safety

Adverse events

The one death in these studies was due to progressive disease. There is no safety concern raised by the pattern of adverse events. It appears that many patients entered in this study had advanced disease that could be responsible for many of the observed adverse events

Vital signs

Vital signs were assessed immediately before and immediately after dosing. Notable changes in vital signs occurred only in a small number of patients. Nothing in the pattern of changes seen raises significant safety concerns

Laboratory Monitoring

The way in which laboratory data have been presented and analyzed, in terms of the sponsor's "standardized values" makes it difficult to draw any meaningful clinical conclusion from these data. It would not be practical for this reviewer to extract the raw data from the patient data tables and perform the analyses himself There are indications from the scatter plots [vol. 2.118, pg. 20.0358, open circles] that Optimark caused a substantial reduction from baseline, in serum calcium, in a substantial number of patients who received a dose of 0.2mmol/kg. This is not unexpected with a drug that has a chelator as a component.

EKG

EKGs were not performed immediately before and immediately after dosing when changes would be most likely to occur. The post dose EKG was performed 24 hours after dosing by which time Optimark would have been cleared from the systemic circulation. EKGs were evaluated by the investigators, not by a blinded cardiologist. The investigators found no EKG changes that they considered clinically significant. The possibility that clin9ically significant EKG changes occurred immediately after dosing cannot be ruled out

Efficacy

The sponsor did not present an analysis of efficacy data for these studies. No conclusion concerning efficacy can be made from the sponsor's presentation.

Conclusions

These studies as analyzed by the sponsor provide no information about efficacy
The data is insufficient to adequately assess safety. Of particular concern is the fact that the EKGs were obtained 24 hours post dose and were interpreted by the investigators. The laboratory data was presented in terms of the sponsor's "standardized values" which makes it difficult to draw any clinically meaningful conclusions from the data

Optimark is a "me too" drug. There are already several gadolinium MRI contrast agents on the market. The sponsor does not claim that Optimark is superior in efficacy to the approved agents. but only that it is equivalent. Under the circumstances it is important to have convincing evidence that the safety profile of Optimark is no worse than the safety profiles of existing agents. Because of the way that both laboratory and EKG data were obtained and analyzed by the sponsor, these studies do not firmly support that conclusion.

Pivotal Study # 490 (Pivotal study "A")

Sponsor's Proposed Indication:
Optimark is a MRI contrast agent providing magnetic resonance contrast enhancement in patients with known or highly suspected liver pathology

Study Title: A Multicenter Randomized Double Blind Study to Evaluate the Safety, Tolerability, and Efficacy of Optimark (Gadoversetamide Injection) Compared to Magnevist (Gadopentetate Dimeglumine Injection) in Patients With Liver Pathology.

Abstract: A total of 198 patients with highly suspected liver pathology were enrolled in this study at 10 study centers. Patients were randomized to receive a single intravenous dose of either 0.1 mmol/kg Optimark (100 patients) or 0.1 mmol/kg Magnevist (97 patients) by IV bolus injection. Patients had a pre dose MRI with both T1 and T2 weighted images covering the entire liver, immediately before dosing. Post dose images were obtained at 20 sec, 60 sec and 5 min. post dosing (arterial phase, venous phase and equilibrium phase). Images were evaluated by the principal investigator at each study site and by 3 blinded readers, each of whom evaluated the scans from 1/3 of the patients. Safety was assessed by monitoring physical examination, vital signs, CBC, serum chemistries, urinalysis, EKG, and adverse events. Efficacy was evaluated by assessing the pre dose images and the combined pre dose and post dose images (pre + post dose) for the following parameters: 1) degree of confidence in diagnosis, 2) level of conspicuity (prominence or visibility) of lesions, 3) ility to delineate lesion borders, 4) total number of lesions, and 5) the degree of confidence in total number of lesions. Each parameter was rated by the reader on a scale of 1 to 10. Pre dose diagnosis and pre + post dose diagnosis were also compared to the final clinical diagnosis, which was determined by the investigator from all available information. The differences in scores between pre dose scans and pre dose + post dose scans ("the difference scores") were obtained, for each patient, for each parameter evaluated. The mean of the difference scores for each parameter was obtained for the group of patients who received Magnevist and for the group of patients who received Optimark. According to the sponsor, equivalence was demonstrated, for each parameter, if the difference between the mean difference scores for Optimark and Magnevist was between -1.5 and 1.5

For two of the sponsor's primary outcome variables, "Degree of confidence in diagnosis" and "Ability to delineate lesion borders" it has been demonstrated that Optimark is equivalent to Magnevist and that Optimark is superior to no contrast scans only. For the third primary outcome variable , "Lesion conspicuity", disagreement between the 3 blinded readers precludes the drawing of any firm conclusions. On the clinically significant endpoint, "Agreement with final diagnosis" it has been demonstrated that Optimark is equivalent to Magnevist, but only because it has also been demonstrated that neither Optimark or Magnevist provide any advantage over the non contrast scans alone In this reviewer's opinion, the data from this study raise no significant safety concerns that would impact the approval decision

Reviewer's Comment *There are several problems associated with an equivalence trial that would not be oblems in a trial designed to demonstrate superiority over placebo. Firstly, the result that A is equivalent to B only meaningful if B has previously been proven effective, for the desired indication, in the first place. Suppose, for example, that Agent B has been approved as an imaging agent based on studies demonstrating the*

ability to detect CNS lesions only, and there were no controlled studies showing that agent B is better than placebo in evaluating liver pathology, then showing that A is equivalent to B in evaluating liver lesions, would t really demonstrate much of anything. Secondly the statistical objective is to demonstrate that the difference , difference scores, for each endpoint, fall in the interval between -1.5 and 1.5. This interval is entirely arbitrary. One could have as easily chosen -0.15 to 0.15. Since most of the outcome variables require a subjective judgment on the part of the reader, it is not clear what a clinically significant numerical difference would be. Since the variables that are assessed are differences of differences they are likely to be small. In particular, if both agents are ineffective (the differences between the post dose scores and the pre dose scores are small), then, using the sponsor 's interval, equivalence would be easily proved.

STUDY OBJECTIVES:

To evaluate the safety, tolerability, and efficacy of intravenously administered 0.1 mmol/kg Optimark (Gadoversetamide Injection), compared to 0.1 mmol/kg Magnevist (Gadopentetate Diglumine Injection) as a MRI contrast agent in patients highly suspected of liver pathology.

To demonstrate that Optimark is equivalent to Magnevist in patients undergoing MRI of the liver

To compare the safety profile of Optimark to Magnevist

To compare the tolerability profile of Optimark to Magnevist

5.1 STUDY DESIGN

This study is a multi-center randomized double blind parallel group study assessing the equivalence, in terms of safety and efficacy, of 0.1mmol/kg Optimark (Gadoversetamide Injection), to 0.1 mmol/kg Magnevist (Gadopentetate Diglumine Injection) as MRI contrast agents in patients with known or highly suspected liver pathology. This is an equivalence trial, whose objective is to demonstrate the equivalence of Optimark and Magnevist (an approved MRI contrast agent) In both safety band efficacy. The trial is not designed to demonstrate superiority.

***Reviewer's Comment:** Although this is a multi-center study with 10 study centers, no attempt appears to have been made to enroll a specific number of patients at each center. Of the 198 patients enrolled,102 (51.5%) were enrolled at 2 study centers (F and G) and one study center (D) enrolled no patients at all.*

Protocol:

Agents: Optimark is a sterile nonpyrogenic 0.5 mmol/aqueous solution of gadoversetamide. Optimark is provided in single dose rubber stoppered glass vials, each containing 20 ml of solution Magnevist is a commercially marketed product provided in 20 ml vials of 0.5 mmol/ml Gd-DTPA

Subjects, Randomization and Dosing:

According to the protocol, approximately 180 patients were to be enrolled and randomized to receive either Optimark or Magnevist on a 2:1 basis (120 Optimark, 60 Magnevist)

.clusion Criteria:

Age 18 years or greater

Patients must be highly suspected of having liver pathology at the time of the qualifying Contrast Enhanced Computed Tomography (CECT) evaluation

Patients must have had a CECT with an approved contrast agent within 3 weeks prior to this contrast enhanced MR imaging examination

Signed informed consent

Reviewer's Comment: *The reason for this "qualifying CECT" (contrast enhanced CT) and it's role in this study is not entirely clear. As this is an inclusion criterion, presumably, in most cases, the CT scan was part of the patient's clinical diagnostic workup and was not part of this study itself (although in the patient data tables (Qualifying Radiological Examination page 14.1971) for patient A-007-46-M it is stated " Participant has baseline liver disease. There was no immediate indication for a CT scan, but the pt. was willing to have one so he could participate in this study"). Presumably the results of this CT scan were available to the investigator before the patient was enrolled and could have influenced the decision to enroll the patient in the study. The results of the qualifying CT are not specifically listed in the report and it appears that the CT scans were not mpared directly to the MRI studies which were part of this protocol. In clinical practice, if the patient had already had a contrast enhanced CT, an MRI would only be ordered if the CT did not determine the diagnosis or did not provide sufficient diagnostic information. The fact that patients must be highly suspected of having liver pathology does not rule out the possibility of the patient having confirmed liver pathology at the time of CT, and having the CT does not rule out the possibility of the patient also having had a diagnostic MRI.*

Exclusion criteria

Pregnant or Nursing Female

Hypersensitivity reaction to any gadolinium based contrast material

Any contrast study within 48 hours

Any contraindication to MRI scan

History of any hemoglobinopathies

Patient's clinical status has changed in the time interval between the CT and the study MRI (for example due to surgery, biopsy etc.)

.ty Monitoring

The following evaluations for safety monitoring were obtained

'story and Physical: A complete history and physical was obtained within 24 hours prior to injection. Physical .amination was repeated at 24 hours after injection

Vital Signs: Vital signs were obtained immediately before injection, immediately after injection, 2 hours after injection, and 24 hours and 3 days after injection. Vital signs to be monitored are: heart rate, blood pressure, and respiration rate. Changes in vital signs greater than specified values were noted;

Systolic or diastolic blood pressure > ± 20 mmHg
Heart rate > ± 15 bpm
Respiratory rate > ± 10 bpm

Clinical Laboratory: Serum laboratory assays were obtained at 24 hours prior to injection and 2 hours, 24 hours and 3 days after injection. These include CBC, chem-screen panel, electrolytes, LFTs and routine urinalysis. All laboratory values were reviewed by the investigator and any changes found by the investigator to be remarkable were entered on the case report forms. Any values falling outside the normal range were assessed by the investigators for clinical significance and relationship to study drug

EKG: 12 lead EKGs were obtained within 24 hours prior to injection and at 24 hours post injection.

TABLE A1 SAFETY MONITORING SCHEDULE

Test	pre-dose		post-dose					
	baseline	immed.	immed.	0-2hr	2hr	24 hr	48hr	3days
Iverse Event Monitoring			x	x	x	x	x	x
CBC, dif, plts.	x				x	x		x
Serum Gd concentration					x	x		x
Chemistries	x				x	x		x
Urinalysis	x				x	x		x
Vital Signs		x	x		x	x		x
EKG	x					x		
Physical Examination	x					x		

Adverse Events

All events involving appearance or worsening of illnesses or signs or symptoms after implementation of study procedures were reported. Adverse events were classified as serious if they were life threatening or permanently disabling, require hospitalization or a prolongation of hospitalization or result in death, cancer, congenital abnormality, or overdose. Non serious adverse events were classified as moderate if they require medication or other treatment by a physician, and were classified as mild if they were self resolving without treatment. "Tolerability" was assessed by monitoring patient's complaints of feelings of warmth or discomfort

:acy

maging

Patients were randomized to receive either Optimark or Magnevist. Scans were performed on a commercially available MRI scanner. Each patient had a T1 weighted and T2 weighted series covering the entire liver. All required sequences were obtained in the axial plane with parameters determined by the principal investigator at each institution. The same imaging plane and imaging parameters were used for both the pre dose and pre dose + post dose images. Post contrast images were obtained at 20 sec. (arterial phase), 60 sec. (portal venous phase) and 5 minutes (equilibrium phase). The images from all three time points constituted the post dose image set.

Image Interpretation

Image sets were interpreted by the principal investigators at each site and by 3 blinded readers. The image sets (pre dose and pre dose + post dose images for each patient) were randomized with each blinded reader reading image sets from approximately 1/3 of the patients. For the blinded read, images were viewed using an electronic system with 4 monitors, each of which could be used to view an entire MR series. For the pre dose reading T1 and T2 images were viewed on 2 separate monitors. For the pre dose + post dose reading T1 and T2 pre dose images were displayed on one monitor and the 20 sec, 60 sec. and 5 min. post dose T1 images were displayed on the other 3 monitors. A separate computer system was used for electronic data recording. Random numbers were assigned to each image set and determine the order of display. The parameters to be evaluated for each image set are: degree of confidence in diagnosis, level of conspicuity for all lesions visualized, ability to delineate lesion borders, ability to distinguish edematous tissue from pathology and degree of confidence in the total number of lesions counted. The readers assigned a number from 1 (worst) to 10 (best) for each

parameter for each image set. The first 3 parameters, degree of confidence in diagnosis, level of conspicuity for all lesions visualized and ability to delineate lesion borders, constitute the primary outcome variables. Readers

will also specify the total number of lesions visualized, mark and number each visualized lesion on an anatomical diagram of the liver, determine a diagnosis for each lesion and an overall diagnosis, make the next management choice for the patient, and note whether the contrast agent impaired the ability to visualize lesions. The principal investigator will also determine the final diagnosis for each patient based on all clinical diagnostic and histological information available up to 30 days after imaging. The pre dose images from this study were also used in making this determination, although the post dose images were not.

