TITLE:

- "A Double-Blind Study to Assess the Dose-Related Safety, Tolerance, and Pharmacokinetics of MP-1177/10 Injection in Normal Healthy Male Volunteers"

STUDY OBJECTIVES:

- The objective of this study was to evaluate the dose-related safety, tolerance, and pharmacokinetics of MP-1177/10 Injection following intravenous administration. In addition, analysis for potential metabolites was performed. [p. 6.0245, Vol. 2.11]
- The Sponsor proposed to assess safety by monitoring clinical signs and symptoms, vital signs, physical examination, electrocardiogram, and adverse effects with the drug or placebo; measuring clinical lab parameters (listed below).
- The Sponsor proposed to evaluate tolerance by recording discomfort associated with injection of the drug.
- Serum and urine gadolinium contents were measured at various timepoints to determine pharmacokinetics; analysis for metabolites will be performed using
- Safety, Tolerance and Pharmacokinetic parameters were assessed as mentioned and as stated in the study protocol. The sponsor included sperm analysis as an additional safety monitoring parameter (see reviewer's note above). Modifications were made with respect to metabolite analysis (p. 6.0027, Vol 2.10, see reviewer's comment in the study section).

STUDY DESIGN/PLAN/METHODOLOGY:

- The study design, plan of the study, inclusion criteria, exclusion criteria, drug administration and methods were carried out as stated in the study protocol except for EKGs (which were not performed on any of the subjects). The sponsor included sperm analysis as an additional safety monitoring parameter (see reviewer's note above).
- This was a double-blind, randomized, placebo-controlled Phase 1 study of four ascending doses of MP-1177/10 Injection in 20 normal male volunteers. There were 4 dose groups (0.1mmol/kg, 0.3mmol/kg, 0.5mmol/kg, and 0.7mmol/kg) of 5 patients each wherein 4 subjects received the test drug (as a single rapid bolus) and 1 received placebo (with matched volumes and rates for that group).
- The volunteers were screened for enrollment as noted in the protocol section (see table above, comments in the protocol section and inclusion and exclusion criteria below). Those subjects who received placebo (normal saline, one from each group-total of four) were the 'control group'.

- The pre-study screening as mentioned in the study protocol were followed at various time points as shown below:

SAFETY: TIME EVENTS: STUDY # 433: PHASE 1: OptiMARK™												
Time	Med Hx	Physical	Vitals	EKG	Labs	Special	Iron	Creatinine Clearance	Gad [2]	Met [3]	AE	Sperm Count[6]
14days pre	X	X	X	X	X	X	X					2X
48hrs pre	X	X	X	X	X	X[1]	X					X
24hrs pre							X	X				
22hrs pre							X					
20hrs pre							X					
16hrs pre							X					
8hrs pre							X					
60mins pre	X[1]	X[1]	X	X	X		X		X	X		
pre-injection			X	X	X		X		--			
DOSE											X	
imm post			X	X							X	
30 mins post			X	X							X	
60 mins post			X	X							X	
2 hrs post			X	X	X						X	
4 hrs post[4]							X				X	
8 hrs post[4]		X	X				X				X	
16 hrs post[4]							X				X	
24 hrs post		X	X	X	X			X			X	
48 hrs post					X							X
72 hrs post[5]		X	X	X								X
7 day ±24hrs												X

Vital signs to include systolic and diastolic blood pressures, pulse rate, respiratory rate, and oral body temperature
EKG - 12-lead electrocardiogram
Labs - hematology (hemoglobin, hematocrit, RBC count, WBC count and differential, platelet count, PT, and PTT), chemistry (Na, K, Cl^-, Ca^{+2}, PO4, alkaline phosphatase, ALT/SGPT, SGOT/AST, GGT, LDH, creatinine, BUN, total protein, total and direct bilirubin, iron), urinalysis (specific gravity, pH, glucose, ketones, bilirubin, protein, urobilinogen, crystals, erythrocytes, leukocytes)
Special - Hepatitis B, HIV, urine drug screen
1Sponsor states that these will be abbreviated
2gadolinium content in urine and serum
3metabolite analysis in urine and serum
4also includes total bilirubin and direct bilirubin
5also includes BUN and creatinine
6Sperm Analysis- - two pre-injection collections within the 14-day pre-study screening period, one 48hours pre-injection collection, one 7 day±24 hours post-injection collection. The subjects were required to be observe sexual abstinence for a 72 hour period prior to all sampling
7excluding hepatitis B and HIV
AE- Adverse Effects Monitoring

~ *Reviewer's Note:*

No extreme values for the lab tests were defined by the Sponsor however, the Sponsor required the Principal Investigator to provide normal value ranges for adult males from the testing lab [p. 6.0249, Vol. 2.11]. Appendix 1.5 [pp.6.0327-6.0331, Vol. 2.11] which provides laboratory normal ranges from "INNOVEX (CLINICAL RESEARCH FOUNDATION)" has been noted (check sperm analysis).

SELECTION CRITERIA AND DEMOGRAPHICS:

- Total number = 20 → four dose groups with five volunteers each (four in each group to receive drug and one to receive placebo)
- Age: range 19 - 43 years; mean 29.4; standard deviation 8.1; median 29.5
- Height (in): range 64-75; mean 70.6; standard deviation2.9; median 71.0

- Weight (lb): range 113-194; mean163.9; standard deviation 19.8; median 164.6
- Race (%): black 12.5; white 87.5
- Sex: male only
- Status: healthy volunteers

Exclusion Criteria:

- any exposure to an investigational drug within the preceding 30 days
- any receipt of prescription medication within the preceding 14 days or any OTC drug within 48 hours prior to test drug/placebo administration
- significant history of allergies or of hypersensitivity (anaphylaxis) to any drug; history of multiple hypotensive episodes with fainting, seizure disorder, headaches (migraine or other chronic headaches), hypertension; presence of sickle cell anemia or other hemoglobinopathy; illicit drug use.
- abnormal clinical examination (at baseline), oral body temperature >99.6°F, clinically significant (per Sponsor or Principal Investigator) abnormal lab values, clinically significant (per Sponsor or Principal Investigator) abnormal 12-lead EKG (at baseline), testing positive for Hepatitis-B and/or HIV

outside 15% of ideal body weight per Statistical Bulletin: Metropolitan Life Insurance Company January - June 1983 [Appendix A - p. 6.0263, Vol. 2.11]

~ Reviewer's Note: The CRF's pertaining to volunteer inclusion/exclusion criteria [pp. 6.0279 - 6.0280 Vol. 2.11], volunteer demographic and medical history data [p. 6.0281, Vol. 2.11], physical exam [p. 6.0282, Vol. 2.11]; the "Requirements for Informed Consent of Human Subjects" [pp. 6.0270 - 6.0272, Vol. 2.11, Appendix E] have been noted.

DRUG ADMINISTRATION AND METHODS*

- As stated in the protocol and as commented in the protocol review section, the drug MP-1177/10 and placebo (normal saline) were administered intravenously at a rate of 1.0mL/kg/min followed by a 10ml normal saline flush completed in 5 seconds. The drug was supplied in 20ml, single dose rubber-stoppered glass vials in a concentration of 0.5mmol/mL.
- The doses were 0.1, 0.3, 0.5 and 0.7 mmol/kg and the volumes were 0.2mL/kg, 0.6mL/kg, 1.0mL/kg and 1.4mL/kg respectively.
- The placebo was normal saline, which was administered at a volume and rate that was equivalent to the study drug MP-1177/10.
- The proposed instructions were followed as follows:
  The volunteers who met the entry requirements were assigned beginning with the lowest dose group (group 1) and ending with the highest dose group (group 11). One volunteer from within each group was randomized to receive placebo. Dosing began with the lowest dose group (0.1mmol/kg) and the sponsor studied the next higher dose group only after all the safety data had been reviewed and the PI and the medical monitor agreed that it was safe [p 6.0252, Vol 2.11] to proceed further.

The Sponsor confined all the volunteers to the research facility from 36 hours prior to the study drug injection to 72 hours following drug administration. This was a non fasting study and the volunteers were given an oral fluid load pre and post study (clear liquids of at least 4ml/kg given 2hrs pre, 1 hr pre, and every hour X4 hrs post). The volunteers were asked to empty their bladder pre injection.

- The sponsor followed these blinding instructions:
  1. The volunteers were informed that they would receiving a "drug" or "placebo".
  2. The PI was blinded.
  3. A "blinder" (not involved in evaluating the volunteers or collecting data) was selected, who was responsible for preparing the drug (loading the syringes, labeling, and logging) and following the randomization schedule.

**The table for dosing: lists a weight range from 54.5 kilograms (120 pounds) to 100 kilograms (220 pounds); maximum volume of 140ml; injection duration time of 12 seconds to 84 seconds; injection rate of 0.9ml/sec to 1.7ml/sec.*

DURATION OF TREATMENT:

- Each patient received a single dose of the drug MP-1177/10 and was monitored for 7 days.

CRITERIA FOR EVALUATION:

- See selection, study design, inclusions above.

- **SAFETY ASSESSMENTS:**

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

VITAL SIGNS, PE AND CARDIOVASCULAR EFFECTS

The Sponsor defined the following changes as extreme and requiring additional comments on the Case Report Forms:

BP : systolic > 35mmHg, diastolic > 25mmHg
pulse rate change > 20 beats per minute
respiratory rate change > 10 breaths per minute

These were later modified to include the following:

Any change in systolic blood pressure > 20 mm Hg
Any change in diastolic blood pressure > 20 mm Hg
Any change in pulse rate of > 15 bpm
Any change in respiratory rate of > 10 breaths per minute

ADVERSE EFFECTS MONITORING

- The Sponsor monitored the volunteers for up to 72 hours following drug administration for any adverse effects in terms of: nature, severity, onset, duration, attributability, and outcome.

CLINICAL LABORATORY STUDIES

- The Sponsor performed the clinical lab studies (to include hematology, serum chemistry, urinalysis, and creatinine clearance at various time points as indicated in the table above) and to record the results on the case report forms-[pp 6.0288-6.0294, Vol 2.11].
- The post-administration "outside the normal range" value/s were appraised by the Sponsor as follows:

1. = No change or change not clinically significant; no follow-up required
2. = Change clinically significant and attributable to disease; no follow-up required
3. = Change clinically significant and attributable to procedure; no follow-up required
4. = Change clinically significant and possibly attributable to the study drug; FOLLOW-UP REQUIRED
5. = Apparent laboratory error
6. = Unevaluable

Additionally, the Sponsor monitored the following:

DRUG ADMINISTRATION TOLERANCE

Any sensation of heat, cold and pain was assessed on a four point scale (none, mild, moderate or severe) following the drug administration.

PHARMACOKINETIC AND METABOLITE PROFILES

The Sponsor obtained serum and urine samples from all groups for pharmacokinetic and metabolite analyses to include:

- Serum gadolinium content (5ml venous blood to be drawn within 30 minutes prior to and at 3, 5, 10, 15, 30 minutes and at 1, 1.5, 2, 4, 8, 24 and 48 hours following injection; the methodology of which has been described in Appendix C-p 6.0268, Vol 2.11) expressed in mgGd/ml
- Urine gadolinium content (5ml of urine will be collected immediately prior to injection (baseline), and pooled samples at 0 to 1 hour, 1-2 hours, 2-4 hours, 4-8 hours, 8-12 hours, 12-24 hours, 24-36 hours, 36-48 hours, 48-60 hours, and 60-72 hours; the methodology of which has been described in Appendix D-p6.0269, Vol 2.11) expressed in mgGd/ml
- Serum Metabolite Analysis (3ml venous blood to be drawn pre-injection and at 5mins, 30 mins and post-injection at 1hour, 2 hours, 4 hours, 8 hours, and 24 hours
- Urine Metabolite Analysis (pre-injection, and 0-1 hour, 1-2 hours, 2-4 hours, 4-12 hours post-injestion- Appendix D-p6.0269, Vol 2.11.

- The least dose (0.1mmol/kg) and the maximum dose (0.7mmol/kg) groups were assessed for pharmacokinetic and elimination parameters in urine and serum for gadolinium content.