In reading the pre dose images, the investigators were specifically asked to:

a) Determine if the pre contrast images are technically satisfactory
b) Determine the type of disease (focal, diffuse or both)

Reviewer's Comment The meaning of "focal" and "diffuse" are not specifically defined

c) Indicate the number of lesions from 0 to 10 or more than 10
d) record the size of the smallest lesion
e) draw each lesion on an anatomical diagram and assign it a number and indicate for each lesion
   i. lesion number
   ii. location (liver segment)
   iii. level of conspicuity on a scale* of 1 to 10
   iv. delineation of lesion border on a scale* of 1 to 10
   v. degree of confidence that lesion exists on a scale of 1 to 10
   vi. diagnosis of lesion
   vii. degree of confidence in diagnosis

f) Indicate overall patient diagnosis(es)
') Indicate degree of confidence in diagnosis on a scale of 1 to 10
.ı) Specify next step in patient management

- for both conspicuity and lesion border delineation , a scale is provided on which 1 and 2 are labeled "barely obvious"5 and 6 are labeled "somewhat obvious" and 9 and 10 are labeled "clearly obvious"

In evaluating the pre dose + post dose images the principal investigator will also answer questions (a) through (h) and
i) Indicate if the contrast impedes your ability to visualize lesions

The principal investigator will also indicate the final clinical diagnosis at 30 days post imaging based on all of the following studies if they have been performed as part of the patient's workup

i. CT scan
ii. previous MRI scans
iii. ***Unenhanced MRI from this study*** *(reviewer's italics)*
iv. Ultrasound
v. Nuclear Medicine Studies
vi. Clinical course
vii. Physical Exam
viii. Laboratory Studies
ix. Biopsy/ Surgery and Histological Findings
x. Autopsy

Reviewer's Comment: *Using the pre dose images from this study in determining the final diagnosis, which will then be compared to the final diagnosis from this study seems circular. Although the post dose scans were not supposed to be used in making the final diagnosis, the principal investigator can not be blinded to the results of the post dose scans, since he will already have read them at the time of making the final diagnosis. Unless a biopsy has been obtained, the most definitive test in determining the diagnosis was the MRI scans, so that in some cases comparing diagnoses will just be comparing the results of the scans obtained in these studies to themselves*

The principal investigator will also indicate a diagnosis for each lesion and will compare his diagnoses from the pre dose and pre dose + post dose scans to the final clinical diagnosis. These comparisons were categorized as

No Agreement....Different diagnoses
Partial Agreement...Incomplete agreement in diagnoses
Basic Agreement.... Diagnoses agree but differ on number of lesions
Absolute Agreement....Both diagnosis and number of lesions agree

The blinded readers will also answer questions (a) through (h) for the pre dose images and questions(a) through i) for the pre dose + post dose images.

fourth independent reader will compare the blinded reader's diagnoses to the principal investigator's final .ıinical diagnoses using the categories a through d above, for the pre dose images and for the pre dose + post dose images

Primary Efficacy Endpoint

The primary efficacy endpoints were the differences between the mean difference scores between Magnevist and Optimark for the endpoints;

1) degree of confidence in the diagnosis
2) level of conspicuity for all lesions visualized
3) ability to delineate lesion borders

Each reader assigned a number between 1 and 10 to each of these parameters, for the pre dose scans and for the pre + post dose scans, for each patient, with 1 indicating the poorest confidence, conspicuity or delineation, and 10 the best. If an image set was unavailable it was assigned a score of 1, the worst possible score.

Reviewer's Comment: Assigning the score of 1 to the pre dose images if that image set were unevaluable, would result in a higher rather than a lower difference score

The difference between the pre dose number and the pre + post dose number was calculated for each parameter for each patient, and was called the "difference score".

For each agent (Optimark or Magnevist) the average difference score was calculated for each parameter for all patients who received that agent

The difference between these average difference scores was calculated for each parameter.

According to the sponsor, if that difference between average differences was between -1.5 and 1.5, the two imaging agents would be equivalent with respect to that parameter. This interval was chosen on the assumption that the on average the difference scores should be about 3.

Secondary Efficacy Endpoints

The secondary outcome variables were the differences in difference scores for:

a) number of lesions
b) degree of confidence in total number of lesions
c) agreement with final clinical diagnosis
d) proportion of patients where pre dose + post dose scan would change patient management
e) proportion of patients where contrast agent impaired visualization of lesions

3.2 RESULTS

Patient disposition

198 patients with highly suspected liver pathology were enrolled in this study. 197 patients were randomized to receive a single intravenous dose of either 0.1 mmol/kg Optimark (100 patients) or 0.1 mmol/kg Magnevist (97 patients).

Demographics: N=197

ıtimark N = 100
_e 54.8 ± 13.2 range 18 - 80

Sex : Male 54 (54%) Female 46 (46%)

Race: White 79 (79%), Black 15 (15%) Asian 5 (5%) Other 1 (1%)

Magnevist; N = 97
age 54.6 ± 11.6 range 31 - 78

Sex : Male 49 (51%) Female 48 (49%)

Race: White 81 (84%), Black 11 (11%) Asian 5 (5%) Other 0 (0%)

Reviewer's Comment: *The randomization was planned to give approximately 120 Optimark patients and 60 Magnevist patients. Why the randomization actually produced a 1:1 ratio instead of a 2:1 ratio is not clear*

193 patients were dosed (99 Optimark and 94 Magnevist) One Optimark patient and 3 Magnevist patients dropped out before dosing for refusal to have MRI scan due to reasons such as claustrophobia. The majority of patients were white, and the male : female ratio was approximately 1:1 There were no statistically significant 'ifferences between the two groups in height, weight , sex, or race. Protocol violations occurred in 12 Optimark nd 7 Magnevist patients. Five Optimark and 1 Magnevist patients had surgery or biopsy during the 3 day safety aluation period, and 2 Optimark patients and 2 Magnevist patients had chemotherapy during that period. One ɔptimark patient and 3 Magnevist patients had doses differing from the prescribed dose and 3 Optimark patients and one Magnevist patients did not have the contrast enhanced CAT scan within 3 weeks before dosing

Reviewer's Comment: *Review of the patient data tables on "Qualifying Radiological Examination"(which appears to give the diagnosis after the contrast enhanced CT scan) and the patient data tables on "Medical and Surgical History" (pages.14.1971 to 14.2039) indicate that many of the patients in this study have a long history of pre existing liver disease for which a final diagnosis has been known before these patients were entered in this study. In the reviewer's opinion this group as a whole may have had more advanced disease than the mix of patients usually referred for a liver MRI. Only 4 patients had a final diagnosis of "normal", whereas 11 patients had end stage liver failure and were referred for imaging for workup for possible liver transplant and 2 other patients had already had liver transplants. Since one of the most important functions of any*

imaging study is the ability to distinguish normals from patients with disease, the very small number of true normals in the patient mix is disturbing

Safety

Overall 82/193 patients who received either contrast agent (42.5%) experienced 154 adverse events
Optimark, 37/99 patients (37.4%) experienced 67 adverse events
Magnevist, 45/94 patients (47.9%) experienced 87 adverse events
Difference was statistically significant (p=0.047)

Deaths 1

1 Magnevist patient (490-C-001)with advanced colon cancer and liver and lung metastases died 1 week after dosing. No clinically significant laboratory, vital sign or EKG changes were observed during the study period. An autopsy was not performed and death was not attributed to the drug

Withdrawals due to adverse events 0

Serious adverse events 0

Severe adverse events Optimark 2, Magnevist 0

One Optimark patient (490-B-021) experienced severe left flank pain, beginning 4 hours post injection and lasting 13 days

One Optimark patient (490-F-0230) experienced severe headache beginning 13 hours after injection and lasting for 10 hours this patient also developed moderate paresthesias and dizziness immediately after injection and subsequently developed rash and diarrhea. Paresthesias, dizziness and rash were attributed to the drug by the principal investigator.

The most common adverse events were headache (10/99 Optimark, 12/94 Magnevist)and taste perversion (6/99 Optimark, 6/94 Magnevist). Other common adverse events included , dizziness, vasodilation, nausea and abdominal pain

Clinical and Laboratory Monitoring

'BC, Serum Chemistry and Urinalysis results were analyzed by evaluating the " standardized result " defined

standard result = (result -lower normal range) / (upper normal range - lower normal range)

Reader's Comment: *The sponsor has presented tables showing the number of patients with a change in laboratory values of greater than 40% of the reference range for that parameter. These tables are not reproduced here because they are clinically meaningless. The value of 40% of the reference range is an arbitrary number with no clinical significance. The importance of the magnitude of the change depends on the parameter being considered. An increase in serum potassium of 40% of the reference range could be life threatening, whereas an increase in serum glucose of 100% of the reference range would just mean that the patient has recently eaten*

Scatter plots of result vs. baseline value were plotted for all parameters
(Pages 14.0530 to 14.0574 vol. 68)
No clinically significant trends in the data were seen
LFTs were high for most patients both baseline and post dose with no large changes. This is what would be expected in patients with liver pathology.
The largest percentage changes were seen in serum glucose and this is due to the fact that these glucose values were random rather than fasting levels.
Except for serum glucose, the mean change in laboratory values for all parameters, for all measurement times and for both Optimark and Magnevist was less than 15% of the reference range

Vital Signs

Vital Signs showed statistically significant decreases in the mean from baseline in diastolic blood pressure in the Optimark group at 2, 24 and 72 hours, but these changes were not clinically significant. A similar decrease astolic blood pressure was seen in the Magnevist group, Scatter plots of results vs. Baseline showed no .inically significant trends in the data.

Using the sponsor's guidelines 57 patients experienced notable clinically significant changes (changes outside the sponsors guidelines and felt by the investigators to be clinically significant) in vital signs. One patient experienced a 44 mm hg increase in systolic BP and a 31 mm increase in diastolic BP during a liver biopsy procedure 2 hours after dosing. No others were considered to be clinically significant

TABLE A2 NUMBER OF PATIENTS WITH CLINICALLY SIGNIFICANT CHANGES IN VITAL SIGNS

Change	OPTIMARK			MAGNEVIST		
	0 hr	2hr	24 hr	0 hr	2hr	24 hr
Systolic BP ± > 20 mm	12	10	17	6	6	6
Diastolic BP ± > 20 mm	2	4	2	3	3	3
Pulse rate ± > 15 bpm	1	0	2	2	5	7
respiration rate ± > 10 bpm	0	0	0	0	0	0

EKG

11 patients had EKG changes from baseline post dose, 8 Optimark and 3 Magnevist. One Optimark patient had poor R wave progression in the anterior leads and this was the only change that was considered to be clinically ignificant. None of the changes were attributed to the drug.

Baseline value and change from baseline at 24 hours (mean, SD and range) for PR,QRS and QT intervals

TABLE A3 EKG PARAMETERS, BASELINE AND CHANGE FROM BASELINE

	OPTIMARK				MAGNEVIST			
	N*	BASELINE	N*	CHANGE	N*	BASELINE	N*	CHANGE
PR	99	153 ± 4 (100, 244)	99	-2.4 ± 14 (-66, 48)	94	157 ± 23 (80, 200)	93	-2.0 ± 11.9 (-60, 32)
QRS	99	84 ± 16 (30, 116)	99	-0.17 ± 4.7 (-10, 20)	94	86 ±20 (50, 164)	93	.06 ±6.2 (-20, 20)
QT	50	373 ± 45 (260,456)	50	2.74 ± 19.9 (-40, 76)	51	376 ± 46.8 (240, 460)	50	.18 ± 14 (-56, 30)
QTc	50	414 ± 27 (318,472)	50	.36± 115 (-41, 35)	51	419 ± 38 (266, 535)	50	-3.5 ± 17 (-44, 36)

* N is the number of patients for which the parameter is available. There were 99 Optimark patients and 94 Magnevist patients. **Note that the QT interval is obtained from the EKGs for only about half of the patients**

Reviewer's Comment: *EKGs were **not** obtained immediately before and immediately after dosing, but at baseline (up to 24 hours pre dose) and at 24 hours post dose. These results do not rule out the possibility of clinically significant, or even potentially life threatening EKG changes immediately after dosing. EKGs were read by the investigators who are not blinded and are not cardiologists, which brings the results of these eadings into question.*

olerance"

35/99 Optimark patients (35.4%), and 21/94 Magnevist reported injection associated discomfort. The most common sensation was cold in 20% of Optimark patients and in 14 percent of Magnevist patients

Reviewer's Comment: What the sponsor refers to as "tolerance" involves only mild to moderate transient patient discomfort which has little or no implications for patient safety

fficacy

Patient Disposition For Efficacy Analysis

198 patients with highly suspected liver pathology were enrolled in this study. 197 patients were randomized to receive a single intravenous dose of either 0.1 mmol/kg Optimark (100 patients) or 0.1 mmol/kg Magnevist (97 patients). 193 patients were dosed (99 Optimark and 94 Magnevist) One Optimark patient and 3 Magnevist patients dropped out before dosing for refusal to have MRI scan due to claustrophobia and other reasons

Primary Efficacy Endpoints

1) degree of confidence in the diagnosis
2) level of conspicuity for all lesions visualized
   ability to delineate lesion borders

***Reviewer's Comment**: These endpoints call for a highly subjective response by the readers, who were asked to rate each of these endpoints for each set of scans on a scale of 1 to 10. Inter reader variability in these ratings 'n not be directly assessed since, with the sponsor's design of the blinded reading, no set of scans would be ad by more than one reader. The actual outcome variable is derived from the reader's responses in a complex manner:*

1) The reader separately evaluates the pre dose scans and the post scans for each patient, for each efficacy endpoint.
2) The difference between the scores for the pre dose image and the pre dose + post dose image set is called the "difference score"
3) The mean difference score is calculated for the group of patients who received the agent (either Optimark or Magnevist
4) The outcome variable, for each endpoint is the difference between the Magnevist difference score and the Optimark difference score for that endpoint

Blinded Reader Results for Primary Efficacy Endpoints

The data below is contained in sponsor's tables 11.4.1.2-2 to 11-4-1.5-7 (vol. 2.67, pgs14-0045 to14-0055)

Indication for liver diagnosis as determined by the investigator

***Reviewer's Comment** These are presumably the diagnoses which the referring physician entered on the equisition for the imaging study although this is not explicitly stated.*

TABLE A4 INDICATION FOR LIVER IMAGING

	OptiMARK n=99	MAGNEVIST n=92*
liver mass/neoplasm	90	91
infection/inflammation	1	0
vascular	4	1
other/unknown	4	0

- In the patient disposition it is stated that there were 99 patients who received Optimark and 94 who received Magnevist. Why only 92 Magnevist patients were listed in this table is not clear.

***Reviewer's Comment:** There is not really a good mix of patients. It appears that over 90% of patients in both treatment groups were referred for MRI either to evaluate or rule out a liver mass or neoplasm. There do not appear to be enough patients with other reasons for referral to evaluate the efficacy of Optimark in patients with other pre-scan diagnoses. However reviewing the tables of final diagnoses as determined by the principal investigator, there seemed to be a much better balance between malignant and non malignant diseases than would appear from the numbers in table 1*

TABLE A5 DEGREE OF CONFIDENCE IN DIAGNOSIS

AGENT/PARAMETER	mean difference score*	95% confidence interval	patients	p value+	ratio++
OPTIMARK	1.465	----------	99	<.001	----------
MAGNEVIST	1.415	----------	94	<.001	----------
Difference**	-0.050	-0.214 - +0.115		----------	-0.035

* difference between pre dose + post dose score and pre dose score

** Difference between Magnevist mean difference score and Optimark mean difference score

+ p value for the difference score. If $p < 0.05$, then the mean difference score is statistically significantly different from 0

++ the "ratio" defined by this reviewer is the difference between the Magnevist mean difference score and the Optimark mean difference score divided by the Magnevist mean difference score

Reviewer's Comment: *The "ratio" defined by this reviewer as the difference between the difference scores divided by the Magnevist difference scores, is the difference between Magnevist and Optimark, as a percentage of the difference between Magnevist and the pre dose scan, and in this reviewer's opinion, gives a better idea of the clinical significance of the difference of difference scores than just that differences of difference scores itself. If the ratio is small it means that the difference between Optimark and Magnevist is small compared to the difference between Magnevist and the pre dose scan, which is what one would want to show in an equivalence trial. If the ratio is negative it means that on the average Optimark has scored higher than Magnevist, while if the ratio is positive, the reverse would be true.*

TABLE A6 BORDER DELINEATION

AGENT/PARAMETER	mean difference score*	95% confidence interval	patients	p value+	ratio++
OPTIMARK	0.768	----------	99	0.036	----------
MAGNEVIST	0.277	----------	94	0.458	----------
Difference**	-0.491	-1.347 - +0.365		----------	-1.77

* difference between pre dose + post dose score and pre dose score

** Difference between Magnevist mean difference score and Optimark mean difference score.

+ p value for the difference score. If $p < 0.05$, then the mean difference score is statistically significantly different from 0

++ the "ratio" defined by this reviewer is the difference between the Magnevist mean difference score and the Optimark mean difference score divided by the Magnevist mean difference score

Reviewer's Comment: *This reviewer has defined the "ratio", r, as a measure of the difference between the Magnevist and Optimark difference scores as a percentage of the Magnevist difference score. Only if $r << 1$, can equivalence be said to have been demonstrated in any meaningful sense. This is certainly true for confidence in diagnosis in table 1. However if $r > 1$, then the mean difference between Optimark and Magnevist is less than the mean difference between pre dose image (i.e. No contrast agent at all) and Magnevist. While equivalence may still be demonstrated statistically, using the sponsor's choice of confidence interval, equivalence would not have been demonstrated in any clinically meaningful sense. This seems to be the case for border delineation given in table A6*

TABLE A7 CONSPICUITY OF LESIONS

Reader	AGENT/PARAMETER	mean difference score*	95% confidence interval	patients	p value+
1	OPTIMARK	1.710	----------	31	0.017
	MAGNEVIST	0.000	----------	33	1.000
	Difference*	-1.710	-2.973 - 0.447	----------	----------
2	OPTIMARK	0.345	----------	29	0.178
	MAGNEVIST	0.314	----------	35	0.478
	Difference*	-0.031	-0.871 - +0.810	----------	----------
3	OPTIMARK	0.333	----------	39	0.177
	MAGNEVIST	0.731	----------	26	0.0132
	Difference*	0.398	-0.483 - +1.279	----------	----------

* Difference between Magnevist mean difference score and Optimark mean difference score

+ p value for the difference score. If $p < 0.05$, then the mean difference score is statistically significantly different from 0

Reviewer's Comment: *Conspicuity is the only one of the primary outcome variables for which the sponsor presented the results for the individual blinded readers in the study report. These results demonstrate considerable reader variability, but this is probably a reflection of the subjective nature of the question. Reader #1 found Optimark better than Magnevist, reader #3 found Magnevist better than Optimark and only for reader #2 were the difference scores for the two agents approximately the same.*

One would expect a strong correlation between these three primary outcome variables. Well delineated borders should increase the conspicuity of the lesions and both conspicuity and border delineation should contribute to confidence in the diagnosis. As expected, there is a strong positive correlation between conspicuity and border delineation but the correlation between border delineation and confidence in diagnosis, and between conspicuity and confidence in diagnosis are weak. The relevant correlation coefficients are shown below.

CORRELATION COEFFICIENTS

Conspicuity - Border Delineation..... r = 0.8551

Conspicuity - Confidence in Diagnosis..... r = 0.0995

Border Delineation - Confidence in Diagnosis..... r = 0.1686

Secondary Efficacy Endpoints

a) **Number of lesions visualized**
b) **Confidence in number of lesions**
c) **Proportion of patients for whom contrast impaired visualization**
d) **Agreement with final diagnosis**

***Reviewer's Comment**: Agreement with final diagnosis is of course the outcome variable with the greatest clinical significance. Number of lesions is the only outcome variable that is actually a cardinal number since readers were asked to do an actual count rather than merely to assign an arbitrary number on a scale of 1 10. It is interesting that both of these were **secondary** outcome variables*

TABLE A8 NUMBER OF LESIONS VISUALIZED				
AGENT/PARAMETER	mean difference score*	confidence interval	patients	ratio***
OPTIMARK	0.606	+0.029 - +1.183	99	----------
MAGNEVIST	0.500	-0.092 - +1.092	94	----------
Difference**	-0.106	-0.794 - +0.582		-0.175

* difference between pre dose + post dose score and pre dose score

** Difference between Magnevist mean difference score and Optimark mean difference score

*** the "ratio" defined by this reviewer is the difference between the Magnevist mean difference score and the Optimark mean difference score divided by the Magnevist mean difference score

***Reviewer's Comments**: Those patients with a diagnosis of either diffuse disease or no disease (normal) would have no (0) lesions visualized, and of course the readers could not evaluate the conspicuity or the border delineation of lesions that they did not see. Review of the patient data reveals that there were 10/98 (10.2%) Optimark patients and 20/93 (21.5%) Magnevist patients for whom the blinded readers found no lesions on either the pre dose pr post dose scans. It appears that these patients were assigned a score of 1 (the lowest possible score) for both conspicuity and lesion visualization, although this is not stated explicitly in the study report.*

TABLE A9 CONFIDENCE IN NUMBER OF LESIONS				
AGENT/PARAMETER	mean difference score*	confidence interval	patients	ratio***
OPTIMARK	1.648	+1.227 - +2.069	99	----------
MAGNEVIST	1.067	+0.626 - +1.508	94	----------
Difference**	-0.581	-1.067 - -0.075		-0.545

* difference between pre dose + post dose score and pre dose score

** Difference between Magnevist mean difference score and Optimark mean difference score

*** the "ratio" defined by this reviewer is the difference between the Magnevist mean difference score and the Optimark mean difference score divided by the Magnevist mean difference score

TABLE A10 Proportion of patients where contrast obscured visualization		
AGENT/PARAMETER	proportion	confidence interval
OPTIMARK (n=99)	6%	5%-7%
MAGNEVIST (n=94)	4%	3%-5%

TABLE A11 Agreement With Final Diagnosis										
ınal diagnosis	non-evaluable		no agreement		partial agreement		basic agreement		absolute agreement	
OPTIMARK PRE DOSE										
disease* n=89	1	1.1%	15	16.9%	26	29.2%	28	31.5%	19	21.4%
no disease* n=4	0		3	75%	1	25%	0		0	
OPTIMARK PRE DOSE + POST DOSE										
disease* n=89	0		15	16.9%	27	30.3%	27	30.3%%	20	21.4%%
no disease* n=4	0		2	50%	2	50%	0		0	
MAGNEVIST PRE DOSE										
disease* n=84	1	1.2%	13	15.5%	21	28.0%	30	35.7%	19	22.6%
no disease* n=6	0		0		2	33.3%	1	16.7%	3	50.0%
MAGNEVIST PRE DOSE + POST DOSE										
disease* n=84	0		17	20.2%	17	20.2%	27	32.1`%	23	27.4%
no disease* n=6	0		1	16.7%	2	33.3%	1	16.7%	2	33.3%

- presumably "disease" and "no disease" refer to the final diagnosis, although this is not explicitly stated. The number of patients with "no disease is, however, larger than the number of patients listed in the patient data tables as having a "final diagnosis" of "normal".

For the "pseudo sensitivity and pseudo specificity table, the categories of "non evaluable", "no agreement", and partial agreement" are combined and called "non agreement". The categories of "basic agreement" and ;reement" are combined and called "agreement"

TABLE A12 "Pseudo Sensitivity and Specificity Table				
final diagnosis	agreement		non-agreement	
OPTIMARK PRE DOSE				
disease n=89*	47	52.8%	42	47.2%
no disease n=4*	0		4	100%
OPTIMARK PRE DOSE + POST DOSE				
disease n=89*	47	52.8%	42	47.2%
no disease n=4*	0		4	100%
MAGNEVIST PRE DOSE				
disease n=84*	49	58.3%	35	41.7%
no disease n=6*	4	66.7%	2	33.3%
MAGNEVIST PRE DOSE + POST DOSE				
disease n=84*	50	59.5%	34	40.5%
no disease n=6*	3	50%	3	50%

* In the patient disposition it is stated that there were 99 patients who received Optimark and 94 who received Magnevist. Why only 93 Optimark patients and 90 Magnevist patients were listed in tables 8 and 9 is not clear. **Non agreement occurs, not only if a normal liver is called diseased or visa versa, but also if a liver is correctly called diseased, but the disease is not correctly identified. For this reason, the terms pseudo-sensitivity and pseudo specificity were used

***Reviewer's Comment**: From the above tables ,taken directly from the sponsor's tables 11.4.1.5-3 and 11.4.1.5-4, it would appear that there are 10 patients with "no disease", 4 in the Optimark group and 6 in the Magnevist group. However, in patient data listing 16.2.6-17, which gives the final clinical diagnosis according to the principal investigator only 4 patients are listed as "normal", 3 in the Magnevist group and 1 in the Optimark group. If the patients were numbered sequentially at each center, data listings for some patients may be missing from this data listing, in particular patients F001 to F003 and G001 to G007*

For comparison, the tables showing agreement with the final diagnosis and for pseudo sensitivity and specificity, for the investigators, are given below. As expected, the agreement with the final diagnosis was much better for the principal investigators who had access to all of the clinical data, was much better than for the blinded readers. Since the pre dose scans were used in the determination of the final diagnosis by the investigators, agreement of the final diagnosis with the investigator's reading of the pre dose scans are not tabulated by the sponsor.