DATA ANALYSIS [pp6.0257-58, Vol 2.11]

The Sponsor analyzed the data as follows:

a) Case report forms were reviewed for legibility, completeness, consistency, and compliance to the study protocol
b) Data summarized to include data listings, extreme values, mean and median values, standard deviation or frequency distribution tables as appropriate
c) Safety and pharmacokinetic statistical analyses were performed. Drug and placebo group comparisons would be performed at the 5% level of significance. All tests were based on null hypothesis of no difference or effect versus the two-sided alternative

SUMMARY:

Patients: enrollment & disposition:

- See table below:

STUDY # 433: PHASE 1: PATIENT ENROLLMENT: OptiMARK™							
		Treatment Group -OptiMARK™ (mmol/kg)					
Number of Subjects		Placebo	0.1	0.3	0.5	0.7	Combined
Entered		4	4	4	4	4	16
Exposed		4	4	4	4	4	16
Completed		4	4	4	4	4	16
Evaluated for Safety		4	4	4	4	4	16
Evaluated for PK (Efficacy)		4	4	4	4	4	16
Dropped pre-dosing		0	0	0	0	0	0
Dropped for adverse event		0	0	0	0	0	0
Demographics							
Age (Years)	N	4	4	4	4	4	16
	mean	30.3	35.8	33.0	22.5	26.3	29.3
	range	21-39	23-43	29-37	19-30	20-27	19-43
Drug Volume							
Total volume (ml)	N	4	4	4	4	4	16
	mean	58.2	15.9	46.4	69.1	98.6	57.5
	range	13.5-94.7	14.8-17.9	40.8-52.5	51.4-79.4	89.3-108.5	14.8-108.5

Safety results:

- **The proposed EKGs were not performed in any of the subjects.** This is a major safety deficiency considering that this was the first-in-human study and some subjects received the maximum dose of 0.7mmol/kg.
  In the case report form [p6.0287. Vol 2.11] in which clinically significant ECG changes were recorded; the sponsor did not define what these clinically significant changes were and what criterion/a were followed. It is important to know this despite

the fact that EKGs were not performed. This would be helpful to know for the other studies.

- No clinically significant changes were noted in:
  1. Physical examination
  2. Vital Signs
  3. Labs (hematology, chemistry, urinalysis, kidney function)
  4. Male reproductive function
- Serum chemistry did not include glucose or bicarbonate. The absence to record the later especially when evaluating a drug that is primarily excreted through the kidneys is not very a thoughtful decision.
- Urinalysis did not specify if centrifuged or uncentrifuged samples were analyzed, but there were no reported clinically significant abnormalities. If only un-centrifuged samples were analyzed, the likelihood of missing abnormalities such as casts, sediments, etc. is a concern-specially in a drug that showed renal changes and damage in the pre-clinical studies, and is primarily excreted through the kidneys.
- Presence of hemoglobinopathies was an exclusion criterion in this Phase 1 trial and has been listed among the warnings in the proposed labeling. Besides medical history, the reviewer has not been able to determine how this diagnosis was made and there are no special tests (e.g., sickle cell screening, hemoglobin electrophoresis) that the Sponsor has provided in this study. Many of the hemoglobinopathies may be asymptomatic (mild) so the patients may not be aware of the condition
- Vasodilation appeared to be dose dependent occurring more often in the higher dose group.
- The adverse events thought to be related to OptiMARK™ (by the principal investigators) were vasodilation, taste perversion, paresthesia, headache, parosmia, dizziness, injection site reactions.

- The table below summarizes some of these adverse events:

SAFETY:ADVERSE EVENTS: STUDY # 433:PHASE 1:OptiMARK™				
SUBJECTS (N) EXPOSED = 16 DEATHS (N) = 0 PATIENT (N) WITH SERIOUS ADVERSE EVENTS = 0 DROPPED (N) DUE TO ADVERSE EVENTS = 0			PATIENTS (N) WITH ADVERSE EVENTS = 23 TOTAL (N) ADVERSE EVENTS = 40 POST-DOSING NON-AE WITHDRAWAL = 0	
Treatment Group	OptiMARK™ (mmol/kg)			
Dose	0.1	0.3	0.5	0.7
N (RECEIVED DOSE)	4	4	4	4
N (EXPERIENCED AE)				
N (ADVERSE EVENTS)				
INTENSITY OF AE MILD (N) MODERATE (N)	Mild to moderate heat, cold and pain during injection Vasodilation was dose dependent			
SEVERE (N)	0	0	0	0
VASODILATION	1/4			3/4
LABORATORY EVENTS:				
Parameters affected	Increase in serum iron			
Dose related	Yes- started with 0.3mmol dose, and at higher doses			
Time related	Yes- started within 4-8 hours after dosing			
Clinically significant (symptomatic)	No			
Statistically significant	?			
Duration (how long lasted)	Transitory			
Resolution time (time to return to baseline)	?			

PK RESULTS:

- Refer to pharmtox/biopharm review comments in the overall safety section and by the respective FDA reviewers.

Conclusion:

1. There were nor deaths or serious adverse events or severe adverse events. Vasodilation was noted that was dose dependent. Lab abnormalities that were of significance were the serum iron changes, which was also dose dependent. There were no significant changes of concern in the other safety parameters. Mild to moderate injection related discomforts were reported by the subjects.
2. Minor deficiencies included the absence of glucose and bicarbonate levels. Hemoglobinopathies was not ruled out besides history.
3. The major concern is the lack of obtaining EKGs.
4. This study subserved the needs in providing pharmacokinetic information in normal subjects; information on the effects on spermatogenesis in males (essentially safe); the possibility that larger doses might have an increased incidence of adverse reactions.

REFER TO THE OVERVIEW OF SAFETY FOR ADDITIONAL COMMENTS
END OF REPORT #433.

NDA # 20 937
IND# [redacted]

OptiMARK™

Report # 1177-01/Phase 1
Japanese Study Report*

Volumes Reviewed: NDA # 20 937 Volumes # 2.1 - 2.168 and additional information from Sponsor with letter dates 24 April 1998 (Volumes # M7.1 - M7.3), 11 September 1998 (BM), September 23, 1998 (letter correspondence to CSO)
Primary Volumes for this study: 2.44

*Study Report Date: 02 December 1994

APPEARS THIS WAY
ON ORIGINAL

TITLE:

- "A Double-blind Study to Assess the Dose-Related Safety, Tolerance, and Pharmacokinetics of MP-1177/10 Injection in Normal Healthy Male Volunteers"

OBJECTIVE:

- "To study the safety and pharmacokinetics of MP-1177/10 Injection (gadoversetamide injection) in healthy adults" [p. 10.0224, Vol.2.44]

STUDY DESIGN AND PATIENT POPULATION & SELECTION:

- This was a double-blind placebo-controlled Phase 1 study to assess the safety and pharmacokinetics of various doses of OptiMARK in 20 healthy adult male volunteers. The subjects were randomized to one of four dose groups -- 0.05mmol/kg, 0.1mmol/kg, 0.3mmol/kg, or 0.5mmol/kg OptiMARK™ – one subject in each group received placebo.

Inclusion Criteria:

- Healthy patient as determined by history, physical examination, EKG, vital signs, chest radiograph, serum labs, and urinalysis
- Men only
- 20 to 40 years old

Exclusion Criteria:

- History of allergies, drug hypersensitivity, epilepsy, fainting, migraine or chronic headache within the preceding 6months, hypertension, anemia
- Participation in a clinical trial for another drug within the preceding 6months
- Ongoing medication use or continuous medication use within the preceding 3months
- donation of more than 200ml of blood in the preceding 3months
- Weight more than 20% discrepant from ideal weight [Sponsor cites "Tables and Figures for Judgement of Obesity and Emaciation", edited by MHW, Health and Medical Bureau, Health Improvement and Nutrition Division, published by Daiichi-Shuppan, 1986]
- "other persons deemed inappropriate by the physicians to participate in this trial" [p. 10.0227, Vol. 2.44]

DRUG ADMINISTRATION:

- Four dose groups: 0.05mmol/kg, 0.1mmol/kg, 0.3mmol/kg, and 0.5mmol/kg – 5 subjects per group, 4 received drug and 1 received placebo (same volume of normal saline as for drug).

- Study progressed from lowest dose group to next higher dose only "after confirming the safety of each prior step" [p. 10.0228, Vol. 2.44].
- The drug was injected IV into antecubital vein at approximately 20ml/min.

CRITERIA FOR EVALUATION

SAFETY ASSESSMENTS:

- **Pre-trial** (within 2months pre):
  history and physical exam; EKG (12-lead); vital signs (systolic & diastolic BP, pulse, respiratory rate, temperature); chest radiograph; labs including hematology (WBC with differential, RBC, hemoglobin, hematocrit, MCV, MCH, MCHC, platelet count, reticulocyte count, PT, and PTT) and chemistry (Na^+, K^+, Cl^-, BUN, creatinine, glucose, total protein, albumin, Ca^{+2}, PO_4^{-3}, total and direct bilirubin, SGOT, alkaline phosphatase, GGT, LDH, CPK, LAP, ChE, cholesterol, lipids, uric acid, Zn, Fe, ferritin, transferrin, TIBC, UIBC); urinalysis (specific gravity, pH, protein, glucose, ketones, blood, urobilinogen, bilirubin, nitrite, sediment); and special labs (HBsAg, HBsAb, Hepatitis C Ab, STD's).
- 1day pre: physical exam, EKG, vitals, hematology, chemistry (total bilirubin, SGOT, SGPT, alkaline phosphatase, LDH, CPK), and urinalysis
- Assessments performed in the immediate pre- and post- dose periods included:

Time	Physical	EKG	Vitals	Heme	Chem	Add'l	U/A	Special	AE
within 30min pre	X	X	X	X	X	X	X	X	X
DOSE									X
30min post	X		X						X
2hrs post	X	X	X			X		X	X
4hrs post	X		X						X
8hrs post	X	X	X			X		X	X
24hrs post	X	X	X	X	X	X	X	X	X
48hrs post	X		X			X	X	X	X

- EKG - 12-lead
- Vitals - blood pressure, pulse, respiratory rate, temperature
- Heme - WBC with differential, RBC, hemoglobin, hematocrit, MCV, MCH, MCHC, platelets, reticulocytes, PT, PTT
- Chem - Na^+, K^+, Cl^-, BUN, creatinine, glucose, total protein, albumin, PO_4^{-3}, SGOT, SGPT, alkaline phosphatase, GGT, LDH, CPK, LAP, ChE, cholesterol, lipids, uric acid
- Add'l - total and direct bilirubin, Ca^{+2}, Zn, Fe, ferritin, transferrin, TIBC, UIBC
- U/A - urinalysis
- Special - blood samples for Ca, Fe, and Zn (atomic absorption spectrophotometry); urine obtained at 0-2hrs, 2-4hrs, 4-8hrs, 8-12hrs, 12-24hrs, and 24-48hrs for same tests

- Post-trial: (1week post) physical exam; EKG; vital signs; labs including hematology and chemistry; urinalysis
- Follow-up: only performed for abnormal findings

Restrictions:

- From enrollment until trial completion, subjects were not to receive other drugs and refrained from alcohol or xanthines (coffee, black tea, green tea, colas, etc.).
- No smoking from arising until end of exam on day of administration and from 1hour before until end of exam on other days.

- Subjects fasted for 12hours before trial start until after blood sampling at 4hours post dose.
- Subjects were encouraged to drink 200ml H_2O 30minutes pre and 1hour post dose.

Pharmaco-kinetic Data: {Please refer to the Biopharmaceutical review by Dr. Choi for details}

Time	Serum Gd	Gd Protein Binding	Serum Metabolites	Urine
within 30 min pre	X		X	X
DOSE				
4min post	X			
7min post	X			
10min post	X		X	
15min post	X	X		
30min post	X		X	
1r post	X			
2hrs post	X	X	X	0-2hrs post
4hrs post	X		X	
6hrs post	X			
8hrs post	X		X	4-8hrs post
12hrs post				8-12hrs post
24hrs post	X		X	12-24hrs post
48hrs post				24-48hrs post

- Serum Gd: plasma emission spectral analysis for plasma Gd concentration
- Gd Protein Binding: rapid centrifugal ultrafiltration of serum without freezing, then protein binding rate measured based on Gd concentration in filtrate
- Metabolites: metabolites in serum assessed using
- Urine: Gd concentration (plasma emission spectral analysis) and metabolites

IMAGING PROTOCOL:

- No imaging was performed in this trial

STATISTICAL ANALYSIS:

- ANOVA for vital signs and labs (administration groups and times as factors) were used.
- If factor showed significance, values before and after compared "with multi comparison method like Dunnett's and Schaffe's, etc." [p. 10.0238, Vol. 2.44]
- "A risk of no more than 5% was taken as a significant difference" [p. 10.0238, Vol. 2.44]

PATIENT CHARACTERISTICS:

[from "Demographic Characteristics and Injection Volume", p. 10.003, Vol. 2.44]

Group	Dose (mmol/kg)	Vol. Injected (ml)	Subject #	Age (yrs)	Height (cm)	Weight (kg)
1	0.05	5.8	1	21	168.1	58.0
1	0.05	6.2	2	26	169.3	61.6
1	placebo	6.6	3	21	165.3	66.0
1	0.05	5.2	4	23	170.5	52.2
1	0.05	6.9	5	23	169.4	68.8
2	0.1	11.5	1	21	170.4	57.6
2	placebo	13.5	2	29	170.6	67.6
2	0.1	11.1	3	22	172.5	55.4
2	0.1	10.7	4	27	168.8	53.6
2	0.1	10.5	5	25	163.8	52.6
3	0.3	32.8	1	28	169.5	54.6
3	0.3	34.7	2	22	168.9	57.8
3	0.3	33.5	3	22	177.0	55.8
3	placebo	37.6	4	23	174.8	62.7
3	0.3	37.5	5	23	169.1	62.5
4	placebo	60.8	1	22	181.7	60.8
4	0.5	72.2	2	22	173.2	72.2
4	0.5	59.0	3	23	176.8	59.0
4	0.5	50.0	4	22	167.9	50.0
4	0.5	76.0	5	28	170.5	76.0
Mean	-	-	Mean	23.7 ± 2.6	170.9 ± 4.2	60.2 ± 7.0

Protocol Deviations:

1. Pt. #3 in Group 3 - blood samples were not obtained from 15min until 8hrs post drug administration due to pain at the phlebotomy site. Data for serum metal in this patient were excluded from the analysis but safety data were included.
2. Pt. #2 in Group 3 - did not complete urine collection for the 8-12hrs post administration interval. The cumulative urine was not included for analysis of urinalysis and pharmacokinetics. These data were also excluded from analyses of urinary metals, urine Gd concentration, and urinary metabolites. Safety data were included.
3. The special tests for metals were performed at [redacted] rather than at [redacted] as originally planned. [redacted] maintained responsibility for specimen delivery and for data management and storage.

Safety Data:

- All patients were reported to have normal screening and 24hr pre-dose physical exam findings. The Sponsor states that the additional physical examinations (as described in the Protocol) showed no clinically significant change compared to pre-dose.
- Vital signs: the reported mean values and ranges of these parameters for each group are presented in the tables below, the placebo group is presented as a separate table [from Sponsor's Tables 1.1-1.5, pp. 10.0028-10.0032, Vol. 2.44]

Group 1 - 0.05mmol/kg

Time	Temp (°C)	Pulse (beats/min)	Systolic BP (torr)	Diastolic BP (torr)	Respirations (breaths/min)
pre dose	36.1 ± 0.2 [35.8-36.3]	48.5 ± 5.7 [45-57]	93.0 ± 9.4 [83-105]	50.8 ± 4.5 [47-57]	16.0 ± 0.0 [16]
30min post	36.2 ± 0.2 [36.1-36.4]	54.5 ± 6.9 [49-64]	98.8 ± 11.2 [90-115]	48.8 ± 8.4 [42-61]	16.0 ± 0.0 [16]
2hrs post	36.5 ± 0.3 [36.1-36.7]	57.8 ± 0.5 [57-58]	108.0 ± 12.8 [96-126]	54.5 ± 7.4 [45-63]	17.5 ± 1.9 [16-20]
4hrs post	36.7 ± 0.2 [36.5-36.9]	55.8 ± 11.9 [42-71]	106.2 ± 12.0 [97-123]	55.0 ± 3.5 [52-60]	16.5 ± 1.0 [16-18]
8hrs post	36.0 ± 0.2 [35.7-36.2]	56.8 ± 3.8 [52-61]	102.5 ± 17.0 [90-126]	53.0 ± 6.5 [47-62]	17.5 ± 1.9 [16-20]
24hrs post	36.2 ± 0.2 [35.9-36.3]	55.0 ± 8.3 [45-65]	104.7 ± 9.0 [97-117]	55.5 ± 4.7 [51-62]	17.0 ± 2.0 [16-20]
48hrs post	36.3 ± 0.3 [35.9-36.6]	66.8 ± 9.9 [57-80]	110.0 ± 8.2 [100-120]	54.5 ± 3.0 [51-57]	16.0 ± 0.0 [16]
7days post	36.4 ± 0.7 [35.3-36.9]	69.5 ± 3.1 [66-73]	114.7 ± 11.6 [103-127]	57.8 ± 5.2 [50-61]	16.0 ± 0.0 [16]

Group 2 - 0.1mmol/kg

Time	Temp (°C)	Pulse (beats/min)	Systolic BP (torr)	Diastolic BP (torr)	Respirations (breaths/min)
pre dose	36.2 ± 0.2 [36.0-36.4]	50.5 ± 8.6 [38-57]	100.3 ± 5.2 [93-104]	55.0 ± 5.1 [50-62]	15.0 ± 2.0 [12-16]
30min post	36.2 ± 0.3 [35.7-36.5]	50.8 ± 10.0 [39-63]	95.0 ± 6.7 [85-99]	51.3 ± 6.9 [42-57]	15.0 ± 2.0 [12-16]
2hrs post	36.3 ± 0.1 [36.3-36.4]	51.0 ± 4.5 [46-57]	98.3 ± 5.0 [93-103]	52.3 ± 4.3 [47-57]	14.0 ± 2.3 [12-16]
4hrs post	36.3 ± 0.3 [35.9-36.6]	52.5 ± 9.7 [45-66]	97.0 ± 2.6 [94-100]	51.5 ± 3.1 [48-55]	15.0 ± 2.0 [12-16]
8hrs post	36.5 ± 0.4 [36.0-37.0]	54.8 ± 6.0 [47-60]	99.8 ± 3.9 [94-103]	52.3 ± 1.0 [51-53]	15.0 ± 2.0 [12-16]
24hrs post	36.1 ± 0.2 [35.9-36.2]	49.8 ± 4.3 [46-54]	100.3 ± 11.2 [94-117]	53.5 ± 3.3 [49-57]	16.0 ± 0.0 [16]
48hrs post	36.5 ± 0.3 [36.3-36.8]	64.0 ± 10.9 [49-73]	99.3 ± 1.5 [98-101]	54.0 ± 2.4 [52-57]	16.0 ± 0.0 [16]
7days post	36.2 ± 0.6 [35.6-36.8]	58.5 ± 4.2 [53-63]	107.5 ± 3.3 [105-112]	59.3 ± 3.0 [55-62]	16.0 ± 0.0 [16]

Group 3 - 0.3mmol/kg

Time	Temp (°C)	Pulse (beats/min)	Systolic BP (torr)	Diastolic BP (torr)	Respirations (breaths/min)
pre dose	35.8 ± 0.0 [35.8]	53.8 ± 11.8 [39-67]	109.3 ± 15.2 [90-127]	57.5 ± 4.7 [53-64]	15.0 ± 2.0 [12-16]
30min post	36.1 ± 0.2 [35.8-36.3]	54.0 ± 6.9 [44-60]	103.0 ± 8.8 [91-111]	54.8 ± 6.5 [49-64]	15.0 ± 2.0 [12-16]
2hrs post	36.3 ± 0.4 [35.7-36.6]	49.0 ± 7.9 [38-56]	100.8 ± 11.7 [86-112]	54.5 ± 2.9 [51-58]	15.0 ± 2.0 [12-16]
4hrs post	36.2 ± 0.5 [35.7-36.8]	51.3 ± 10.8 [37-61]	99.0 ± 7.9 [89-108]	53.8 ± 2.9 [52-58]	14.0 ± 2.3 [12-16]
8hrs post	36.4 ± 0.2 [36.1-36.6]	50.0 ± 7.7 [40-57]	98.3 ± 13.4 [83-110]	52.3 ± 5.0 [45-56]	16.0 ± 0.0 [16]
24hrs post	36.1 ± 0.4 [35.6-36.4]	56.0 ± 12.4 [38-65]	101.0 ± 11.6 [91-112]	55.8 ± 5.4 [49-61]	16.0 ± 0.0 [16]
48hrs post	36.2 ± 0.2 [35.9-36.4]	61.8 ± 7.1 [53-70]	110.5 ± 11.0 [99-123]	56.3 ± 3.4 [53-61]	16.0 ± 0.0 [16]
7days post	36.3 ± 0.2 [36.0-36.4]	62.8 ± 12.4 [47-77]	118.0 ± 13.5 [101-134]	60.3 ± 10.2 [49-73]	17.0 ± 2.0 [16-20]

Group 4 - 0.5mmol/kg

Time	Temp (°C)	Pulse (beats/min)	Systolic BP (torr)	Diastolic BP (torr)	Respirations (breaths/min)
pre dose	36.1 ± 0.3 [35.7-36.4]	56.3 ± 6.5 [53-66]	104.0 ± 10.4 [90-115]	60.5 ± 5.4 [55-68]	16.0 ± 0.0 [16]
30min post	36.2 ± 0.3 [36.0-36.5]	53.3 ± 6.4 [45-60]	109.5 ± 6.1 [102-115]	60.0 ± 4.7 [55-64]	16.0 ± 0.0 [16]
2hrs post	36.3 ± 0.2 [36.1-36.4]	53.5 ± 7.9 [45-64]	108.8 ± 10.8 [101-124]	57.5 ± 5.9 [52-64]	17.0 ± 2.0 [16-20]
4hrs post	36.4 ± 0.1 [36.2-36.4]	55.5 ± 9.3 [44-64]	111.3 ± 13.1 [95-127]	62.3 ± 6.1 [56-70]	16.0 ± 0.0 [16]
8hrs post	36.5 ± 0.4 [36.0-36.8]	57.5 ± 4.5 [51-61]	107.8 ± 9.5 [99-116]	58.3 ± 6.7 [54-68]	18.0 ± 2.3 [16-20]
24hrs post	36.2 ± 0.5 [35.6-36.6]	56.3 ± 11.0 [44-70]	108.0 ± 14.4 [94-128]	58.8 ± 6.2 [51-66] → **$p < 0.05$ vs. placebo**	14.0 ± 2.3 [12-16]
48hrs post	36.2 ± 0.2 [36.0-36.4]	71.8 ± 7.4 [63-81]	113.5 ± 4.4 [110-120]	62.5 ± 3.1 [58-65]	16.0 ± 0.0 [16]
7days post	36.2 ± 0.3 [35.9-36.5]	67.3 ± 9.4 [56-75]	121.5 ± 6.8 [115-131]	64.0 ± 3.9 [60-69]	16.5 ± 1.0 [16-18]

Placebo 'Group'

Time	Temp (°C)	Pulse (beats/min)	Systolic BP (torr)	Diastolic BP (torr)	Respirations (breaths/min)
pre dose	36.1 ± 0.2 [35.9-36.4]	52.0 ± 7.8 [41-58]	95.0 ± 2.3 [93-97]	51.3 ± 3.3 [47-55]	16.0 ± 0.0 [16]
30min post	36.5 ± 0.2 [36.2-36.7]	49.8 ± 4.7 [43-54]	97.5 ± 9.3 [90-110]	53.8 ± 8.4 [47-66]	16.0 ± 0.0 [16]
2hrs post	36.4 ± 0.5 [35.7-37.0]	54.3 ± 6.3 [47-60]	93.5 ± 10.0 [84-104]	52.0 ± 6.7 [43-58]	16.0 ± 0.0 [16]
4hrs post	36.5 ± 0.4 [36.0-36.8]	54.3 ± 3.8 [49-57]	103.3 ± 9.1 [95-113]	54.3 ± 1.7 [52-56]	16.0 ± 0.0 [16]
8hrs post	36.4 ± 0.4 [36.1-37.0]	51.3 ± 5.7 [47-59]	96.3 ± 5.7 [90-102]	48.5 ± 5.6 [41-54]	17.0 ± 2.0 [16-20]
24hrs post	36.2 ± 0.4 [35.7-36.7]	48.8 ± 5.9 [40-52]	94.0 ± 6.8 [87-103]	47.0 ± 2.2 [45-50]	16.0 ± 0.0 [16]
48hrs post	36.5 ± 0.2 [36.3-36.7]	65.0 ± 8.7 [54-75]	111.5 ± 10.2 [101-125]	57.8 ± 2.2 [55-60]	16.0 ± 0.0 [16]
7days post	36.6 ± 0.3 [36.3-37.0]	74.5 ± 3.1 [72-79]	116.3 ± 7.3 [111-127]	60.8 ± 1.5 [59-62]	16.0 ± 0.0 [16]

- Vital Signs:
  The Sponsor identified a statistically significant difference in diastolic blood pressure between the placebo group and 0.5mmol/kg dose group at 24hrs post dose. The magnitude of the difference was reported to be 11.8torr (higher in 0.5mmol/kg group compared to placebo) and was not considered to be clinically significant by the Sponsor.
- EKG:
  The Sponsor stated that 11 of the 20 subjects had sinus bradycardia at some point in the trial and considered this a normal finding in young healthy people.
  "atrioventricular interference dissociation" [p. 10.0004, Vol.2.44] was noted by the Sponsor at 2hrs and 8hrs post dose in one athletic subject who also had bradycardia (39 beats/min). The Sponsor attributed this to "clinostatic bradycardia in parasympathetic nervous system dominant state" [p. 10.0004, Vol. 2.44], also citing the finding that the serum concentration of OptiMARK™ at 8hrs post-dose was nearly below the limit of detection.

~ Reviewers's comment: does "atrioventricular interference dissociation" mean atrioventricular block and, if so, what degree? Does "clinostatic bradycardia" refer to the same phenomenon as in a vaso-vagal reaction or does it only mean orthostatic hypotension? The Sponsor refers to disappearance of the "clinostatic bradycardia" following "clinostatic resting period", the terminology is unfamiliar to the reviewers. It is unclear whether the Sponsor is referring to this episode as a "vaso-vagal" reaction in which case the above-mentioned "atrioventricular interference dissociation" should be interpreted as being an abnormal EKG with A-V nodal dysfunction (not sinus bradycardia), indicating that this may be an Adverse Event possibly attributable to the drug.