TABLE A13 Agreement With Final Diagnosis-Investigators Intent to Treat										
final diagnosis	non-evaluable		no agreement		partial agreement		basic agreement		absolute agreement	
OPTIMARK PRE DOSE + POST DOSE										
disease n=89	1	1.1%	5	5.6%	10	11.2%	15	18.9%	58	65.2%
no disease n=4	0		2	50%	1	25%	0		1	25%
MAGNEVIST PRE DOSE + POST DOSE										
disease n=84	0		8	9.5%	12	14.3%	20	23.8%%	44	52.4%%
no disease n=6	0		0		1	16.7%	1	16.7%	4	66.7%

TABLE A14 "Pseudo Sensitivity and Specificity Table - Investigators Intent to Treat				
final diagnosis	agreement		non- agreement	
OPTIMARK PRE DOSE + POST DOSE				
disease n=89	73	82.0%	16	18.0%
no disease n=4	1	25.0%	3	75.0%
MAGNEVIST PRE DOSE + POST DOSE				
disease n=84	64	76.2%	20	23.8%
no disease n=6	5	83.3%	1	16.7%

***Reviewer's Comments:** Of all the endpoints considered by the sponsor, agreement with the final diagnosis is the most clinically significant. If the post contrast scans cannot be used to help make the correct diagnosis, then conspicuity of the lesions, border delineation etc. are of no clinical consequence. If the diagnosis is incorrect, then increased confidence in that diagnosis would be a liability rather than an asset. Problems with the determination of the final diagnosis in this protocol have already been discussed above. However, even granting the validity of the sponsor's implicit assumption that the final diagnosis is the "correct" diagnosis, the results in tables A11, and A12 do not support a conclusion in favor of the efficacy of Optimark. Comparing the results for the Optimark pre contrast scans and the Optimark post contrast scans, there appears to be virtually no difference between pre dose and pre dose + post dose scans (in table A12 the numbers are exactly the same) With Magnevist the differences between pre dose and pre dose + post dose scans are also very small.*

A conclusion that may be drawn from all of this is that although Optimark is equivalent to Magnevist for this group of patients and for this group of readers, neither agent contributes significantly to the ability to make the correct diagnosis, over what would have been achieved with the pre dose images alone. If this conclusion were to be generalized, it would be that contrast agents in general do not play as important role in determining the final diagnosis for liver lesions as for CNS lesions. Since there have been no studies to specifically assess the efficacy of Magnevist in the diagnosis of liver lesions, such a conclusion would not contradict existing data.

Of particular concern is that, for Optison the pre dose + post dose diagnosis differed from the final diagnosis for almost half the patients with disease, and for all 4 patients without disease. A useful diagnostic modality should be able to make the "correct" diagnosis more than half of the time.

Recalling how the final diagnosis was determined, these results are not unexpected. The pre dose scans from this study were considered part of the workup that determined the final diagnosis! It is therefore not surprising that good agreement between the pre dose scan diagnosis and the final diagnosis was seen in the data. It could be argued that with that definition of the "final diagnosis" it would be virtually impossible to demonstrate better agreement between the pre dose + post dose scans and the final diagnosis than between the pre dose scans and the final diagnosis. In fact, any attempt to obtain sensitivity and specificity, without using a single reliable "standard of truth" for all patients, would be fatally flawed.

The investigators were asked to list the diagnostic tests that were used to determine the final diagnoses and these were listed in the patient data tables. The pre-dose scan from this study was used in determining the final diagnosis for 173 out of 193 patients (88%) whereas biopsy was used for only 29 patients (15%) For those patients who did not have a biopsy, the pre dose MRI may have been the most influential test in determining the final diagnosis. The rationale for using a contrast agent in the first place is that the combination of the pre dose scan and the pre dose + post dose scan are supposed to improve the ability to make a diagnosis over the pre dose scan alone so that using the pre dose scan as part of the comparator by which the pre dose + post dose scan was evaluated makes little sense.

Sponsor's Conclusion:

Optimark and Magnevist were equivalent in providing contrast enhancement in this study of adults with known or highly suspected liver pathology

3.3 REVIEWER'S ANALYSIS

Safety

In this study,193 patients were dosed. 99 patients received Optimark and 94 patients received Magnevist

Adverse events

There was one death. One Magnevist patient died 1 week after dosing. Death was not attributable to the drug

There were no serious adverse events

Two Optimark patients experienced severe adverse events
One Optimark patient (490-B-021) experienced severe left flank pain, beginning 4 hours post injection and lasting 13 days

ne Optimark patient (490-F-023) experienced severe headache beginning 13 hours after injection and lasting for 10 hours this patient also developed moderate paresthesias and dizziness immediately after injection and

subsequently developed rash and diarrhea. Paresthesias, dizziness and rash were attributed to the drug by the principal investigator

Vital signs

There were no clinically significant changes in vital signs in either treatment group. However, vital signs were monitored 24 hours before dosing and 24 hours after dosing. Vital signs were not monitored immediately before and immediately after dosing

Physical Examination

There were no clinically significant changes on physical examination in either treatment group.

Laboratory Monitoring

There were no clinically significant changes in laboratory values in either treatment group.

EKG

There were no clinically significant changes in EKGs in either treatment group. However, EKGs were obtained 24 hours before dosing and 24 hours after dosing,. EKGs were not obtained immediately before and immediately after dosing

Efficacy

General

In this reviewer's opinion, the two most important indications of the clinical usefulness of any diagnostic test are:

1) The test's ability to distinguish between normal and disease (in this case, the ability to distinguish a normal liver from a diseased liver, irrespective of the type of pathology in that diseased liver)

2) The test's contribution to the determination of the final diagnosis in those cases in which disease is found.

Distinguishing a Normal Liver From a Diseased Liver

In order for a study to be able to demonstrate the ability of a test to distinguish normal from disease, a substantial number of subjects in the study would have to be normal. This could be insured by deliberately including normal subjects in the study, but even if the study included only patients who are referred for the test because of a suspicion of disease, a substantial proportion of these patients would turn out to be normal. In this study, in the patient data tables of Final Clinical Diagnosis According to the Principal Investigator, only 4 patients are listed as normal. In contrast, in the patient data table titled "Qualifying Radiological Examination" (which presumably lists the referring diagnoses) 11 patients are listed as "pre liver transplant" or "liver transplant candidate" and 2 patients are listed as "liver transplant" or "history of liver transplant". (Interestingly, no patient has a pre dose, post dose or final diagnosis of "status post liver transplant") In reviewing the diagnoses it appears that the patient population is weighted towards patients with advanced liver isease, with fewer patients who are undergoing initial evaluation to rule out possible liver disease than might oe expected. This may be due to a bias introduced into the patient selection process by the requirement that patients entered in the study have had a "qualifying" CT scan while , at the same time that they be "highly

suspicious" of having liver pathology. Since the CT results were probably available to the investigator at the time that most patients were entered into the study, some investigators could have concluded that patients with CT scans read as normal were no longer "highly suspicious" for liver pathology, and such patients were not entered into the study. Since there is no data available for patients who were not entered in the study because the investigator did not think that they met the entry criteria, there is no way that this hypothesis about selection bias could be tested.

Since this study had only 4 patients with a final clinical diagnosis of normal, the results of this study can not be used to demonstrate the equivalence of Optimark to Magnevist in the ability to distinguish a normal liver from a diseased liver. Even for the few normals actually in the study the results are not reassuring. Table 9. The "pseudo sensitivity -specificity table for the blinded readers. Contains 10 patients with "no disease" (how this can be reconciled with the 4 patients listed as having a normal final diagnosis in the patient data tables is not clear. However it should be noted that the listings are incomplete as there is no final diagnosis listed for patients B-010, F-001, F-002, G-001, G-002, G-003, G-004, G-005, G-006 and G-007) Of the 4

patients in the Optimark group with "no disease' the pre +post dose scan diagnosis agrees with the final diagnosis for 0 patients (0%) and disagrees for 4 patients (100%)

Agreement With Final Diagnosis

To conclude that a contrast agent contributes to the ability to make a correct diagnosis, it should be shown that there is better agreement with the final diagnosis for the set of pre dose + post dose scans, than for the pre dose scans alone (assuming that the final diagnosis is in fact the "correct" diagnosis). Referring again to Table A12, this does not appear to be the case for Optimark. In fact for Optimark, for both disease and non disease, the number of patients for which the pre dose scan diagnosis agrees with the final diagnosis, is exactly the same as the number of patients for whom the pre +post dose scan diagnosis agrees with the final diagnosis For Magnevist, the numbers are not identical, but the differences are very small. In terms of the ability to achieve agreement with the final diagnosis, the data may support the conclusion that Optimark is equivalent to Magnevist, but the same data would support the conclusion that both Optimark and Magnevist are equivalent to Pre dose scans, that is to no contrast agent at all. Such a demonstration could hardly lead to the conclusion that Optimark is clinically useful.

This result may be due to the way that the "final diagnosis" was defined. The pre dose scans from this study were one of the tests that were used in determining the final diagnosis. Substantial agreement between the pre dose diagnosis and the final diagnosis would be expected, and it would be very difficult to demonstrate better agreement between the pre + post dose diagnosis and the final diagnosis, than between the pre dose diagnosis alone and the final diagnosis alone.

Sponsor's Primary Endpoints

The Sponsor's primary endpoints for this were
1) degree of confidence in the diagnosis
2) level of conspicuity for all lesions visualized
3) ability to delineate lesion borders

For each of the endpoints the blinded readers were asked to assign a number between 1 and 10, going from worst to best, for each patient's pre dose scans and for each patient's set of pre dose +post dose scans. For each patient the difference between the post dose score and the pre dose score was called the difference score for that

endpoint. For the group of patients who received Optimark, the average difference score was calculated for each endpoint and for the group of patients who received Optimark, the average difference score was also calculated or each endpoint. For each endpoint, the difference between the difference score for Magnevist and the ifference score for Optimark was the outcome variable. For Optimark and Magnevist to be considered to be equivalent, the difference between these difference score s should be small, but the question remains , "small with respect to what?" The sponsor arbitrarily chose the value of 1.5 on a scale of 1 to 10 as "small" and says that equivalence is demonstrated if the difference of difference scores can be shown to be between -1.5 and 1.5 with 95 % confidence. This reviewer believes that equivalence is not demonstrated in any clinically meaningful sense unless the difference of difference scores is small compared to the difference score for Magnevist.

Assessing these endpoints calls for highly subjective responses on the part of the readers. Since no scans were read by more than one reader it is impossible to determine directly if two different readers would have read the same scan differently. In assigning values from 1 to 10, the readers are really ordering the sets of scans from best to worst in regard to each endpoint. The assigned numbers are therefore **ordinal** numbers rather than **cardinal** numbers. It is not clear that performing arithmetic manipulations on ordinal numbers (calculating means and differences of means, means of differences etc.,) makes any sense, especially when calculating averages of ordinal numbers assigned by different readers. It is therefore not clear that the difference of mean difference scores represents anything meaningful at all and whether showing that the absolute value of this number is less than 1.5 demonstrates anything meaningful.

1) Degree of Confidence in Diagnosis

The results for degree of confidence in diagnosis for the blinded readers are given in table A5. The confidence nterval for the difference of difference scores does include 0 so equivalence is demonstrated. The p value for ne Optimark difference score is $p < 0.001$ so that it is also demonstrated that for Optimark, the mean difference ore is statistically different from 0. Therefore the superiority of the pre dose +post dose image set over the pre se images alone has been demonstrated for Optimark.

Conclusions for this endpoint supported by the data
a) Optimark is equivalent to Magnevist
b) Optimark Pre-dose +post dose images are superior to pre-dose images alone

Reviewer's comments: *Because of the known difficulties with equivalence trials this reviewer considers the demonstration of the superiority of Optimark images over pre dose images alone to be a much stronger result than the demonstration of the equivalence of Optimark and Magnevist. Inherent in the use of "confidence in diagnosis" as an outcome variable is the implicit assumption that a higher confidence in diagnosis demonstrates superiority. However a higher confidence in diagnosis would be good only when the correct diagnosis is made. A high confidence in the diagnosis when the diagnosis is wrong would be dangerous. It is not clear that the parameter "confidence in diagnosis" alone , without assessing the correlation with the other outcome variable "agreement with final diagnosis" is really meaningful at all*

2) Overall Level of Conspicuity For All Lesions

The results for Conspicuity of lesions, for the blinded readers, are given in table A7. Since there is significant variation in responses between the 3 readers, these result are given for each blinded reader separately.

For **reader #1**, the mean difference score for Optimark was 1.710 The mean difference score for Magnevist was 0.000. The difference was therefore -1.710. The confidence interval for the difference did not

include 0. So the data for this reader would that Optimark is superior to rather than equivalent to Optimark. The p value for the Optimark difference is 0.017, so the data for this reader would support the conclusion that ptimark is superior to pre dose images alone.