- Labs:
  The Sponsor found no clinically significant changes in hematology, chemistry, or urinalysis results.
  "slightly high values of total bilirubin" [p. 10.0005, Vol. 2.44] were reported in some patients at the pre-injection collection. The Sponsor reported "normal hepatic function (e.g., GOT, GPT)" [p. 10.0005, Vol. 2.44] in these subjects. It was stated that the total bilirubin levels gradually declined post-injection in the affected subjects.

~ Reviewers' Comment: The Sponsor's Tables 2.1-2.2, pp. 10.0033-10.0034, Vol. 2.44] list the values for total and direct bilirubin for the various doses and placebo at different timepoints. Five of the volunteers had total bilirubin levels higher than 1.5mg/dl (i.e., 1.7-2.0mg/dl) at the pre-dose time which decreased in 7 days to values of 0.9-1.3mg/dl except in one whose post-dose level was 1.7mg/dl (pre-dose level of 1.8mg/dl). The direct bilirubin for these subjects was 0.3-0.4mg/dl pre-dose and was 0.2-0.3mg/dl 7days post dose. The significance of these findings is unclear given that the related hepatic enzyme levels at baseline are reported to be normal by the Sponsor.

Calcium:

- Hypocalcemia was observed at 2 hours and upto 8 hours post dosing in the 0.3 mmol and 0.5 mmol groups. The Sponsor stated that there were no associated clinical signs or symptoms of hypocalcemia.
- The hypocalcemia was regarded as an artificial error and attributed to a chemical interference caused by the active ingredient additives (MP-1196). The Sponsor stated that this was confirmed using atomic absorption spectrophotometric measurement (verification on methodology made with Dr. Choi).

*~ Reviewer's comment: Comments on the methodology are reserved for bio-pharm/chemistry reviewers. The onset, duration of the bradycardia syndrome discussed above (with EKG changes) correlates and overlaps with the noted hypocalcemia. It is well known that calcium (hyper or hypo) affects the heart in many ways, and particularly hypocalcemia causes QT prologation and bradycardia. This association exists enough to warrant that these should be reflected in the ~**labeling** (lab value changes + bradycardia + ?EKG changes + ?predisposition to arrhythmias).*

Iron:

The Sponsor states that there were no significant changes in serum iron or ferritin or transferrin or TIBC or UIBC.
Significant urinary iron increases (in 24 hours cumulated samples) were noted with the 0.3 mmol and 0.5mmol doses that lasted for upto ~ 24 hours post-dosing.

Zinc:

A significant decrease in serum zinc level was noted with the 0.1 mmol, 0.3 mmol and 0.5mmol dose groups that lasted for upto ~ 24 hours post dosing.

Copper:

No significant changes in serum copper changes were noted. Urinary copper was increased at the 0.3mmol dose group, and lasted for upto ~ 24hours post dosing.

ADVERSE EVENTS:

None reported

Conclusion

- This PK study from Japan on healthy male volunteers did not report any adverse events. However, the bradycardia in 11 out of the enrolled 20 subjects, in particular the subject with associated EKG change (AV dissociation) is significant. It is worth noting that the period of the bradycardia (at 2hrs and at 8 hours) with the associated EKG change correlated and overlapped with the noted hypocalcemia. The Sponsor implies that the hypocalcemia is not a true hypocalcemia, but an artifactual one due to chemical interference as confirmed by the spectrophometric methodology. It is well known that hypocalcemia can affect the heart. Assuming that there was no true hypocalcemia (measurement of total calcium is an inaccurate parameter to assess the true manifestations of hypocalcemia because it is the ionized calcium that is the "active"moiety behind the symptoms. One cannot rule out true hypocalcemia (which is a measure of the ionized calcium) in this case. Additionally, interpreting total calcium without knowing the total protein/albumin level is meaningless. The Sponsor has obtained AA levels of calcium and total calcium levels in other trials (including phase 3 studies-liver) and has demonstrated that the ionized calcium levels are normal, but the total calcium levels are low-implying that there is no true hypocalcemia. In this situation, the only way one can attribute these bradycardic events associated with EKG change in one subject in the absence of true hypocalcemia would be drug effect. This is a concern and therefore, it is important on the part of the Sponsor to monitor patients during dosing and at regular frequent intervals at least for 24 hours.
- Other transient lab abnormalities were noted.
- Hypocalcemia, bradycardia and EKG changes have been the notable adverse reactions.
- The proposed or intended objectives have been demonstrated and accomplished with adequate data and monitoring. However, complete data on the labs, vitals, EKGs are not provided. Reporting of events is more subjective than objective. Nonetheless, an informative study.

END OF STUDY REPORT 1177-01

NDA # 20 937
IND#

OptiMARK™

Report # 538/Phase 1
Protocol # 1177-96-08.01

- Volumes Reviewed: NDA # 20 937 Volumes # 2.1 - 2.168 and additional information from Sponsor with letter dates 24 April 1998 (Volumes # M7.1 - M7.3), 11 September 1998 (BM), September 23, 1998 (letter correspondence to CSO)
- Primary Volumes for this study: 2.30-2.40

OVERVIEW: 538-PHASE 1 STUDY: OptiMARK™ : NDA # 20937

Phase Start * End @	Study # Protocol #	Title	Study Design	Objective	Population Exposed N = 54
1 06/02/97 11/15/97	538 1177-96-08.01	"A Study Comparing the Pharmacokinetics of OptiMARK™ (Gadoversetamide Injection) in Normal Subjects, Patients with Central Nervous System or Liver Pathology Who May Have Renal Insufficiency and Patients Who Have Renal Insufficiency and No Pathology"	Open-label, Single-dose, Multi-center	PK, Elimination, Metabolites, Safety, Tolerance (No Imaging)	Normal Adults, Adults with CNS/Liver pathology ± renal or hepatic impairment
Centers: Total = 6 US centers = 6 Outside US = 0					

APPEARS THIS WAY
ON ORIGINAL

TITLE:

- "A Study Comparing the Pharmacokinetics of OptiMARK™ (Gadoversetamide Injection)
  in Normal Subjects, Patients with Central Nervous System or Liver Pathology Who May
  Have Renal Insufficiency and Patients Who Have Renal Insufficiency and NO Pathology".

OBJECTIVES: (Vol. 2.34, p. 8.1087)

- The objective of this study was to evaluate:
  "The pharmacokinetic profile of OptiMARK™ at the standard clinical dose of 0.1 mmol/kg in patients diagnosed with central nervous system (CNS) or liver pathology, patients with CNS or liver pathology who also demonstrate renal insufficiency, and
  patients without pathology who demonstrate renal insufficiency. These results were compared with those obtained in healthy subjects".

METHODLOGY: (Vol. 2.34, p. 8.1088)

- This was a Phase 1, Open-label, single-dose, multi-center study. Per protocol: 42 patients and subjects were to be enrolled- 12 with liver pathology, 4 to 6 of whom demonstrated renal insufficiency; 12 with central nervous system pathology, 4 to 6 of whom demonstrated renal insufficiency; 12 renally impaired patients without pathology; and 6 healthy subjects.

DIAGNOSIS/INCLUSION CRITERIA: (Vol. 2.34, pp. 8.1088-8.1090)

- Males or females 18 years of age or older who had CNS (brain and/or spine) or liver pathology, with or without renal insufficiency (for which a contrast-enhanced MRI was indicated).
- Patients and subjects consented to be housed within the investigational facility for a minimum of 48 hours.

DRUG ADMINISTRATION AND METHODS: (Vol. 2.30, p. 8.0019; see table above)

- A single intravenous dose of 0.1 mmol/kg OptiMARK™, was administered at a rate of 1 – 2 mL per second, followed by a normal saline flush.

~ Reviewer's comment: Similar methodology such as rate, technique (hand held bolus), etc. as noted in other studies were followed. See comments in other review sections.

DURATION OF TREATMENT:

- Each patient and subject received a single dose of OptiMARK™ and was monitored for 7 days.

CRITERIA FOR EVALUATION:

Safety:

- Safety was monitored in terms of pre- and post-contrast physical examinations, vital signs, electrocardiograms (ECGs), and clinical laboratory measurements.
- Tolerance was assessed through the grading of heat, cold, and/or occurrence of pain at the injection site.
- Adverse events were collected throughout the study.

~ Reviewer's Note:
The submitted CRF's (Vol. 2.34, pp. 8.1141-8.1168) have been noted.

- The table summarizes these time events.

SAFETY: PHASE 1: STUDY 538 - TIMING OF EVENTS							
Times	Pre-Dose	0 to < 2 hrs	2 hrs to < 4 hrs	4 hrs to 8 hrs	24 hrs to 48 hrs	72 hrs	>72hrs
LABS	X		X		X	X	
VITALS	X	X			X	X	
EKG	X	X	X		X		
PE	X				X	X	

Pharmacokinetics:

- The pharmacokinetics and elimination of OptiMARK in six groups of patients and subjects was characterized through analysis of plasma and urine samples of total gadolinium (ICP-AES) and gadoversetamide

~ Reviewer's comment: Detailed information and comments are provided in the pharmtox/biopharm sections in the overall safety and by the respective FDA reviewers.

STATISTICAL METHODS:

- "Continuous variables were summarized using N, mean, standard deviation, minimum, and maximum. Categorical variables were summarized using N and percent. Change from baseline was analyzed using analysis of variance".

~ Reviewer's comment: Refer to the Statistician's review for additional comments.

SUMMARY:

- **Safety:**

General comments and Concerns:

1. The Sponsor has used similar parameters to define values as extreme or of clinical significance, for: vital signs (Vol. 2.34, p. 8.1093), EKG (Vol. 2.34, p. 8.1093), Physical Examination (Vol. 2.34, p. 8.1100), and Labs (Vol. 2.34); as in most of the other trials in this application.
2. Vital signs did not include temperature recording.
   There was no monitoring during dosing.
3. Clinical Laboratory Extreme Values" and "Out-Of-Range Laboratory Instructions" are provided in the CRFs and in the Appendix section.
   Special labs were performed (IgA, IgG, IgM, GGT, and as in study 489).
   Serum bicarbonate is not listed
   Urinalysis (microscopy) does not specify whether the analysis performed was on a centrifuged specimen..
   In the urinalysis, the Sponsor allows for >10WBC/HPF and for >100RBC/HPF as extreme values without specifying the sex of the patient, both of these values are clearly abnormal in men and in certain women.
   The Sponsor considers a positive urobilinogen in the urinalysis as an extreme value; but traces of urobilinogen can be excreted in urine in normal people.
4. History of hemoglobinopathies is an exclusion criterion in this Phase 1 trial and has been listed among the warnings in the proposed labeling. Besides medical history, the reviewers have not been able to determine how this diagnosis was made and there are no special tests (e.g., sickle cell screening, hemoglobin electrophoresis) that the Sponsor has provided in this study. Several of the hemoglobinopathies may be asymptomatic (mild) so the patients may not be aware of the condition.
5. As indicated elsewhere, the qualifications and background of the EKG readers is being provided by the Sponsor. The Sponsor indicated that the majority of the EKGs were read by the site principal investigator/s. It was noted in the pivotal phase three study (#488), that all the site principal investigators had a radiology and or a neurology training/background. The tracings are not included in the application. Additionally, the information whether the tracings were read manually or were automated readings is in the process of being furnished by the Sponsor to the agency (upon request from the agency). Further comments will be made pending review of this information when available.
   In this study there were 3 patients (n=54) who were reported by the Sponsor to have significant changes from the baseline of which 1 had clinically significant EKG changes. These included T wave inversions, QT interval changes, and PVCs (Vol. 2.39).
6. **History of Allergies:**
   It is noted in this study, that there were 3 patients (3/54= 5.5%%) who had a history of allergy to iodine or other contrast agents (amongst other allergies) and 2/3 (C-001-

42-M, D-002-51-F) also experienced adverse event during the study on exposure to OptiMARK™ (2/3=66.6%).

As discussed elsewhere and in the overall safety section, appropriate instructions in the (~) **label** should be provided to reflect this concern (such as, greater caution should be exercised in patients with known history of allergy to iodine agents...etc). Similar observations have been made in other trials/studies of this application. See comments in the overall safety section.

7. **Concomitant Meidcations:**
   It is noted in this study that ~9 patients (9/54=16.6%%) received either steroids or antihistamines (for various reasons) amongst other medications during the study period.
   Both steroids and antihistamines can mask (or decrease or curb) some of the symptoms and signs of drug reactions. In fact, it is a well known and an accepted practice in clinical medicine to administer these drugs to treat allergic reactions to drugs. The observed adverse reactions in this study may therefore not reflect the true incidence or severity of the event/s. The adverse events so projected in this study are probably lesser (in number and severity) than what might have been the true (not being on these medications) occurrence. See overall safety section for additional comments.
8. See below for comments on serious v/s severe events.

PATIENTS: ENROLLMENT & DISPOSITION: (Vol. 2.30, p. 8.0019)

- See table below:

REPORT # 538: PHASE 1: PATIENT ENROLLMENT/DISPOSITION: OptiMARK™ NDA 20937							
		Treatment Group					
		OptiMARK™ : Dose = 0.1 mmol/kg					
Number of Patients							
Entered/enrolled		58					
Exposed to study drug		54					
Completed study		54					
Evaluable for Safety		54					
Evaluable for PK (Efficacy)		54					
Dropped pre-dosing		4					
Dropped for adverse event		0					
Demographics							
		Normal	Liver	CNS	Liver & Renal	CNS & Renal	Renal
Age (years)	N	8	12	12	2	7	13
	mean	38.5	48.7	45.6	57.5	51.3	53.3
	range	26-75	35-62	29-78	51-64	35-72	31-72
Drug Volume							
Total volume (mL)	N	8	12	12	2	7	13
	mean	15.0	15.6	17.5	23.0	18.6	15.9
	range	11.5-18.8	11.2-20.9	12.2-23.7	17.0-29.0	13.3-24.1	11.9-19.4

Renal insufficiency defined as serum creatinine of $\geq$ 1.5mg/dL.

The following conclusions are drawn:

1. There was no statistically significant difference between treatment subgroups with respect to frequency or rating or intensity or demographics of AE.

2. There was no clustering or a trend to suggest that one particular group was more at risk.
3. The three most body systems to be affected were:
   Digestive system=8 patients (14.8%) Nervous system=7 patients (13.0%) Cardio/Respiratory=6 patients (11.1%) Others- Body as a whole=24 patients (44.4%)
4. The most frequently reported adverse events were:
   Headache=20 (37%), Nausea=4 (7.4%), Dizziness=4 (7.4%)
5. The majority of adverse events were of mild or moderate intensity (83/85=97.6%)
6. Changes in the clinical chemistry, hematology, urinalysis, vital signs, EKGs, physical examinations, or injection reactions/tolerance were not clinically meaningful or significant.
7. Lab deficiencies and lack of monitoring during dosing are noted as in the other phase one trials.
8. There were 2 serious adverse events and 2 severe events (se below). Seizures as an adverse event cannot be ruled out in patient 538-G-010. There were no deaths.
9. The table below summarizes some of these observations:

SAFETY: STUDY # 538 - PHASE 1:OptiMARK™ ADVERSE EVENTS:		
SUBJECTS (N) EXPOSED = 54 DEATHS (N) = 0 PATIENT (N) WITH SERIOUS ADVERSE EVENTS = 2 DROPPED (N) DUE TO ADVERSE EVENTS = 0		PATIENTS (N) WITH ADVERSE EVENTS = 32 (59.3%) TOTAL (N) ADVERSE EVENTS = 85 POST-DOSING NON-AE WITHDRAWAL = 0
Treatment Group	Dose = OptiMARK™ (0.1mmol/kg)	
N (RECEIVED DOSE)	54	
N (PATIENTS WITH AE)	32	
N (ADVERSE EVENTS)	85	
INTENSITY OF AE: MILD (N) MODERATE (N) SEVERE (N)	97.6% were mild or moderate (see comment above).	
	2	

Serious Adverse Events:

- This is one of the few instances in this application where there is inconsistency/difference between different sections in the information submitted on the same matter/s. These make interpretation difficult and at times even confusing that one rises questions on the validity of entire data that is presented in this application. Given that these stem from a single application and that the difference/s is attributable to a single issue, it is meaningless to believe one and ignore the other. Clarifications are further needed on these issues from the Sponsor. Determination on whether these constitute innocent editorial mistakes or over-looked modifications and manipulations, is something that the reviewer feels is outside the scope of this review.
- In particular, in the Overview of Clinical program (p.1.0361, Vol.2.2), the Sponsor has stated that there were two patients who experienced serious adverse events for this study 538 in the second paragraph of the summary (with description on only one of the patients-538-C-010). However, in the same page and on the fourth paragraph, the Sponsor states that there was only one severe adverse event in this study

(1/85=1.2%). The description that follows appears to be similar to the patient 538-C-010. It appears as though the Sponsor is attributing events of similar nature either under serious or severe but categorizes these differently, thereby giving a different statistical safety profile. Additionally, the second patient (not described on this page or in this section) has been listed as (538-G-010) one of the eight patients who experienced serious adverse event for the entire study. See also the overall safety review section (serious adverse events) for additional comments and other such inconsistencies. The reviewer will consider two as the number of serious adverse events for this study and for the overall safety review (as the Sponsor has identified the patient in the safety section). Further clarification from the Sponsor and verification on regulatory compliance is necessary. See comments in reports 489, 465, 464,543, and ?526).

The details of these serious adverse reactions are also commented in the overall safety review section.

- Two patients described below and in the overall safety section experienced serious adverse events during study participation:

SAFETY: SERIOUS ADVERSE EVENT: STUDY # 538 - PHASE 1:OptiMARK™		
	Patients	
Parameters	**538-C-010**	**538-G-010**
Dose received	0.1mmol/kg	0.1mmol/kg
Immediate Events	None	None
Onset of symptoms	~ 3 days post-drug exposure	Same day
Presenting symptoms	Generalized aches, confusion, lethargy	Mild to moderate facial numbness & tingling
When evaluated	Same day as onset-3 days post	~ two days later post-exposure
Findings	+ history of accidental water intake Confusion Hyponatremic (Na 123)	+ symptoms but no neurological deficits (ER) at ~ 48 hours + symptoms but no findings at 72 hr follow up + symptoms but no findings 7 days post exposure
Actions, treatment, investigations, disposition	Admission Normal saline iv adminstration Discharged ~6 days from exposure and followed up	NCCT, CBC, Coags- normal at ~ 48 hours Started on ticlopidine at ~ 48 hours Seen for 72 hr follow-up study PE Seen 7 day follow-up 54 days later- MRI and MRA- unremarkable
Resolution of symptoms	Yes, in ~ 6 days	No
Reviewer's Comments:	***Probably not related to study drug.*** ***Better instructions to patient would have prevented this.***	***Less likely related to study drug, but cannot rule out seizure phenomenon or TIA.*** ***Problem should have been addressed earlier if patient was available.*** ***Work-up should have included EEG**** ***The conducted work-up and the timings are meaningless if TIA was the clinical suspicion and working diagnosis.***

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

Pharmacokinetics:

The following conclusions can be made:

1. Renal impairment emerged as a significant factor, and not the other associated disease processes (CNS pathology, Liver pathology).

2. Serum iron changes as noted in the phase 1 #433 PK study were attributable to diurnal variability.
3. There was a 3-4 fold increase in the mean apparent elimination half-life of the drug when compared to the other groups in this study including those with CNS or Liver pathology but without associated renal impairment.
4. Renal impairment affects only the rate of excretion of the drug, and not the extent of excretion.
5. There was no metabolic breakdown of the drug.

~ Reviewer's comment: refer to the pharmtox/biopharm reviewers' review section for detailed comments.
~ Renal impairment and its effect on gadolinium kinetics should be incorporated in the labeling section.

CONCLUSIONS:

1. Refer to the overall safety section for additional comments.
2. Pharmacokinetic data and findings were informative and useful particularly in patients with renal insufficiency.
3. There were no deaths but there were 2 serious adverse events (in one seizures cannot be ruled out).
4. The minor lab deficiencies are noted in this study as well (433, 1177), but EKGs were performed and read completely. However, the chosen parameters are too wide and unacceptable. Therefore the reported data has no real significance.
5. The description of the patients with serious adverse events are different in the study volume and in the ISS. Such typographical and reporting differences are worrisome as to the validity of the material presented. Clarification form the Sponsor is necessary.

END OF STUDY REPORT 538

NDA # 20 937 **OptiMARK™** **Report # 543/Phase 1**
IND# **Protocol # 1177-97-02.01**

- Volumes Reviewed: NDA # 20 937 Volumes # 2.1 - 2.168 and additional information from Sponsor with letter dates 24 April 1998 (Volumes # M7.1 - M7.3), 11 September 1998 (BM), September 23, 1998 (letter correspondence to CSO)
- Primary Volumes for this study: 2.41-2.43

OVERVIEW: PHASE 1 STUDY 543*: OptiMARK™ : NDA # 20937					
Phase Start * End **	Study # Protocol #	Title	Study Design	Objective	Population Exposed (N=8)
1 10/20/97 11/25/97	543 1177-97-02.02	"An Open-Label, Phase 1 Study to Determine the Safety and Dialysis Clearance Rate of OptiMARK™ (Gadoversetamide Injection) in Patients with End-Stage Renal Disease Undergoing Hemodialysis"	Open-label, Single-dose, Single-center	PK, Safety, Dialysis Clearance (No Imaging)	Adults with ESRD on Hemodialysis
Centers = 1 Outside US = 0					

*Original Protocol (Protocol # 1177-97-02): 29 August 1997
First Amendment (Protocol # 1177-97-02.01): 10 October 1997

APPEARS THIS WAY
ON ORIGINAL

TITLE

- "An Open-Label, Phase 1 Study to Determine the Safety and Dialysis Clearance Rate of OptiMARK™ (Gadoversetamide Injection) in Patients with End-Stage Renal Disease Undergoing Hemodialysis"

OBJECTIVES [pp. 9.0251-9.0252, Vol. 2.42]

- Were:

1. "To characterize the pharmacokinetic profile and dialysis clearance rate of OptiMARK in patients with end-stage renal disease currently maintained on hemodialysis."
2. "To determine the safety profile of OptiMARK at a dose of 0.1mmol/kg in patients with end-stage renal disease currently maintained on hemodialysis."

STUDY DESIGN

- This was a Phase 1, open-label, single-center study in 8 patients with end-stage renal disease maintained on hemodialysis. Each patient received an intravenous dose of 0.1mmol/kg OptiMARK™ approximately 2 hours prior to a scheduled dialysis session. Safety and pharmacokinetic data were collected (as shown below) at multiple points through 3 dialysis sessions.

DOSE

- 0.1mmol/kg OptiMARK™ IV bolus at approximately 1-2ml/sec followed by a normal saline flush of at least 5ml.

DURATION OF TREATMENT:

- Each patient received a single intravenous dose of OptiMARK™.

PATIENT ENROLLMENT:

- 8 adults (either sex) requiring hemodialysis due to stable end-stage renal disease.
- **Inclusion Criteria:** [p. 9.0253, Vol. 2.42]

1. "Male or female patients at least 18 years of age"
2. "Renally impaired and maintained on hemodialysis for at least 6 months"
3. "Willing to be housed within the investigational facility a minimum of 72 hours (24 hours preceding drug administration through approximately 50 to 55 hours following drug administration) and to return for the third dialysis session"

4. "Within ±40% of the desirable range of body weights (1983 Metropolitan Weight Tables)"
5. "Negative pregnancy test (urine or serum) within 24 hours of OptiMARK administration, if female and of child-bearing potential. In addition, all female patients of childbearing potential must use a medically accepted method of contraception throughout the study"
6. "Provide written, informed consent prior to any study-related procedures being performed"

- **Exclusion Criteria:** [pp. 9.0253-9.0254, Vol. 2.42]

1. "The patient has concurrent uncontrolled cardiovascular, hepatic, endocrinologic, neoplastic, vascular, hemorrhagic, hematologic, or immunologic disease".
2. "The patient has a history of neurologic disease, psychiatric disorder, or emotional instability"
3. "The patient has received any investigational drug within 30 days of admission into this study"
4. "The patient has been previously entered in this study, or has participated in a previous study involving OptiMARK"
5. "The patient has had a hypersensitivity reaction to a gadolinium-based contrast agent or any other contraindication to MRI contrast agents, such as a history of hemoglobinopathies (e.g., sickle cell disease, hemolytic anemia)"
6. "The patient has undergone any contrast-enhanced examination (x-ray [including barium], magnetic resonance imaging, ultrasound, etc.) within 7 days prior to both the collection of baseline laboratory specimens and drug administration, or during the course of this study"
7. "The patient has a medical condition, associated illness, or extenuating circumstance that would significantly decrease study compliance, including all prescribed follow-up"
8. "The patient has undergone a major surgical procedure within 2 weeks (14 days) prior to admission into this study (not inclusive of percutaneous biopsies)"

PROTOCOL SUMMARY:

- Patients were fasting for 2 hours prior to receiving dose
- Patients were injected with 0.1mmol/kg of OptiMARK by intravenous bolus at approximately 1-2ml/sec, followed by a normal saline flush (≥ 5ml)
- Dialysis was scheduled to begin 2 hours after injection of dose and expected to last 3-5hrs
- A 24-hour urine collection was performed prior to dose administration in patients who produce urine to assess urine volume and creatinine clearance.