For the **reader #2**, the Optimark difference score is 0.345 and the difference score for Magnevist is 0.314, the difference is 0.031, and since the confidence interval for the difference is -0.871 - +0.810, the data would support equivalence However the difference scores for both Optimark and Magnevist are not statistically significant so that superiority of ether Optimark or Magnevist over pre dose images alone

For reader #3, the Optimark difference score is 0.333 and the difference score for Magnevist is 0.731, the difference is 0.391, and since the confidence interval for the difference is -0.483 - +1.279 the data would support equivalence However the difference scores for Optimark is not statistically significant while the difference score for Magnevist is statistically significant

Conclusions for this endpoint supported by the data

In the reviewer's opinion, because of the disparity in results between the 3 blinded readers, no firm conclusions can be drawn for this endpoint for this data

3) **Ability to Delineate Lesion Borders**

The results for ability to delineate lesion borders, for the blinded readers, are given in table A6. The confidence interval for the difference of difference scores does include 0 so equivalence is demonstrated. The p value for the Optimark difference score is p = 0.036 so that it is also demonstrated that for Optimark, the difference in ıean difference scores between the pre dose +post dose images and pre dose images alone is statistically ⁴ifferent from 0. Therefore the superiority of the pre dose +post dose image set over the pre dose images alone s been demonstrated for Optimark

Conclusions for this endpoint supported by the data

a) **Optimark is equivalent to Magnevist**
b) **Optimark Pre-dose +post dose images are superior to pre-dose images alone**

Sponsor's Secondary Outcome Variables

a) **Number of lesions visualized**
b) **Confidence in number of lesions**
c) **Proportion of patients for whom contrast impaired visualization**
d) **Agreement with final diagnosis**

Number of Lesions Visualized

The results for the blinded readers for number of lesions visualized are given in table A8. This outcome variable is the only cardinal number in the entire set of outcome variables, since the readers are actually asked to count lesions rather than to rank images in order of superiority The confidence interval for the difference of difference scores does include 0 so equivalence is demonstrated. The confidence interval for the OptiMARK difference score does not include 0, therefore the superiority of the pre dose +post dose image set over the pre dose images alone has been demonstrated for Optimark

Conclusions for this endpoint supported by the data

a) **Optimark is equivalent to Magnevist**
Optimark Pre-dose +post dose images are superior to pre-dose images alone

Confidence in Number of Lesions

The results for confidence in number of lesions, for the blinded readers, are given in table A9. The confidence interval for the difference of difference scores does not include 0 so equivalence is not demonstrated. The ›nfidence interval for the Optimark difference score does not include 0, Therefore the superiority of the pre ɔse +post dose image set over the pre dose images alone has been demonstrated for Optimark

Conclusions for this endpoint supported by the data

a) Equivalence of Optimark and Magnevist has not been demonstrated

b) Optimark Pre-dose +post dose images are superior to pre-dose images alone

Proportion of Patients For Whom Contrast Impaired Visualization

The results, for the blinded readers, for Proportion of Patients For Whom Contrast Impaired Visualization are given in table A10. The number of patients for whom contrast obscured the visualization of lesions was small for both agents, 6% for Optimark and 4% for Magnevist . The confidence intervals for these percentages for both agents overlapped, therefore equivalence is demonstrated

Conclusions for this endpoint supported by the data

Equivalence of Optimark and Magnevist has been demonstrated

Agreement with Final Diagnoses (Sensitivity and Specificity)

Reviewer's Comment: *In the reviewer's opinion, this is the endpoint with the greatest clinical significance. Other properties of the images are useful only if they aid in making a correct final diagnosis. Since this was not ›ne of the sponsor's primary outcome variables one might conclude that the sponsor does not agree*

: results for agreement with the final diagnosis for the blinded readers are given in tables A11 and A12.Corresponding results for the investigators are given in tables A13 and A14. There is obviously much better agreement with the final diagnosis for the investigators than for the blinded readers. This is expected since the investigators had available to them, all the clinical and diagnostic information for each patient, and since the final diagnosis was, in fact determined by the investigators on the basis of that clinical and diagnostic information, including the pre dose scans from this study. Thus the investigators for the Optimark pre +post dose set of scans, agreement with the final diagnosis was 65.2% and for the Magnevist pre +post dose set of scans, agreement with the final diagnosis was 52.4%. The corresponding percentages for the blinded readers were 21.4% and 27.4% respectively. The investigators responses were obviously influenced by the additional information available to them, that was not available to the blinded readers. The results for the investigators for this endpoint and for other endpoints will not be discussed further

Although p values are not given, the equivalence between Optimark and Magnevist should be obvious from the numbers in tables A11 and A12. However even more striking is the agreement between the Optimark pre dose scans and the Optimark Pre +post dose scans. This can be best seen in table A12 where the 5 possible outcomes in table 8 have been reduced to 2 possible outcomes. For Optimark pre dose scans there is agreement for 47 patients with disease and non agreement for 42 patients for patients with disease. and there is agreement for 0 patients and non agreement for 4 patients without disease. For the Optimark pre +post dose scans for patients with disease there is agreement for 47 patients and non agreement for 42 patients, and for patients without disease , there is agreement for 0 patients and non agreement for 4 patients. The numbers are identical!. Thus if :quivalence has been demonstrated between Optimark and Magnevist, for this endpoint, it is because neither appears to increase the agreement with the final diagnosis over what would be achieved with the pre dose scans ›ne. For this endpoint, the two imaging agents are equivalent because they are equally ineffective.

Conclusions

Safety

There was one death. One Magnevist patient died 1 week after dosing. Death was not attributable to the drug

There were no serious adverse events

Two Optimark patients experienced severe adverse events. In the reviewer's opinion, one (490-B-021) was not related to the drug, and the other (490-F-023) may have resulted from a reaction to the drug, which occurred immediately after administration. Neither resulted in death or permanent sequelae.

There are no significant safety concerns raised by the data presented in this study. That data, however is incomplete Vital signs and EKGs should have been obtained immediately before and immediately after dosing. This shortcoming could however be addressed by a phase 4 post marketing commitment.

In this reviewer's opinion, the data presented in these studies raise no significant safety concerns that would impact the approval decision. However the data is incomplete. EKGs were obtained 24 hours before and 24 hours after dosing. Changes would be most likely to occur immediately after dosing. The data is inadequate to rule out life threatening EKG changes immediately after dosing. For the EKGs that were done, QT and QTc intervals are available for only a fraction of the patients. The EKGs were read by the investigators, not by blinded cardiologists. Chemistries were not obtained immediately after dosing but at 2 hours after dosing

Efficacy:

The objective of this study has been to demonstrate the equivalence of Optimark to Magnevist, an approved MRI contrast agent.

For the group of patients studied, for two of the three of the sponsor's primary outcome variables:

Degree of confidence in the diagnosis
Ability to delineate lesion borders

Equivalence between Optimark and Magnevist has been demonstrated. Superiority of the Optimark pre + post dose images over the pre dose images alone has also been demonstrated.

For the sponsor's third primary outcome variable:

level of conspicuity for all lesions visualized

Because of the disparity in results between the 3 blinded readers, no firm conclusions can be drawn for this endpoint for this data

For the sponsor's secondary outcome variables:

Number of lesions visualized
Confidence in number of lesions

Equivalence between Optimark and Magnevist has been demonstrated. Superiority of the Optimark pre + post dose images over the pre dose images alone has also been demonstrated.

For the sponsor's secondary outcome variable:

roportion of patients for whom contrast impaired visualization

Equivalence between Optimark and Magnevist has been demonstrated

For the sponsor's secondary outcome variable:

Agreement with final diagnosis

Equivalence between Optimark and Magnevist has been demonstrated

Reviewer's Interpretation

In the reviewer's opinion, equivalence between Optimark and Magnevist for "Agreement with final diagnosis" between Optimark and Magnevist has been demonstrated because of the excellent agreement of both Optimark and Magnevist with the pre dose scans. In other words, both Optimark and Magnevist are equally ineffective in increasing the rate of agreement with the final diagnosis. Since there were only 4 patients with a final diagnosis of "normal" the ability of Optimark to improve the radiologist's ability to distinguish a normal from a diseased liver has not been tested. Even so it is interesting to note that the none of the patients with no disease were correctly identified as such in the blinded reading of the Optimark pre + post dose image set. The sponsor has demonstrated both the equivalence of Optimark and Magnevist and the superiority of Optimark to no contrast agent for: Degree of confidence in the diagnosis, Ability to delineate lesion borders, Number of sions visualized. and Confidence in number of lesions. Equivalence between Optimark and Magnevist has been demonstrated for Proportion of patients for whom contrast impaired visualization.

In assessing the endpoints: Degree of confidence in the diagnosis, Ability to delineate lesion borders and Confidence in number of lesions, The readers were asked to rate the scans on these endpoints on a scale of 1 to 10, which , of course calls for a highly subjective judgment o n the part of the readers. These endpoints are not directly clinically meaningful, but are only clinically useful if they allow the radiologist to make a diagnosis and in particular, to distinguish a normal liver from a liver with disease. Number of lesions is a "hard" number but the fact that more lesions are seen with contrast than without does not necessarily demonstrate efficacy. To insure that the "additional lesions" seen with contrast are not merely artifacts, there existence would have to be verified, for example with a biopsy.

The objective of this study was to demonstrate the equivalence of Optimark to Magnevist. The results of such a study could only demonstrate the efficacy of Optimark in conjuction with another study that demonstrated the efficacy of Magnevist. Magnevist is approved as a contrast agent to enhance the visualization of intracranial lesions and lesions in the spine and the body. While the body does include the liver, there is no specific liver indication for Magnevist. A positive result in an equivalence trial would not justify a specific liver indication. The sponsor has demonstrated the equivalence of OptiMARK and Magnevist for a number of endpoints which are not in themselves clinically meaningful. For the clinically meaningful endpoint of agreement has been demonstrated only because neither Optimark nor Magnevist improve the ability to make a correct diagnosis over what would be achieved with the pre dose scans alone. The efficacy of Optimark has not been demonstrated and a specific Liver indication for Magnevist has not been demonstrated.

It should also be noted that the patient data tables supplied by the sponsor are incomplete. It has already been noted that the QT and QTc intervals are not available for all patients. Although these deficiencies occur in several places, one more example should suffice. The study centers are identified by letters, A, B, C, etc. At each study center, patients are numbered consecutively, A-001, A-002 etc. Therefore gaps in the data tables are

easy to spot. Table 16.2.6-14, beginning on page 14.2501 vol.74 gives the final diagnoses. No final diagnosis is given for patients B-010, F=001, F-002, F-003, F-033, G-001, G-002, G-003, G-004,-G-005, G-006, G-007.G-'4, G-018 and G-028.

Pivotal Phase 3 Study # 526 (Pivotal Trial "B")

Reviewer's Comment: This study is identical in design to Study # 490

Sponsor's Proposed Indication:
Optimark is a MRI contrast agent providing magnetic resonance contrast enhancement in patients with known or highly suspected liver pathology

Study Title: A Multicenter Randomized Double Blind Study to Evaluate the Safety, Tolerability, and Efficacy of Optimark (Gadoversetamide Injection) Compared to Magnevist (Gadopentetate Dimeglumine Injection) in Patients With Liver Pathology.

Abstract: A total of 212 patients with highly suspected liver pathology were enrolled in this study at 14 study centers. 6 patients were not randomized for such reasons as contraindications to MRI scans 206 patients were randomized to receive a single intravenous dose of either 0.1 mmol/kg Optimark (102 patients) or 0.1 mmol/kg Magnevist (104 patients) by IV bolus injection. Patients had a pre dose MRI with both T1 and T2 weighted images covering the entire liver, immediately before dosing. Post dose images were obtained at 20 sec, 60 sec and 5 min. post dosing (arterial phase, venous phase and equilibrium phase). Images were evaluated by the principal investigator at each study site and by 3 blinded readers, each of whom evaluated the scans from 1/3 of the patients. Safety was assessed by monitoring physical examination, vital signs, CBC, serum chemistries, urinalysis, EKG, and adverse events. Efficacy was evaluated by assessing the pre dose images and the combined pre dose and post dose images (pre + post dose) for the following parameters: 1) degree of confidence in diagnosis, 2) level of conspicuity (prominence or visibility) of lesions, 3) ability to delineate lesion borders, 4) total number of lesions, and 5) the degree of confidence in total number of lesions. Each parameter was rated by the reader on a scale of 1 to 10. Pre dose diagnosis and pre + post dose diagnosis were also compared to the final clinical diagnosis, which was determined by the investigator from all available information. The differences in scores between pre dose scans and pre dose + post dose scans ("the difference scores") were obtained, for each patient, for each parameter was evaluated. The mean of the difference scores for each parameter was obtained for the group of patients who received Magnevist and for the group of patients who received Optimark. According to the sponsor, equivalence was demonstrated, for each parameter, if the difference between the mean difference score for Optimark and Magnevist was between -1.5 and 1.5
For two of the sponsor's primary outcome variables, "Degree of confidence in diagnosis" and "Ability to delineate lesion borders" it has been demonstrated that Optimark is equivalent to Magnevist and that Optimark is superior to no contrast scans only. For the third primary outcome variable , "Lesion conspicuity", disagreement between the 3 blinded readers precludes the drawing of any firm conclusions. On the clinically significant endpoint, "Agreement with final diagnosis" it has been demonstrated that Optimark is equivalent to Magnevist, but only because it has also been demonstrated that neither Optimark or Magnevist provide any advantage over the non contrast scans alone In this reviewer's opinion, the data from this study raise no significant safety concerns.