SAFETY ASSESSMENTS:

- Safety was monitored in terms of pre- and post-dose vital signs, physical examinations, electrocardiograms, and clinical laboratory measurements.
- Tolerance was assessed through the patient's grading of heat, cold, and/or occurrence of pain at the injection site.
- Adverse events were recorded throughout the study.
- These were obtained at various time points as shown in the table below:

SAFETY:PHASE 1: STUDY 543 –TIMINGS OF EVENTS: OptiMARK™ NDA 20937										
Time	Med Hx	Meds	Phys Exam	Vitals	EKG	Labs	AE	Syst Venous	Art. & Ven.	Dialys.
Within 24hrs pre	X	X	X			X	X			
immed pre		X		X	X		X	X		
DOSE										
immed post		X		X			X			
30min post		X					X	X		
1hr post		X		X	X		X	X		
2hr post		X		X		X	X	X		X
Dialysis 1										
2.5hrs post		X					X		X	X
3hrs post		X					X		X	X
4hrs post		X					X		X	X
5hrs post end dialysis 1		X		X			X		X	X
8hrs post		X					X	X		
24hrs post		X		X	X	X	X	X		
36hrs post		X					X	X		
Pre dialysis 2		X	X	X	X	X	X	X		X
Dialysis 2										
1hr dia. 2		X					X		X	X
2hrs dia 2		X					X		X	X
3hrs end dialysis 2		X		X			X		X	X
5hrs dia 2		X					X	X		
Discharge										
pre dialysis 3		X		X			X	X		X
Dialysis 3										
1hr dia. 3		X					X		X	X
2hrs dia 3		X					X		X	X
3hrs end dialysis 3		X	X	X			X		X	X

Med Hx: medical and surgical history, specifically including eye, ear, nose, throat, cardiac, peripheral vascular, respiratory, musculoskeletal, gastrointestinal, genitourinary, neurological, endocrine, dermatologic, and allergic
Meds: concomitant medications, including over-the-counter agents
Phys Exam: physical examination, specifically including general appearance, skin, head/neck, eyes, ears, nose, throat, cardiac, chest/lungs, abdomen, extremities, and neurologic
Vitals: include systolic and diastolic blood pressure, pulse rate, respiratory rate
Labs: include hematology (WBC count with differential, RBC count, hemoglobin, hematocrit, and platelets) and serum chemistry (Na^+, K^+, Cl^-, BUN, creatinine, glucose, total protein, albumin, Ca^{+2}, PO_4^{-3}, ALT/SGPT, AST/SGOT, GGT, alkaline phosphatase, TIBC, Fe, transferrin, and ferritin)
AE: monitoring for adverse events
Syst Venous: systemic venous blood drawn for pharmacokinetic analysis
Art. & Ven.: arterial and venous blood samples will be assayed for BUN, creatinine, chemistry, and hematology. Arterial samples will be analyzed for hematocrit
Dialys.: dialysate samples for pharmacokinetic analysis, BUN, and creatinine.

The submitted CRF's (Vol. 2.42, pp. 9.0329-9.0420) pertaining to medical and surgical history, concomitant medications, physical examination, vital signs, EKG, Clinical Labs, adverse events, and tolerability have been noted.
The 24-hour urine collection is only performed pre-dose. If the patient produces urine, analysis of urine collected post-dose may be useful to assess the proportion of the dose that is eliminated by the patient's residual renal function

PHARMACOKINETIC ANALYSIS:

- Gadolinium concentration in dialysate and plasma (arterial & venous) samples determined using ICP-AES methods (Inductively-Coupled Plasma Atomic Emission Spectroscopy)
  - dialysance: clearance (Cl_D) of OptiMARK, BUN, and creatinine calculated using formula with plasma concentration data:
  a) $Cl_D = [(A - V) / A] \cdot Q_B \cdot (1\text{-hematocrit})$ [p. 9.0264, Vol. 2.42]
  b) A = arterial plasma concentration; V = venous plasma concentration
  c) Q_B = rate of blood flow through dialyzer
- Recovery: clearance of OptiMARK, BUN, and creatinine calculated using formula based on recovery of complex in dialysate:
  a) $Cl_D = X_D / AUC_D$ [p. 9.0264, Vol. 2.42]
  b) X_D = recovered OptiMARK / BUN / creatinine in dialysate
  c) AUC_D = area under arterial concentration-time curve for given dialysis session
  d) total dialysis recovery = sum of X_D for all dialysis sessions
- Total clearance: of OptiMARK estimated from formula -
  a) Cl_T = Dose / AUC_T [p. 9.0264, Vol. 2.42]
  b) AUC_T = area under plasma concentration-time curve (estimated) from time of dose administration until end of study
- Elimination half-life: estimated for each dialysis session using log-linear regression of arterial concentration-time data
  a) elimination rate constant = k_{el}
  b) elimination half-life = $t_{½}$

IMAGING PROTOCOL

- No imaging was proposed for this study

STATISTICAL METHODS

- Desciptive statistics for weight, height, vital signs (result and change from baseline for each timepoint), EKG changes, and pharmacokinetic data; counts and percents for sex, race, and number of patients with abnormal physical exam findings
- $\alpha = 0.05$
- adverse events reported by number, body system and term, severity, and relation to drug
- for lab data, "Standard result = (result - lower normal range)/(high normal range - low normal range)" [p. 9.0266, Vol. 2.42] were used for summary table

SUMMARY – CONCLUSIONS:

PHARMACOKINETIC RESULTS:

- "The mean dialysis clearance of gadoversetamide, estimated from the recovery rate in dialysate was 93.2 ± 17.1 mL/min, or 48% of the creatinine clearance (194 ± 18.6 mL/min)".
- "At the end of the 5-day period (encompassing three dialysis sessions) about 98% of the drug had been cleared based on plasma concentrations, with about 70% recovered in the dialysis fluid of most patients. The difference between these numbers is attributed to a small residual renal clearance in the patients, which could be observed as a decline in plasma concentrations during the inter-dialytic periods. Within the blood flow range of 400-600 mL/min, no significant effect of this parameter on clearance was noted".
- "The mean dialysis half-life of gadoversetamide was 1.74 ± 0.37 hr".

~ Reviewer's comment: Refer to the pharmtox/biopharm FDA review section for further comments.

PATIENT ENROLLMENT/DISPOSITION

REPORT # 543: PHASE 1: PATIENT ENROLLMENT/DISPOSITION OptiMARK™ NDA 20937		
		Treatment Group
		OptiMARK™ 0.1 mmol/kg
Number of Patients		
Entered/Enrolled		10
Exposed to study drug		8
Completed study		8
Evaluable for Safety		8
Evaluable for Efficacy (PK)		8
Dropped pre-dosing		2
Dropped for adverse event		0
Demographics		
Age (Years)	N	8
	mean	50.0
	range	32-68
Drug Volume		
Total Volume (ml)	N	8
	mean	15.4
	range	13-18

SAFETY

1. The Sponsor has used similar parameters to define values as extreme or of clinical significance, for: vital signs (Vol. 2.42, p. 9.0299), EKG (Vol. 2.42, p. 9.0300), Physical Examination (Vol. 2.42, p. 9.0299), and Labs (Vol. 2.42, p. 9.0301), as in most of the other trials in this application; commendable for uniformity. Comments have been made in the overall safety review section.

2. Medical History:
   a) History of hemoglobinopathies is an exclusion criterion in this Phase 1 trial and has been listed among the warnings in the proposed labeling. Besides medical history, the reviewers have not been able to determine how this diagnosis was made and there are no special tests (e.g., sickle cell screening, hemoglobin electrophoresis) that the Sponsor has provided in this study. Several of the hemoglobinopathies may be asymptomatic (mild) so the patients may not be aware of the condition.
   b) History of Allergy:
      It is noted in this study, that there were 2 patients (2/8= 25%) who had a history of allergy to iodine or other contrast agents (amongst other allergies) and one of them experienced an adverse event during the study on exposure to OptiMARK™ (1/2=50%).
      As discussed in other studies and in the overall safety section, appropriate instructions in the **label** should be provided to reflect this concern (such as, greater caution should be exercised in patients with known history of allergy to iodine agents...etc). See comments in the overall safety section.
3. Vital signs did not include temperature recording. It is not clear if there was any monitoring (EKG or Vitals) during the drug injection/dosing.
4. Labs: (see Appendix for"Clinical Laboratory Extreme Values and in the CRF's for "Out-Of-Range Laboratory Instructions")
   a) Special labs were performed (gadolinium, zinc, iron, creatinine levels in serum and/or urine).
   b) Urinalysis (microscopy) does not specify whether the analysis performed was on a centrifuged specimen.
      In the urinalysis, the Sponsor allows for >10WBC/HPF and for >100RBC/HPF as extreme values without specifying the sex of the patient, both of these values are clearly abnormal in men and in certain women.
      The Sponsor considers a positive urobilinogen in the urinalysis as an extreme value; but traces of urobilinogen can be excreted in urine in normal people.
   c) Serum bicarbonate is not listed.
5. EKG:

a) As indicated in the overview of safety, the qualifications and background of the EKG readers is being verified. The Sponsor indicated that the majority of the EKGs were read by the site principal investigator/s. It was noted in the pivotal phase three study (#488) and others, that all the site principal investigators had a radiology and or a neurology training/background.
b) The tracings are not included in the application.
c) Additionally, the information whether the tracings were read manually or were automated readings is in the process of being furnished by the Sponsor to the agency (upon request from the agency). Its importance rests with the clinical significance that QT changes/intervals are not measured accurately in the face of associated hypocalcemia and hypokalemia by automated readings and therefore cannot have clinical meaningfulness.
d) The Sponsor chosen parameters (see above) are too wide.

e) This was one of the few studies in this clinical program with EKGs that were adequate (note that there were only 8 patients in this study) in terms of recording all the intervals (QT intervals in particular). Interpretations were portrayed without actual baseline values.

f) There were no EKG changes that were reported to have changes from baseline or that were clinically significant.

6. Regulatory concerns:

a) This is one of the few instances in this application where there is inconsistency/difference between different sections in the information submitted on the same matter/s. In particular, the serious adverse event described on patient 543A003, there are typographic and reporting differences between the study volume and the ISS volume (This adverse event has been reported as a serious adverse event in the integrated summary of safety (Vol. 2.147, p. 26.0092). These make interpretation difficult and at times even confusing that one rises questions on the validity of entire data that is presented in this application. Given that these stem from a single application and that the difference/s is attributable to a single issue, it is meaningless to believe one and ignore the other. Clarifications are further needed on these issues from the Sponsor. Determination on whether these constitute innocent editorial mistakes or over-looked modifications and manipulations, is something that the reviewer feels is outside the scope of this review.

7. Other safety comments:

- Adverse Events:

a) There were no deaths; one serious adverse event (described below) was observed.

b) The number of patients reporting adverse events were 7/8 (87.5%)- one of the highest reported in this clinical program.

c) The majority of adverse events in the Optimark™ group were in the mild category- 29/30 (96.7%).

d) Dizziness was the most common adverse event occurring in 3 (37.5%).

e) The onset for a majority of these events occurred when the second session of dialysis was initiated.

f) There were no demographically statistically significant differences in the adverse events.

g) All the changes with reference to safety- adverse events, vital signs, labs, EKGs, were attributable to the ESRD and chronic hemodialysis.

h) There were no procedural related events.

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

j) The table below summarizes some of these observations:

SAFETY:ADVERSE EVENTS: STUDY # 543 - PHASE 1:OptiMARK™		
SUBJECTS (N) EXPOSED = 8 DEATHS (N) = 0 PATIENT (N) WITH SERIOUS ADVERSE EVENTS = 1 DROPPED (N) DUE TO ADVERSE EVENTS = 0		PATIENTS (N) WITH ADVERSE EVENTS = 7 (87.5%) TOTAL (N) ADVERSE EVENTS = 30 POST-DOSING NON-AE WITHDRAWAL = 0
Treatment Group	Dose = OptiMARK™ (0.1mmol/kg)	
N (RECEIVED DOSE)	8	
N (PATIENTS WITH AE)	7	
N (ADVERSE EVENTS)	30	
INTENSITY OF AE: MILD (N) MODERATE (N)	96.7% were mild or moderate (see comment above).	
SEVERE (N)	1	dyspnea

Serious Adverse Event:

- One patient 543-A-003 experienced serious adverse event during this study. The table below summarizes the findings:

SAFETY STUDY # 543 - PHASE 1:OptiMARK™	
SERIOUS ADVERSE EVENT:	
Parameters	**Patient**
	543-A-003
Dose received	0.1mmol/kg
Immediate Events	None
Onset of symptoms	~ 2 days post drug exposure
Presenting symptoms	Dizziness, Diaphoresis, palpitations, SOB
When evaluated	Same day as onset-2 days post-drug exposure
Findings	Suspicion of cardiac arrhythmia Abnormal EKG (no mention if change from base-line)
Actions, treatment, investigations, disposition	Admission for cardiac monitoring Discharged ~ 4 days post exposure
Resolution of symptoms/Outcome	Improved-clear Discharged
Reviewer's Comments:	***Probably not related to study drug.*** ***But cannot exclude association to drug: as patient has a history of renal ESRD; there were no other attributing factors.***

FINAL COMMENTS

1. This PK study on 8 patients on hemodialysis established the following:

a) OptiMARK™ is dialysable

2. The incidence of adverse was the highest for all the studies combined together, but there were only 8 patients in this study who were all on hemodialysis (anticipated to a certain extent).
3. Minor lab deficiencies, in particular the absence of bicarbonate is noted.
4. The EKG concerns as to the background of the readers, methodology of reading (manual v/s automated), Sponsor chosen wide parameters; all noted in other studies as well exists in this study.
5. There was one patient with a serious adverse event with an abnormal EKG (symptomatic) that was not attributed by the Sponsor to OptiMARK™. Given that this was a patient with ESRD and the known PK of OptiMARK™ in such patients, one cannot rule out drug attribution. See comments in the overall safety section. Labeling should probably provide caution or warning to indicate a) cardiac arrhythmias/delayed adverse reactions in renal patients.
6. There was a 50% correlation between history of allergy to iodine or other contrast agents and the development of an adverse event to OptiMARK™. Appropriate labeling cautions or warnings should be incorporated.

END OF STUDY REPORT 543

NDA # 20 937
IND#

OptiMARK™

Report # 489/Phase 1
Protocol # 1177-95-04.03

- Volumes Reviewed: NDA # 20 937 Volumes # 2.1 - 2.168 and additional information from Sponsor with letter dates 24 April 1998 (Volumes # M7.1 - M7.3), 11 September 1998 (BM), September 23, 1998 (letter correspondence to-CSO)
- Primary Volumes for this study: 2.12-2.29

The comments on the safety section are abbreviated. Detailed comments have been made in the over-all safety review section.

OVERVIEW: 489*-PHASE I STUDY: OptiMARK™ : NDA # 20937					
Phase Start * End @	Study # Protocol #	Title	Study Design	Objective	Population Exposed (N=121+42=163)
I 06/04/96 08/12/97	489 1177-95-04.03	"A Study to Evaluate the Pharmacology of OptiMARK™ (Gadoversetamide Injection) in Patients with Central Nervous System or Liver Pathology"	Double-blind, Single dose, Randomized, Placebo-controlled, Parallel group, Multi-center	Dose related pharm. effects, Safety, Tolerance, (No Imaging)	>2 years, Liver/CNS pathology ± renal impairment
Centers: Total = 10 US = 10 Outside US = 0					

* Original Protocol (Protocol # 1177-95-04): 04 December 1995; First Amendment (Protocol # 1177-95-04.01): 03 January 1996; Second Amendment (Protocol # 1177-95-04.02): 20 March 1996; Third Amendment (Protocol # 1177-95-04.03): 23 September 1996

TITLE

- "A study to Evaluate the Pharmacology of OptiMARK™ (Gadoversetamide Injection) in Patients with Central Nervous System or Liver Pathology".

OBJECTIVES (Vol. 2.15, p. 7.1268)

- The objectives of this phase I study were to evaluate the dose-related effects of intravenously administered OptiMARK™ as an MRI contrast agent in patients with existing CNS or liver pathology, utilizing doses of 0.1 mmol/kg, 0.3 mmol/kg, 0.5 mmol/kg.
  The primary objective was to evaluate the pharmacological dose-related effects on vital signs, electrocardiograms and clinical laboratory measurements.
  Secondary objectives included determination of the safety and tolerability profiles of OptiMARK™.
- As stated- "The primary objective of this trial is: [p. 7.1268, Vol. 2.15]
  "To determine the **pharmacological dose related effects** of OptiMARK™ on vital signs, electrocardiograms, and clinical laboratory measurements (chemistry, hematology, urinalysis, iron and zinc profiles, and gadolinium content in the serum and urine)."
  The secondary objectives of this trial are: [p. 7.1268, Vol. 2.15]
  "To determine the **safety** profile of OptiMARK™ utilizing a dose of 0.1 mmol/kg, 0.3mmol/kg, or 0.5mmol/kg. Safety will be assessed in terms of clinical signs and symptoms including physical examinations, monitoring of vital signs and electrocardiograms, incidence and nature of adverse events, and clinical laboratory measurements."
  "To determine the **tolerability** of OptiMARK™ by evaluating the incidence of heat, cold, and pain at the injection site during and immediately following intravenous administration."

STUDY DESIGN/METHODOLOGY: (Vol. 2.15, p. 7.1269)

- This was a multicenter (10 centers, all in the US), double-blind, randomized, placebo-controlled, parallel-group, study designed to evaluate the dose related effects of OptiMARK™ in patients with existing CNS or liver pathology with or without renal insufficiency. A total of 201 potential subjects were enrolled. Of these patients, 171 were randomized using two stratifications, the presence or absence or renal insufficiency and for renally sufficient patients, pathology (CNS or liver). Of these patients who were randomized, 163 subjects received one of the following doses: 0.1 mmol/kg, 0.3 mmol/kg, 0.5 mmol/kg or placebo.
- Pharmacodynamic dose-related effects, safety and tolerability were assessed pre- and post-dose, and for up to 7 days following administration of OptiMARK™ or placebo.

Inclusion Criteria:

- Male or female (inpatients or outpatients) and at least 2 years of age or older.
- Have CNS or hepatic pathology for which contrast-enhanced MRI was indicated.
- Patients remained in-house at the investigative site beginning 24 hours preceding drug administration and through 24 hours following drug administration.
- Informed consent.

Exclusion Criteria:

- If inclusion criteria were not met.
- If patient was pregnant or lactating (exclusion of pregnancy based on urine HCG or appropriate history depending on menstrual history).
- Any previous exposure to OptiMARK™.
- Any exposure to an investigational drug within the preceding 30 days.
- Any previous hypersensitivity reaction to gadolinium agents.
- History of hemoglobinopathies (see comments below).
- Any contrast-enhanced examination (including barium) within 72 hours prior to or during this study.
- Any major surgical procedures within 14 days prior to this study (not including percutaneous biopsies).
- Receipt of chemotherapy or radiation therapy within 4 weeks prior to and/or during this study.
- Receiving hemodialysis.

Reviewers' Note: The submitted CRFs pertaining to enrollment [p. 7.1312, Vol. 2.15], demographics [p. 7.1313, Vol. 2.15], and drug administration [p. 7.1318, Vol. 2.15]; Appendix B - Randomization Scheme [p. 7.1290, Vol. 2.15] has been noted.

DOSE/DRUG ADMINISTRATION: (Vol. 2.12, p. 7.0021)

- A single intravenous dose of 0.1 mmol/kg OptiMARK™, 0.3 mmol/kg OptiMARK™, or 0.5 mmol/kg OptiMARK™, or placebo (normal saline) was administered at a rate of 1-2 mL per second, followed by a saline flush.
- Supplied as 20ml single-dose vial of OptiMARK™ with concentration of 0.5mmol/ml
- Based on the randomization (see above), each patient received a single IV hand-administered bolus injection (approximately 1-2ml/sec) followed by a normal saline flush (≥5ml) at a dose of 0.1mmol/kg or 0.3mmol/kg or 0.5mmol/kg or normal saline (placebo)
- The volumes of placebo administered are either 0.2mL/kg, 0.6mL/kg, or 1.0mL/kg, equivalent in volume to 0.1mmol/kg or 0.3mmol/kg or 0.5mmol/kg of OptiMARK™ respectively
- The Principal Investigator and patient were blinded as to which dose and which drug was administered because a "third party blind" prepared the appropriate dose and drug as per the randomization scheme. The "third party blind" had no contact with

enrolled patients. The date, time, duration of injection, volume administered, and injection site were recorded on the Case Report Form [p. 7.1318, Vol. 2.15].

- The Sponsor stated that each patient should be dosed between 07:00AM and 08:00AM if possible [p. 7.1272, Vol. 2.15]-? rationale

~ Reviewer's comment: Similar methodology such as rate, technique (hand held bolus), etc. as noted in other studies were followed.

DURATION OF TREATMENT:

- Following drug administration, each patient was monitored for 7 days thereafter.

CRITERIA FOR EVALUATION:

PHARMACODYNAMIC ANALYSIS

- Dose related effects on vital signs, electrocardiograms, and clinical laboratory measurements were evaluated.

PHARMACOKINETIC ANALYSIS

- The pharmacokinetics and urinary excretion of OptiMARK™ were characterized in these patients through analysis of serum and urine samples for total gadolinium (ICP-AES).

SAFETY ASSESSMENTS

- The Sponsor collected the following data at various time points as indicated in the table below.
  1. Medical and Surgical History (see comments below)
  2. Concomitant Medications (Meds) - included all medications as well as over-the-counter medications taken within 24hours prior to drug administration through 7days following drug administration. See comments below (safety concern)
  3. Physical Examinations (Physical) - conducted by medically-certified individual (medical doctor, doctor-in-training, physician assistant, or nurse practitioner). The Sponsor defined a clinically significant change as "any variation in physical findings which has medical relevance resulting in alteration in medical care" [p. 7.1273, Vol. 2.15]
  4. Vital Signs (Vitals) - included systolic and diastolic blood pressure, pulse, and respiratory rate. The Sponsor defined the following changes as extreme and requiring additional comments on the Case Report Forms:
     - BP : systolic > 35mmHg, diastolic > 25mmHg
     - radial pulse > 20 beats per minute
     - respiratory rate > 10 breaths per minute

     These were later modified to include the following:
     - Any change in systolic blood pressure > 20 mm Hg

- Any change in diastolic blood pressure > 20 mm Hg
- Any change in pulse rate of > 15 bpm
- Any change in respiratory rate of > 10 breaths per minute

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

5. EKG - 12-lead electrocardiogram. The Sponsor defined the following changes as extreme and requiring additional comments on the Case Report Forms:

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

The Sponsor used the same definition for clinically significant change as in the physical examination section (see #3 above). These chosen parameters are too wide. See comments below and in the safety overview.

6. Clinical Labs (Blood and Urine) -
   - Blood included hematology (hemoglobin, hematocrit, RBC count, WBC count and differential, platelet count); chemistry (glucose, Na+, K+, Cl-, Ca+2, PO4, alkaline phosphatase, SGOT/AST, LDH, creatinine, BUN, total iron, iron binding capacity, ferritin, total protein, total and direct bilirubin, uric acid); serum iron, zinc, and Gd; serum creatinine; clotting factors
   - Urine included serial urine collections for Gd, iron and zinc, creatinine, and urinalysis
   - ❖ For each parameter (as mentioned above) that the Sponsor intended to monitor, extreme values which required comment on the Case Report Forms were listed in the "Out-Of-Range Laboratory Instructions" section of the Case Report Forms. These were interleaved with the sections for recording out-of-range lab results. The values were expressed as multiples (i.e., not absolute values) of the upper or lower limit of normal for each of the parameters.
   - ❖ Baseline out-of-range values were recorded. Values that were out-of-range and of clinical significance (possibly attributable to OptiMARK™) were documented on the Case Report Forms and the Principal Investigator would repeat these tests at his/her medical discretion.
   - ❖ The Sponsor used the same definition for clinically significant change as in the physical examination section (see #3 above)
7. Adverse Events (AE) - "An adverse event is defined as any undesirable experience occurring to the patient following drug administration, regardless of attribution" [p. 7.1279, Vol.2.15]. The Sponsor stated "serious adverse events are defined as those events which constitute a significant hazard to the patient and may include, but are not limited to the following: life threatening, persistent or significant disability/incapacity, requires hospitalization or extends inpatient hospitalization, events with the following outcomes: death, unusual or unexpected reactions, unusual frequency of reactions" [p. 7.1279, Vol. 2.15]
8. Tolerability Assessments (Tol) - sensations or discomfort (heat, cold, and/or pain) that the patient experienced at the injection site were recorded on the Case Report

Forms and are graded as: mild (slight sensation/discomfort), moderate (definite but tolerable sensation/discomfort), or severe (excruciating sensation/discomfort).

9. Patients remained in the investigative facility from 24 hours before drug administration until 24 hours after drug administration.
10. Safety was monitored in terms of pre- and post-dose vital signs, physical examinations, electrocardiograms, and clinical laboratory measurements. These were obtained at various time points as shown in the table below:

SAFETY: TIME EVENTS: STUDY # 489: PHASE 1:OptiMARK™									
Time	Med Hx	Meds	Physical	Vitals	EKG	Blood*	Urine^	AE	Tol
within 2wks pre	X								
within 24 hrs pre		X	X	X	X	creatinine only			
immediate pre		X		X	X	X	X		
DOSE		X						X	
immed post dose		X		X	X			X	X
15min post		X		X	X			X	
30min post		X			X			X	
1hr post		X	X	X	X	X	X	X	
2 hrs post		X		X	X			X	
4hrs post		X		X		X	X	X	
8hrs post		X		X		X	X	X	
16hrs post		X				X	X	X	
24 hrs post		X	X	X	X	X	X	X	
48 hrs post		X	X	X		X	X	X	
72 hrs post		X	X	X		X	X	X	
7 days post		X				X	X	X	

Meds = continuous evaluation of concomitant medications

*Blood: includes hematology (hemoglobin, hematocrit, RBC count, WBC count and differential, platelet count); chemistry (glucose, Na^+, K^+, Cl^-, Ca^{+2}, PO4, alkaline phosphatase, SGOT/AST, LDH, creatinine, BUN, total iron, iron binding capacity, ferritin, total protein, total and direct bilirubin, uric acid); serum iron, zinc, and Gd; serum creatinine; clotting factors

^Urine: includes serial urine collections (for Gd, iron and zinc, creatinine, and urinalysis) at various timepoints as noted in Appendix A [p. 7.1289, Vol. 2.15]

AE = adverse event monitoring

Tolerability: patient will be asked about sensations of heat, cold, or pain at injection site and whether it was mild, moderate, or severe.