Reviewer's Comment The problems with the sponsor's design of these equivalence trials are contained in the reviewer's comment in the review of study 490

STUDY OBJECTIVES:

Same as for study 490

STUDY DESIGN

In overall design, objective and patient selection criteria, the design of this multi-center, randomized double blind parallel group equivalence study, is identical to the design of study 490 .

Reviewer's Comment: Although this is a multi-center study with 14 study centers, no attempt appears to have been made to enroll a specific number of patients at each center.

Safety Monitoring

Safety Monitoring is the same as in study 490

TABLE B1 SAFETY MONITORING SCHEDULE

Test	pre-dose		post-dose					
	baseline	immed.	immed.	0-2hr	2hr	24 hr	48hr	3days
Adverse Event Monitoring			x	x	x	x	x	x
CBC, dif, plts.	x				x	x		x
Serum Gd concentration					x	x		x
Chemistries	x				x	x		x
Urinalysis	x				x	x		x
Vital Signs		x	x		x	x		x
EKG	x					x		
Physical Examination	x					x		

Adverse Events

Monitoring for adverse events is the same as in study 490

Efficacy

Efficacy evaluation is the same as in study 490

Primary Efficacy Endpoints

Primary efficacy endpoints are the same as in study 490

Secondary Efficacy Endpoints

Secondary efficacy endpoints are the same as in study 490

RESULTS

Patient disposition

2 patients with highly suspected liver pathology were enrolled in this study. 206 patients were randomized to ceive a single intravenous dose of either 0.1 mmol/kg Optimark (102 patients) or 0.1 mmol/kg Magnevist (104 patients).

Reviewer's Comment: *The randomization was planned to give approximately 120 Optimark patients and 60 Magnevist patients, Why the randomization actually produced a 1:1 ratio instead of a 2:1 ratio is not clear*

202 patients were dosed (100 Optimark and 102 Magnevist) 2 Optimark patients and 2 Magnevist patients dropped out before dosing because of refusal of MRI scan or inability to obtain venous access for dosing. The majority of patients were White, 98 were male and 108 were female. There were no statistically significant differences between the two groups in height, weight , sex, or race. 154 of the 202 patients dosed were white.93/100 (93%) of the patients dosed with Optimark and 90/102 (88.2%) of the patients dosed with Magnevist were referred for suspicion or evaluation of liver mass / neoplasm

Demographics: N=206

Optimark N = 102
age 53.9 ± 14.1 range 18 - 82

Sex : Male 46 (45%) Female 56 (55%)

Race: White 78 (76%), Black 10 (10%) Asian 5 (5%) Other 9 (9%)

Magnevist; N = 104
age 57 ± 15 range 23 - 86

Sex : Male 48 (46%) Female 56 (54%)

Race: White 76 (73%), Black 15 (14%) Asian 3 (3%) Other 10 (10%)

Safety

Overall 71/202 patients who received either contrast agent (35.1%) experienced 143 adverse events
Optimark, 37/100 patients (37%) experienced 79 adverse events
Magnevist, 34/102 patients (33.3%) experienced 64 adverse events
The difference was not statistically significant.
There was 1 death in the Optimark group
There were 4 severe adverse events in 2 Magnevist patients and none in the Optimark group

Deaths 1
Patient 526-A-026 with advanced hepatocellular carcinoma received 0.1 mmol/kg Optimark on 3/27/97. No adverse events, or significant clinical or laboratory changes were noted during the 3 day observation period. The patient presented to the ER on 4/13/97 with liver failure and died on 4/14/97. Death was attributed to disease progression. Because of the timing, this event was not considered to be associated with the drug

Withdrawals due to adverse events 0

Serious Adverse Events: 2 Magnevist patients experienced 6 serious adverse events
Patient 526-E-037 developed dizziness, melena dyspepsia and asthenia 24 hours after dosing. She was admitted to hospital with a diagnosis of bleeding stomach ulcer. The ulcer was cauterized and the patient was discharged. These events were not considered to be drug related
Patient 56-J-001 with a diagnosis of cirrhosis and ascites developed shortness of breath , loss of appetite and pedal edema 2 days after dosing and was admitted with a diagnosis of recurrent ascites, and esophageal varices. Both conditions were considered to result from progressive disease, and were not considered to be drug related

The most common adverse event was headache (4/100 Optimark, 9/102 Magnevist). Other common adverse events included taste perversion, asthenia, nausea and paraesthesia.

Clinical and Laboratory Monitoring

CBC, Serum Chemistry and Urinalysis results were analyzed by evaluating the " standardized result " defined as;

standard result = (result -lower normal range) / (upper normal range - lower normal range)

Scatter plots of result vs. baseline value were plotted for all parameters (P
No clinically significant trends in the data were seen
LFTs were high for most patients both baseline and post dose with no large changes. This is what would be expected in patients with liver pathology.
The largest percentage changes were seen in serum glucose and this is due to the fact that these glucose values were random rather than fasting levels.
None of the statistically significant changes from baseline were clinically significant

Vital Signs showed a statistically significant increase from baseline in pulse rate at 2 and 72 hours, and a statistically significant decrease in respiration rate immediately after injection in the Magnevist group, but these changes were not clinically significant. Scatter plots of results vs. Baseline showed no clinically significant trends in the data .

Vital Signs

Vital Signs showed statistically significant decreases in the mean from baseline in diastolic blood pressure and pulse rate, and a decrease in diastolic pressure at 24 hours in the Optimark group. In the Magnevist group, a decrease in respiratory rate was seen immediately after injection, and an increase in pulse rate at 2 and 24 hours was also seen. Scatter plots of results vs. Baseline showed no clinically significant trends in the data.

TABLE B2 NUMBER OF PATIENTS WITH CLINICALLY SIGNIFICANT CHANGES IN VITAL SIGNS						
Change	OPTIMARK			MAGNEVIST		
	0 hr	2hr	24 hr	0 hr	2hr	24 hr
Systolic BP ± > 20 mm	9	10	12	9	15	8
Diastolic BP ± > 20 mm	2	2	4	2	2	3
Pulse rate ± > 15 bpm	7	12	12	7	7	8
respiration rate ± > 10 bpm	0	1	0	0	1	2

EKG

9 patients had EKG changes from baseline post dose, 4 Optimark and 5 Magnevist. 2 Optimark patients and 2 Magnevist patients showed changes in rhythm but none of these changes were considered to be clinically significant.

Baseline value and change from baseline at 24 hours (mean, SD and range) for PR,QRS and QT intervals

TABLE B3 EKG PARAMETERS, BASELINE AND CHANGE FROM BASELINE								
	OPTIMARK				MAGNEVIST			
	N*	BASELINE	N*	CHANGE	N*	BASELINE	N*	CHANGE
PR	99	156 ± 25 (106, 252)	99	.08 ± 12 (-42, 20)	102	162 ± 26 (116, 280)	102	-1.8 ± 12.9 (-60, 40)
QRS	100	92 ± 16 (40, 152)	100	0.11 ± 7.5 (-20, 20)	102	92 ±16 (66, 160)	102	.045 ±10.9 (-50, 56)
QT	78	365 ± 33 (301, 476)	78	7.3± 22.2 (-80, 40)	77	389 ± 32.4 (306, 508)	77	-36.7 ± 23 (-68, 48)
QTc	78	418 ± 25 (356, 487)	78	-4.8 ± 19.4 (-75, 44)	77	420 ± 28.5 (360, 495)	77	-.4 ± 20 (-51, 71)

* N is the number of patients for which the parameter is available. There were 99 Optimark patients and 94 Magnevist patients. **Note that the QT interval is obtained from the EKGs for only about 80% of the patients**

***Reviewer's Comment**: EKGs were not obtained immediately before and immediately after dosing, but at baseline (up to 24 hours pre dose) and at 24 hours post dose. These results do not rule out the possibility of clinically significant, or even potentially life threatening EKG changes immediately after dosing*

"Tolerance"

34/100 Optimark patients (34%), and 30/102 (29.4%) Magnevist patients reported injection associated discomfort. The most common sensation was cold in 16% of Optimark patients and in 21.6 percent of agnevist patients

Reviewer's Comment: *What the sponsor refers to as "tolerance" involves only mild to moderate transient patient discomfort which has little implications for patient safety*

Efficacy

Patient Disposition For Efficacy Analysis

212 patients with highly suspected liver pathology were enrolled in this study. 206 patients were randomized to receive a single intravenous dose of either 0.1 mmol/kg Optimark (102 patients) or 0.1 mmol/kg Magnevist (104 patients). 202 patients were dosed (100 Optimark and 102 Magnevist) 2 Optimark patients and 2 Magnevist patients dropped out before dosing because of refusal of MRI scan or inability to obtain venous access for dosing

Primary Efficacy Endpoints

1) degree of confidence in the diagnosis
2) level of conspicuity for all lesions visualized
3) ability to delineate lesion borders

Reviewer's Comment: These endpoints call for a highly subjective response by the readers, who were asked to te each of these endpoints for each set of scans on a scale of 1 to 10. Inter reader variability in these ratings can not be directly assessed since, with the sponsor's design of the blinded reading, no set of scans would be read by more than one reader. The actual outcome variable is derived from the reader's responses in a complex manner:

1) The reader separately evaluates the pre dose scans and the pre dose + post dose set of scans for each patient, for each efficacy endpoint.
2) The difference between the scores for the pre dose image and the pre dose + post dose image set is called the "difference score"
3) The mean difference score is calculated for all patients who received either agent (Optimark or Magnevist)
4) The outcome variable is the difference between the Magnevist mean difference score and the Optimark mean difference score

Blinded Reader Results for Primary Efficacy Endpoints
The data below is contained in sponsor's tables 11.4.1.3-2 to 11.4.1.5-7 (vol. 2.77, pgs15-0048 to15-0056)

Indication for liver diagnosis as determined by the investigator

Reviewer's Comment These are presumably the diagnoses which the referring physician entered on the equisition for the imaging study although this is not explicitly stated.

TABLE B4 INDICATION FOR LIVER IMAGING

	OptiMARK n=100	MAGNEVIST n=102
liver mass/neoplasm	93	90
infection/inflammation	0	1
vascular	2	2
trauma	1	3
no data	1	0
other/unknown	3	6

Reviewer's Comment: *There is not really a good mix of patients. It appears that about 90% of patients in both treatment groups were referred for MRI either to evaluate or rule out a liver mass or neoplasm. There do not appear to be enough patients with other reasons for referral to evaluate the efficacy of Optimark in patients with other referral diagnoses.*

TABLE B5 DEGREE OF CONFIDENCE IN DIAGNOSIS					
AGENT/PARAMETER	mean difference score*	95% confidence interval	patients	p value⁺	ratio⁻⁺
OPTIMARK	1.260	----------	100	<.001	----------
MAGNEVIST	1.0109	----------	102	<.001	----------
Difference**	-0.241	-0.504 - +0.102		----------	-0.238

* difference between pre dose + post dose score and pre dose score

** Difference between Magnevist mean difference score and Optimark mean difference score

⁺p value for the difference score. If $p < 0.05$, then the mean difference score is statistically significantly different from 0

⁻⁺the "ratio" defined by this reviewer is the difference between the Magnevist mean difference score and the Optimark mean difference score divided by the Magnevist mean difference score

Reviewer's Comment: *The "ratio" defined by this reviewer as the difference between the difference scores divided by the Magnevist difference scores, is the difference between Magnevist and Optimark, as a percentage of the difference between Magnevist and the pre dose scan, and in this reviewer's opinion, gives a better idea of the clinical significance of the difference of difference scores than just that difference of difference scores itself. If the ratio is small it means that the difference between Optimark and Magnevist is small compared to the difference between Magnevist and the pre dose scan, which is what one would want to show in an equivalence trial. If the ratio is negative it means that on the average Optimark has scored higher than Magnevist, while if the ratios positive, the reverse would be true.*

TABLE B6 BORDER DELINEATION					
AGENT/PARAMETER	mean difference score*	95% confidence interval	patients	p value⁺	ratio⁻⁺
OPTIMARK	0.690	----------	100	<.001	----------
MAGNEVIST	0.854	----------	102	<.001	----------
Difference**	0.164	-0.095 - +0.423		----------	0.192

* difference between pre dose + post dose score and pre dose score

** Difference between Magnevist mean difference score and Optimark mean difference score.

value for the difference score. If $p < 0.05$, then the mean difference score is statistically significantly different from 0

++the "ratio" defined by this reviewer is the difference between the Magnevist mean difference score and the Optimark mean difference score divided by the Magnevist mean difference score

TABLE B7 CONSPICUITY OF LESIONS					
AGENT/PARAMETER	mean difference score*	95% confidence interval	patients	p_ value+	ratio++
OPTIMARK	0.750	----------	100	<.001	----------
MAGNEVIST	0.777	----------	102	<.001	----------
Difference**	0.027	-0.371 - +0.425		----------	0.035

* difference between pre dose + post dose score and pre dose score

** Difference between Magnevist mean difference score and Optimark mean difference score.

+ p value for the difference score. If $p < 0.05$, then the mean difference score is statistically significantly different from 0

++the "ratio" defined by this reviewer is the difference between the Magnevist mean difference score and the Optimark mean difference score divided by the Magnevist mean difference score

Secondary Efficacy Endpoints

a) **Number of lesions visualized**
b) **Confidence in number of lesions**
c) **Proportion of patients for whom contrast impaired visualization**
d) **Agreement with final diagnosis**

*Reviewer's Comment: Agreement with final diagnosis is of course the outcome variable with the greatest clinical significance. Number of lesions is the only outcome variable that is actually a cardinal number since the readers were asked to do an actual count rather than merely to assign an arbitrary number on a scale of 1 to 10. It is interesting that both of these were **secondary** outcome variables*

TABLE B8 NUMBER OF LESIONS VISUALIZED++				
AGENT/PARAMETER	mean difference score*	confidence interval	patients	ratio***
OPTIMARK	0.995	+0.811 - +1.179	85+	----------
MAGNEVIST	1.067	-0.884 - +1.249	86+	----------
Difference**	-0.072	-0.144 - +0.288		0.167

* difference between pre dose + post dose score and pre dose score

** Difference between Magnevist mean difference score and Optimark mean difference score

*** the "ratio" defined by this reviewer is the difference between the Magnevist mean difference score and the Optimark mean difference score divided by the Magnevist mean difference score

+ Why all the patients dosed are not included is not clear

Reviewer's Comments: Those patients with a diagnosis of either diffuse disease or no disease (normal) would have no (0) lesions visualized, and of course the readers could not evaluate the conspicuity or the border delineation of lesions that they did not see and report.

TABLE B9 CONFIDENCE IN NUMBER OF LESIONS				
AGENT/PARAMETER	mean difference score*	confidence interval	patients	ratio***
OPTIMARK	0.370	-0.139 - +0.879	100+	----------
MAGNEVIST	0.495	-0.007 - +0.997	102+	----------

Difference**	0.125	-0.470 - +0.721		0.253

* difference between pre dose + post dose score and pre dose score

** Difference between Magnevist mean difference score and Optimark mean difference score

*** the "ratio" defined by this reviewer is the difference between the Magnevist mean difference score and the Optimark mean difference score divided by the Magnevist mean difference score

+ Although "number of lesions" is given for 85 Optimark patients and 86 Magnevist patients in table B8. Confidence in number of lesions is given for all 100 Optimark patients and all 102 Magnevist patients in table B9. The reason for this discrepancy is not clear

++ Table B8 and B9 correspond to the sponsor's table 11.4.1.5.1 The number of degrees of freedom for each endpoint should be 1 less than the number of patients evaluated for that endpoint

TABLE B10 Proportion of patients where contrast obscured visualization		
AGENT/PARAMETER	proportion	confidence interval
OPTIMARK (n=100)	0%	0%-0%
MAGNEVIST (n=102)	2%	1%-3%

TABLE B11 Agreement With Final Diagnosis									
final diagnosis	non-evaluable		no agreement		partial agreement		basic agreement		absolute agreement	
OPTIMARK PRE DOSE										
disease* n=89	0		11	12.2%	13	14.4%	37	41.1%	29	32.2%
no disease* n=4	0		2	22.2%	0		3	33.3%	4	44.4%
OPTIMARK PRE DOSE + POST DOSE										
sease* n=89	1	1.1%	8	8.9%	14	15.6%	33	36.7%	34	37.8%%
o disease* n=4	0		3	33.3%	1	11.1%	2	22.2%	3	33.3%
MAGNEVIST PRE DOSE										
disease* n=84	0		17	17.4%	24	24.5%	29	29.6%	28	28.6%
no disease* n=6	0		2	50%	1	25%	0		1	25%
MAGNEVIST PRE DOSE + POST DOSE										
disease* n=84	0		13	13.3%	15	15.3%	37	37.8`%	33	33.7%
no disease* n=6	0		1	25%	2	50%	0		1	25%

- presumably "disease" and "no disease" refer to the final diagnosis, although this is not explicitly stated.

To obtain the entries for the "pseudo sensitivity and specificity" table, table B12 below, the categories "non evaluable", "no agreement" and partial agreement have been combined into "non agreement", and the categories "basic agreement" and "agreement" have been combined into "agreement"

TABLE B12 "Pseudo Sensitivity and Specificity"				
final diagnosis	agreement		non-agreement	
OPTIMARK PRE DOSE				
disease n=90*	66	73.3%	24	26.7%
no disease n=9*	7	77.8%	2	22.2%
OPTIMARK PRE DOSE + POST DOSE				
disease n=90*	67	74.4%	23	25.6%
no disease n=9*	5	55.6%	4	44.4%
MAGNEVIST PRE DOSE				
disease n=98	57	58.2%	41	41.8%
no disease n=4	1	25%	3	75%
MAGNEVIST PRE DOSE + POST DOSE				
disease n=98*	70	71.4%	28	28.6%
no disease n=4*	1	25%	3	75%

* In the patient disposition it is stated that there were 100 patients who received Optimark and 102 who received Magnevist. Why only 99 Optimark patients were listed in tables B11 and B12 is not clear.
**Non agreement occurs, not only if a normal liver is called diseased or visa versa, but also if a liver is correctly called diseased, but the disease is not correctly identified. For this reason, the terms pseudo-sensitivity and pseudo specificity were used

For comparison, the tables showing agreement with the final diagnosis and for pseudo sensitivity and specificity, for the investigators, are given below. As expected, the agreement with the final diagnosis for the principal investigators who had access to all of the clinical data, was much better than for the blinded readers. Since the pre dose scans were used in the determination of the final diagnosis by the investigators, agreement of the final diagnosis with the investigator's reading of the pre dose scans were not tabulated by the sponsor

TABLE B13 Agreement With Final Diagnosis-Investigators.Intent to Treat										
final diagnosis	non-evaluable		no agreement		partial agreement		basic agreement		absolute agreement	
OPTIMARK PRE DOSE + POST DOSE										
disease n=90	2	2.2%	1	1.1%	9	10.0%	13	14.4%	65	72.2%
no disease n=4	1	11.1%	1	1.1%	0		3	33.3%	4	44.4%
MAGNEVIST PRE DOSE + POST DOSE										
disease n=84	0		4	4.1%	13	13.3%	13	13.3%	68	69.4%%
no disease n=6	0		2	50.0%	0		1	25.0%	1	25.0%

TABLE B14 "Pseudo Sensitivity and Specificity Table - Investigators Intent to Treat				
final diagnosis	agreement		non- agreement	
OPTIMARK PRE DOSE + POST DOSE				
disease n=90	78	86.7%	12	13.3%
no disease n=9	7	77.8%	2	22.2%
MAGNEVIST PRE DOSE + POST DOSE				
disease n=98	81	82.7%	17	23.8%
no disease n=4	2	50.0%	2	50.0%

Reviewer's Comments: *Of all the endpoints considered by the sponsor, agreement with the final diagnosis (tables B11 and B12) is the most clinically significant. In general, better agreement with the final diagnosis was seen for both agents than was seen in study 490. (table B12) However, for Optimark there is little improvement from pre dose to pre + post dose (from 73.3% to 74.4% for patients with disease). In contrast, there is substantial improvement in agreement for Magnevist from pre dose to pre + post dose (from 58.2% to 71.4% for patients with disease). There are too few patients without disease to draw any conclusions.*

Sponsor's Conclusion:

Optimark and Magnevist were equivalent in providing contrast enhancement in this study of adults with known or highly suspected liver pathology

4.3 REVIEWER'S ANALYSIS

Safety

In this study,202 patients were dosed. 100 patients received Optimark and 102 patients received Magnevist

Adverse events

There was one death. One Optimark patient died 2 weeks after dosing. Death was attributed to progressive liver disease

There were 6 serious adverse events in 2 Magnevist patients. In both cases these events were unrelated to the drug

Vital signs

There were no clinically significant changes in vital signs in either treatment group.

Physical Examination

There were no clinically significant changes on physical examination in either treatment group.

Laboratory Monitoring

There were no clinically significant changes in laboratory in either treatment group.

EKG

There were no clinically significant changes in EKGs in either treatment group. However, EKGs were obtained 24 hours before dosing and 24 hours after dosing,. EKGs were not obtained immediately before and immediately after dosing

Efficacy

General

In this reviewer's opinion, the two most important indications of the clinical usefulness of any diagnostic test are:

) The test's ability to distinguish between normal and disease (in this case, the ability to distinguish a normal liver from a diseased liver, irrespective of the type of pathology in that diseased liver)

2) The test's contribution to the determination of the final diagnosis in those cases in which disease is found.

Distinguishing a Normal Liver From a Diseased Liver

In order for a study to be able to demonstrate the ability of a test to distinguish normal from disease, a substantial number of subjects in the study would have to be normal. This could be insured by deliberately including normal subjects in the study, but even if the study included only patients who are referred for the test because of a suspicion of disease, a substantial proportion of these patients would turn out to be normal. In this study, in the patient data tables of Final Clinical Diagnosis According to the Principal Investigator's "final clinical diagnosis", only 5 patients (4 Optimark and 1 Magnevist) are listed as normal.

Agreement With Final Diagnosis

To conclude that a contrast agent contributes to the ability to make a correct diagnosis, it should be shown that there is better agreement with the final diagnosis for the set of pre dose + post dose scans, than for the pre dose scans alone (assuming that the final diagnosis is in fact the "correct" diagnosis). Referring again to Table 9, this does not appear to be the case for Optimark. In fact for Optimark, for both disease and non disease, the number of patients for which the pre dose scan diagnosis agrees with the final diagnosis, is almost the same as the number of patients for whom the pre +post dose scan diagnosis agrees with the final diagnosis For Magnevist, the data indicates that the pre + post dose images do have an advantage over the pre dose images

alone. The agreement between the pre dose diagnosis and the "final diagnosis" for Magnevist diagnosis may be due to the way that the "final diagnosis" was defined. The pre dose scans from this study were one of the tests at were used in determining the final diagnosis. Substantial agreement between the pre dose diagnosis and the .nal diagnosis would be expected, and it would be very difficult to demonstrate better agreement between the pre + post dose diagnosis and the final diagnosis, than between the pre dose diagnosis alone and the final diagnosis alone.

Sponsor's Primary Endpoints

The Sponsor's primary endpoints for this were
1) degree of confidence in the diagnosis
2) level of conspicuity for all lesions visualized
3) ability to delineate lesion borders

For each of the endpoints the blinded readers were asked to assign a number between 1 and 10, going from worst to best, for each patient's pre dose scans and for each patient's set of pre dose +post dose scans. For each patient the difference between the post dose score and the pre dose score was called the difference score for that endpoint. For the group of patients who received Optimark, the average difference score was calculated for each endpoint and for the group of patients who received Optimark, the average difference score was also calculated for each endpoint. For each endpoint, the difference between the difference score for Magnevist and the difference score for Optimark was the outcome variable. For Optimark and Magnevist to be considered to be equivalent, the difference between these difference score s should be small, but the question remains , "small with respect to what?" The sponsor arbitrarily chose the value of 1.5 on a scale of 1 to 10 as "small" and says at equivalence is demonstrated if the difference of difference scores can be shown to be between -1.5 and 1.5 with 95 % confidence. This reviewer believes that equivalence is not demonstrated in any clinically meaningful sense unless the difference of difference scores is small compared to the difference score for Magnevist.

Assessing these endpoints calls for highly subjective responses on the part of the readers. Since no scans were read by more than one reader it is impossible to determine if two different readers would have read the same scan differently. In assigning values from 1 to 10, the readers are really ordering the sets of scans from best to worst in regard to each endpoint. The assigned numbers are therefore **ordinal** numbers rather than **cardinal** numbers. It is not clear that performing arithmetic manipulations on ordinal numbers (calculating means and differences of means, means of differences etc.,) makes any sense, especially when calculating averages of ordinal numbers assigned by different readers. It is therefore not clear that the difference of mean difference scores represents anything meaningful at all and whether showing that the absolute value of this number is less than 1.5 demonstrates anything meaningful.

1) Degree of Confidence in Diagnosis

The results for degree of confidence in diagnosis for the blinded readers are given in table B5. The confidence interval for the difference of difference scores does include 0 so equivalence is demonstrated. The p value for the Optimark difference score is $p < 0.001$ so that it is also demonstrated that for Optimark, the mean difference score is statistically different from 0. Therefore the superiority of the pre dose +post dose image set over the pre dose images alone has been demonstrated for Optimark.

nclusions for this endpoint supported by the data
.) Optimark is equivalent to Magnevist
b) Optimark Pre-dose +post dose images are superior to pre-dose images alone

Reviewer's comments: *Because of the known difficulties with equivalence trials this reviewer considers the demonstration of the superiority of Optimark images over pre dose images alone to be a much stronger result than the demonstration of the equivalence of Optimark and Magnevist. Inherent in the use of "confidence in diagnosis" as an outcome variable is the implicit assumption that a higher confidence in diagnosis demonstrates superiority. However a higher confidence in diagnosis would be good only when the correct diagnosis is made. A high confidence in the diagnosis when the diagnosis is wrong would be dangerous. It is not clear that the parameter "confidence in diagnosis" alone , without assessing the correlation with the other outcome variable "agreement with final diagnosis" is really meaningful at all*

2) Overall Level of Conspicuity For All Lesions

The results for overall conspicuity of lesions, for the blinded readers, are given in table B7. The confidence interval for the difference of difference scores includes 0 so equivalence has been demonstrated. The p value for the Optimark difference score to be different from 0 is $p < 0.001$ So the superiority of Optimark pre + post dose scans over pre dose scans alone has been demonstrated

Conclusions for this endpoint supported by the data

a) Optimark is equivalent to Magnevist

b) Optimark Pre-dose +post dose images are superior to pre-dose images alone

3) Ability to Delineate Lesion Borders

The results for ability to delineate lesion borders, for the blinded readers, are given in table B6. The confidence interval for the difference of difference scores does include 0 so equivalence is demonstrated. The p value for the Optimark difference score is $p = 0.036$ so that it is also demonstrated that for Optimark, the mean difference score is statistically different from 0. Therefore the superiority of the pre dose +post dose image set over the pre dose images alone has been demonstrated for Optimark

Conclusions for this endpoint supported by the data

a) Optimark is equivalent to Magnevist

b) Optimark Pre-dose +post dose images are superior to pre-dose images alone

Sponsor's Secondary Outcome Variables

a) Number of lesions visualized

b) Confidence in number of lesions

c) Proportion of patients for whom contrast impaired visualization

d) Agreement with final diagnosis

Number of Lesions Visualized

The results for the blinded readers for number of lesions visualized are given in table B8. This outcome variable is the only cardinal number in the entire set of outcome variables, since the readers are actually asked to count lesions rather than to rank images in order of superiority The confidence interval for the difference of difference scores does include 0 so equivalence is demonstrated. The confidence interval for the OptiMARK difference score does not include 0, Therefore the superiority of the pre dose +post dose image set over the pre dose images alone has been demonstrated for Optimark

Conclusions for this endpoint supported by the data

a) Optimark is equivalent to Magnevist

b) Optimark Pre-dose +post dose images are superior to pre-dose images alone

.onfidence in Number of Lesions

The results for confidence in number of lesions, for the blinded readers, are given in table B9. The confidence interval for the difference of difference scores does not include 0 so equivalence is not demonstrated. The

confidence interval for the Optimark difference score does not include 0, Therefore the superiority of the pre dose +post dose image set over the pre dose images alone has been demonstrated for Optimark

Conclusions for this endpoint supported by the data

a) Equivalence of Optimark and Magnevist has not been demonstrated

b) Optimark Pre-dose +post dose images are superior to pre-dose images alone

Proportion of Patients For Whom Contrast Obscured Visualization

The results, for the blinded readers, for Proportion of Patients For Whom Contrast Obscured Visualization are given in table B10. The number of patients for whom contrast obscured the visualization of lesions was small for both agents, 6% for Optimark and 4% for Magnevist . The confidence intervals for these percentages for both agents overlapped, therefore equivalence is demonstrated

Conclusions for this endpoint supported by the data

Equivalence of Optimark and Magnevist has been demonstrated

greement with Final Diagnoses (Sensitivity and Specificity)

Reviewer's Comment: *In the reviewer's opinion, this is the endpoint with the greatest clinical significance. Other properties of the images are useful only if they aid in making a correct final diagnosis. Since this was not one of the sponsor's primary outcome variables one might conclude that the sponsor does not agree*

The results for agreement with the final diagnosis for the blinded readers are given in tables B11 and B12.Corresponding results for the investigators are given in tables B13 and B14. There is obviously much better agreement with the final diagnosis for the investigators than for the blinded readers. This is expected since the investigators had available to them, all the clinical and diagnostic information for each patient, and since the final diagnosis was, in fact determined by the investigators on the basis of that clinical and diagnostic information, including the pre dose scans from this study. The results for the investigators for this endpoint and for other endpoints will not be discussed further

Although p values are not given, the equivalence between Optimark and Magnevist is not clear from the numbers in tables B11 and B12. However there is agreement between the Optimark pre dose scans and the Optimark Pre +post dose scans. This can be best seen in table B12 where the 5 possible outcomes in table B11 have been reduced to 2 possible outcomes. For Optimark pre dose scans there is agreement for 66 patients with disease and non agreement for 24 patients for patients with disease. and there is agreement for 7 patients and non agreement for 2 patients without disease. For the Optimark pre +post dose scans for patients with disease 'here is agreement for 67 patients and non agreement for 23 patients, and for patients without disease , there is agreement for 5 patients and non agreement for 4 patients. For Magnevist the results for patients without disease e the same for pre dose and pre + post dose scans, while for patients with disease, agreement is achieved for / patients with the pre dose scans and for 70 patients with the pre +post dose scans.

Conclusions

ıfety

There was one death. One Magnevist patient died 1 week after dosing. Death was not attributable to the drug

There were 6 serious adverse events in 2 Magnevist patients. In both cases these events were unrelated to the drug

There are no significant safety concerns raised by the data presented in this study. That data however, is incomplete. EKGs should have been obtained immediately before and immediately after dosing. This shortcoming could however be addressed by a phase 4 post marketing commitment.

In this reviewer's opinion, these data raise no significant safety concerns that would impact the approval decision. However the data is incomplete. EKGs were obtained 24 hours before and 24 hours after dosing. Changes would be most likely to occur immediately after dosing. The data is inadequate to rule out life threatening EKG changes immediately after dosing. For the EKGs that were done, QT and QTc intervals are available for only a fraction of the patients. The EKGs were read by the investigators, not by blinded cardiologists. Chemistries were not obtained immediately after dosing but at 2 hours after dosing. This agent has a chelator as a component and a fall in serum calcium, at the time of the highest serum concentration can not be ruled out.

Efficacy:
The objective of this study has been to demonstrate the equivalence of Optimark to Magnevist, an approved MRI contrast agent.

For the group of patients studied, the three of the sponsor's primary outcome variables:

Degree of confidence in the diagnosis
Ability to delineate lesion borders
level of conspicuity for all lesions visualized
Equivalence between Optimark and Magnevist has been demonstrated. Superiority of the Optimark pre + post dose images over the pre dose images alone has also been demonstrated.

For the sponsor's secondary outcome variables:

Number of lesions visualized
Confidence in number of lesions

Equivalence between Optimark and Magnevist has been demonstrated. Superiority of the Optimark pre + post dose images over the pre dose images alone has also been demonstrated.

For the sponsor's secondary outcome variable:

Proportion of patients for whom contrast impaired visualization

ıuivalence between Optimark and Magnevist has been demonstrated

For the sponsor's secondary outcome variable:

Agreement with final diagnosis

Equivalence between Optimark and Magnevist has been demonstrated for the sponsor's primary endpoints

In the reviewer's opinion, equivalence between Optimark and Magnevist for "Agreement with final diagnosis" between Optimark and Magnevist has been demonstrated because of the excellent agreement of both Optimark and Magnevist with the pre dose scans. In other words, both Optimark and Magnevist are equally ineffective in increasing the rate of agreement with the final diagnosis. Since there were only 4 patients with a final diagnosis of "normal" the ability of Optimark to improve the radiologist's ability to distinguish a normal from a diseased liver has not been tested. Even so it is interesting to note that the none of the patients with no disease were correctly identified as such in the blinded reading of the Optimark pre + post dose image set. The sponsor has demonstrated both the equivalence of Optimark and Magnevist and the superiority of Optimark to no contrast agent for: Degree of confidence in the diagnosis, Ability to delineate lesion borders, Number of lesions visualized. and Confidence in number of lesions. Equivalence between Optimark and Magnevist has been demonstrated for Proportion of patients for whom contrast impaired visualization.

'n assessing the endpoints: Degree of confidence in the diagnosis, Ability to delineate lesion borders and 'onfidence in number of lesions, The readers were asked to rate the scans on these endpoints on a scale of 1 to , which , of course calls for a highly subjective judgment o n the part of the readers. These endpoints are not uirectly clinically meaningful, but are only clinically useful if they allow the radiologist to make a diagnosis and in particular, to distinguish a normal liver from a liver with disease. Number of lesions is a "hard" number but the fact that more lesions are seen with contrast than without does not necessarily demonstrate efficacy. To insure that the "additional lesions" seen with contrast are not merely artifacts, there existence would have to be verified, for example with a biopsy.

The objective of this study was to demonstrate the equivalence of Optimark to Magnevist. The results of such a study could only demonstrate the efficacy of Optimark in conjuction with another study that demonstrated the efficacy of Magnevist. Magnevist is approved as a contrast agent to enhance the visualization of intracranial lesions and lesions in the spine and the body. While the body does include the liver, there is no specific liver indication for Magnevist. A positive result in an equivalence trial would not justify a specific liver indication. The sponsor has demonstrated the equivalence of OptiMARK and Magnevist for a number of endpoints which are not in themselves clinically meaningful. For the clinically meaningful endpoint of agreement has been demonstrated only because neither Optimark nor Magnevist improve the ability to make a correct diagnosis over what would be achieved with the pre dose scans alone. The efficacy of Optimark has not been demonstrated and a specific Liver indication for Magnevist has not been demonstrated. It should also be noted that the patient data tables supplied by the sponsor are incomplete. It has already been noted that the QT and QTc intervals are not available for all patients. Perusal of the data tables indicates that occasionally data for individual patients is missing. This is likely due to sloppiness in the way these tables were compiled or sloppiness in the performance of the studies themselves.

commendations

1) The pattern of adverse events in the Optimark group compared to the Magnevist group does not raise any significant safety concerns. There are no specific safety concerns raised by the clinical or laboratory patient monitoring data. This data is, however incomplete, since EKGs were not performed immediately after dosing, the development of transient life-threatening EKG changes cannot be ruled out.

2) The sponsor claims to have demonstrated the equivalence of Optimark and Magnevist in the evaluation of liver lesions. Equivalence has been demonstrated for 2 out of 3 of the sponsor's primary outcome variables in pivotal study A and for 3 out of 3 in pivotal study B. Equivalence has also been demonstrated in both studies for "Agreement with Final Diagnosis', but only because neither agent increases the agreement with the final diagnosis over what is achieved with non-contrast scans alone. There was no uniform "gold standard" for determining " final diagnosis". Rather the "final diagnosis" was made on the basis of the entire workup that each particular patient had, **including the pre-contrast scans from these studies**. The choice of primary outcome variables is, of course arbitrary, and in this reviewer's opinion the sponsor has not chosen the outcome variables with the greatest clinical importance. The "bottom line" should be whether the agent helps the radiologist to make the "correct" diagnosis

3) While Magnevist is approved for imaging of the brain and of the body, there is no specific indication for Magnevist for imaging the liver. Without data specifically supporting the efficacy of Magnevist in the imaging of liver lesions, this equivalence trial, demonstrating the equivalence of Optimark and Magnevist, does not, by itself, demonstrate the efficacy of Optimark for the liver indication. An equivalence trial is unacceptable as a demonstration of efficacy, unless the comparitor has already been approved for the desired indication.

4) Optimark is a "me too" drug. There are already several Gadolinium MRI contrast agents on the market, although none are *specifically* indicated for imaging of the liver. The sponsor does not claim that Optimark is *superior* to any of these agents, but only that Optimark is equivalent to Magnevist

5) The effectiveness of Optimark in the imaging of liver lesions has not been demonstrated. Because of incomplete safety data, the occurrence of transient life threatening EKG changes, at the time of infusion, can not be ruled out. For these reasons **this reviewer recommends non-approval of Optimark for the liver indication.**

6) The sponsor has also requested approval for a CNS indication, and that indication is being addressed by another medical reviewer. If the sponsor has demonstrated the equivalence of Optimark and Magnevist for CNS imaging, this would demonstrate the efficacy of Optimark, since the efficacy of Magnevist has already been demonstrated for the CNS indication. If the sponsor desires the liver indication, it should be possible to reanalyze the data and also analyze the efficacy data for studies 486 and 487 to demonstrate the superiority of Optimark scans over non-contrast scans alone.. The sponsor could then reapply on that basis.

EKG data obtained immediately after infusion does not exist for any of the sponsor's phase 3 studies. The sponsor would have to perform additional safety studies to obtain such data. EKG data should include all relevant parameters, including the QT interval, and should be read by a board certified cardiologist(s)

Robert J. Yaes, Sc.D. MD. Medical Officer

A.E. Jones, MD. Medical Team Leader

/S/

Robert J. Yaes, Sc.D. MD. Medical Officer

/S/ 12/4/98

A.E. Jones, MD. Medical Team Leader

Memo to the File Regarding Safety Update

According to the Sponsor, "there has been no new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions and adverse reactions in the draft labeling." Please note comments on SU made by Medical Team Leader.

James Moore
Project Officer, HFD-160
December 18, 1998