The submitted CRF's pertaining to medical and surgical history [p. 7.1314, Vol. 2.15], concomitant medications [pp. 7.1315-7.1316, Vol. 2.15], physical examination [p. 7.1357, Vol. 2.15], vital signs [p. 7.1320, Vol. 2.15], EKG [pp. 7.1322-7.1336, Vol. 2.15], Clinical Labs [pp. 7.1337-7.1355, Vol. 2.15], adverse events [p. 7.1367, Vol. 2.15], and tolerability [p. 7.1318, Vol. 2.15] have been noted.

All labs in USA were shipped to [redacted] which shipped all serum and all urine samples for Gd levels to

EFFICACY CONSIDERATIONS

- There was no imaging performed during this study.

STATISTICAL CONSIDERATIONS

1. Safety Indicators were:
   - Vital Sign measurements (absolute and changes from baseline)
   - Lab measurements (absolute and changes from baseline)
   - EKG measurements (absolute and changes from baseline)
   - Physical Examination changes from baseline

- Incidence of Adverse Events

2. Tolerability Indicators:
   - grades of heat, cold, and pain

Sample Size Rationale -

The Sponsor made the following assumptions –

- the coefficient of variance (analogous to standard deviation) of the vital signs and lab tests is 20% (per results of Phase 1 and Phase 2 studies)
- the study should detect a difference in the means of 12.5%
- a two-sided test with $\alpha = 0.05$ would be used
- the desired power of the test was 80%

Based on these assumptions, the Sponsor calculated the minimum sample size to be 40 patients.

~ Reviewers' Note: $n = 2[(z_\alpha - z_\beta)\sigma]^2 / [\mu_1 - \mu_2]^2 = 2\{[1.96-(-0.825)](0.2)\}^2 / (0.125)^2 = 39.71 \approx 40$

[formula from pp. 119-120 Basic & Clinical Biostatistics, 2nd Edition by B. Dawson-Saunders and R. G. Trapp]

- All testing was two-sided with $\alpha = 0.05$
- For vital signs, labs, and some EKG parameters (PR, QRS, and QT intervals), the paired t-test was used to assess for changes from pre-dose to post-dose.
- Labs were categorized (below, within, or above normal range) for pre-dose and each post-dose timepoint. The Stuart-Maxwell test was used to compare the distributions of abnormal measurements for each timepoint.
- ANOVA was used at each post-dose timepoint to compare dosage groups relative to vital signs, lab measurements, PR, QRS, and QT interval. The following linear model was used: " $Y_{ijk} = \mu + \beta pre_{ijk} + S_i + D_j + \varepsilon_{ijk}$ where Y_{ijk} was the post-dose measurement, pre_{ijk} was the corresponding pre-dose measurement with regression coefficient ß, S_i was the effect for the i^{th} site, D_j was the effect of dose j, and ε_{ijk} was the error." [p. 7.1283, Vol. 2.15]
- The Mantel-Haenszel chi-square statistic was used for incidence parameters (dose effects) and for tolerability (dose effects)
- Pharmacologic parameters were reported using descriptive statistics.
- Subgroup analyses:
  pathology (CNS or hepatic)
  renal (normal or renal insufficiency defined as creatinine $\geq$ 1.5mg/dl per Sponsor)

SUMMARY – CONCLUSIONS:

PATIENT ENROLLMENT/DISPOSITION:

- The table below summarizes the extent of exposure, demographics, drug dosing, disposition:

STUDY REPORT # 489: PHASE 1: PATIENT ENROLLMENT: OptiMARK™ NDA 20937					
	Treatment Group -OptiMARK™ (mmol/kg)				
Number of Patients	Placebo	0.1	0.3	0.5	Combined
Entered/Enrolled	42	43	43	43	129
Exposed to Drug	42	40	42	39	121
Completed Study	42	40	42	39	121
Evaluated for Safety	42	40	42	39	121
Evaluated for PK (Efficacy)	42	40	42	39	121
Dropped pre-dosing	0	3	1	4	8
Dropped for adverse event	0	0	0	0	0
Demographics					
Age (Years) N	42	40	42	39	121
mean	45.8	43.7	45.5	47.9	45.7
range	23-73	20-76	18-71	19-72	18-76
Drug Volume					
Total volume (ml)	42	40	42	39	121
N mean	48.1	16.1	47.9	79.4	47.5
range	11.4-108.0	10.8-24.1	16.0-74.5	38.5-115.1	10.8-115.1

PHARMACOKINETIC RESULTS

- The following conclusions can be drawn from the data in this study:

1. In patients either with CNS or liver disease, but with normal renal function, neither sex, age nor differing pathology had any significant effect on the kinetics or elimination of gadoversetamide.
2. In subjects with renal impairment, the pharmacokinetics of gadoversetamide is dependent on the severity of the renal insufficiency. This resulted in a prolongation of the half life ($t_{\frac{1}{2}}$), a decrease in renal clearance (CL_T) and a slight increase in V_{DSS}. Serum clearance of gadolinium and baseline creatinine clearance were noted to be linearly related. Patients with moderate to severe renal impairment were noted to have a two to four fold increase in the exposure compared with liver or CNS patients without renal disease. Elimination is prolonged leading to increased exposure that is dependent on the degree of renal impairment.

SAFETY RESULTS AND COMMENTS:

1. The Sponsor has used similar parameters to define values as extreme or of clinical significance, for: vital signs (Vol. 2.15, p. 7.1274), EKG (Vol. 2.15, p. 7.1274), Physical Examination (Vol. 2.15, p. 7.1273), and Labs (Vol. 2.15, p. 7.1277), as in most of the other trials in this application. This uniformity was helpful in the review process.
2. In the medical history (including concomitant medications) the following are the concerns:

   History of Allergy:

   a) It is noted in this study, that there were 5 patients (5/121= 4.1%) who had a history of allergy to iodine or other contrast agents (amongst other allergies) and all five of them (B-004-45-F, E-009-44-F, E-013-44-F, J-006-56-F, J-015-59-F) experienced an adverse event during the study on exposure to OptiMARK™ (5/5=**100%**).

   b) As discussed in the overall safety section, appropriate instructions in the **label** should be provided to reflect this concern (such as, greater caution should be exercised in patients with known history of allergy to iodine agents...etc). Similar observations have been made in other trials/studies of this application. See comments in the overall safety section. The importance of this observation can be realized when one requires a MRI scan with a gadolinium agent in whom a iodinated imaging study cannot be performed due to a history of allergy to iodine. The ordering physician and the patient need to be aware of this possibility.

   Concomitant medications:

   a) It is noted in this study that ~8 patients (8/121=6.61%) received either steroids or antihistamines (for various reasons) amongst other medications during the study period.

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

   History of hemoglobinopathies:

   An exclusion criterion in this clinical program for all the clinical trials, this has been listed among the warnings in the proposed labeling. Besides medical history, the reviewer has not been able to determine how this diagnosis/or its exclusion, was made and there are no special tests (e.g., sickle cell screening, hemoglobin electrophoresis) that the Sponsor has provided in this study. Several of the hemoglobinopathies may be asymptomatic (mild) so the patients may not be aware of the condition.

3. Vital signs did not include temperature recording.
   It is not clear if there was any monitoring (EKG or Vitals) during the drug injection/dosing.
4. Lab concerns: (ref: Appendix E "Clinical Laboratory Extreme Values" [p. 7.1308, Vol.2.15] and in the CRF's "Out-Of-Range Laboratory Instructions)
   a) Urinalysis (microscopy) does not specify whether the analysis performed was on a centrifuged specimen.
      In the urinalysis, the Sponsor allows for >10WBC/HPF and for >100RBC/HPF as extreme values without specifying the sex of the patient, both of these values are clearly abnormal in men and in certain women.
      The Sponsor considers a positive urobilinogen in the urinalysis as an extreme value; but traces of urobilinogen can be excreted in urine in normal people.
   a) Serum bicarbonate is not listed as a lab parameter that was monitored. Determination of ones metabolic status (acidosis or alkalosis) is impossible without this parameter. The need to monitor urine and bicarbonate appropriately is particularly significant because of a) the pharmacokinetics of OptiMARK™ and b) renal impaired patients were studied in this trial.
   c) Serum Ca^{+2} was measured using atomic absorption assay because Sponsor stated that OptiMARK™ interfered with colorimetric assay causing a lab artifact of hypocalcemia. See comments in study 1177.
5. EKG:
   a) As indicated in the overview of safety, the qualifications and background of the EKG readers is being verified. The Sponsor indicated that the majority of the EKGs were read by the site principal investigator/s. It was noted in the pivotal phase three study (#488) and others, that all the site principal investigators had a radiology and or a neurology training/background.
   b) The tracings are not included in the application.
   c) Additionally, the information whether the tracings were read manually or were automated readings is in the process of being furnished by the Sponsor to the agency (upon request from the agency). Its importance rests with the clinical significance that QT changes/intervals are not measured accurately in the phase of associated hypocalcemia and hypokalemia by automated readings and therefore cannot have clinical meaningfulness.
   d) The Sponsor chosen parameters (see above) are too wide.
   e) This was one of the few studies in this clinical program with EKGs that were adequate in terms of recording all the intervals (QT intervals in particular). Interpretations were portrayed without actual baseline values.
   f) There were 12/121 (~10%) incomplete records.
   g) The Sponsor identified 18 patients with significant changes from baseline for OptiMARK™ of which 5 were designated to be clinically significant (QT changes and S-T changes in 4). There were 6 in placebo group with changes from baseline (considered non significant clinically). See comments in the safety overview.

6. Regulatory concerns:

a) The definition of serious adverse events (Vol. 2.15, p. 7.1279) and the scales for tolerability at site of injection (Vol. 2.12, p. 7.0027) are similar as for the other studies. Further clarification was sought from the Sponsor on these issues. However, the concerns on the issue of the disparity between the 'stated terminology of serious v/s severe' and the 'implementation of the same' by the Sponsor is mentioned below and in other parts of the review; as it may have a direct impact on the statistical safety profile. Further clarification from the Sponsor and verification on regulatory compliance is probably necessary. See comments in reports 538, 465, 464, and 543.

b) This is one of the few instances in this application where there is inconsistency/difference between different sections in the information submitted on the same matter/s. In particular, the serious adverse event described on patient 489D012, there is typographic and reporting differences between the study volume and the ISS volume. These make interpretation difficult and at times even confusing that one rises questions on the validity of entire data that is presented in this application. Given that these stem from a single application and that the difference/s is attributable to a single issue, it is meaningless to believe one and ignore the other. Clarifications are further needed on these issues from the Sponsor. Determination on whether these constitute innocent editorial mistakes or over-looked modifications and manipulations, is something that the reviewer feels is outside the scope of this review.

7. Other safety comments:

- Adverse Events:

a) There were no deaths; one serious adverse event (described below) was observed.

b) The number of patients reporting adverse events were 88/121 (72.7%)- one of the highest reported in this clinical program; but twenty-one subjects (21/42) in the placebo group (50%) reported a total of 80 adverse events.

c) The majority of adverse events in the Optimark™ group were in the mild category and similar in profile to the placebo group, including the lab changes.

d) The most frequently reported adverse events were headache, vasodilation, dizziness, taste perversion, nausea, asthenia, and dyspepsia.

e) The frequency of adverse events were directly proportional to dose increase, i.e., they were dose related.

f) There were no statistically significant differences either in the intensity or demographics between the various groups.

- There were no clinically significant or unexpected changes in physical examination, vital signs, EKGs (see above) and labs from base line.
- There were no consistent dose related changes in vital signs.

- The table below summarizes some of the observations:

SAFETY: STUDY # 489: PHASE 1:OptiMARK™			
ADVERSE EVENTS:			
PATEINTS (N) EXPOSED = 121 (total 163; placebo= 42) DEATHS (N) = 0 PATIENT (N) WITH SERIOUS ADVERSE EVENTS = 1 DROPPED (N) DUE TO ADVERSE EVENTS = 0		PATIENTS (N) WITH ADVERSE EVENTS = 88 (72.7%) TOTAL (N) ADVERSE EVENTS = 250 POST-DOSING NON-AE WITHDRAWAL = 0	
Treatment Group	**OptiMARK™ (mmol/kg)**		
Dose	**0.1**	**0.3**	**0.5**
N (RECEIVED DOSE)	40	42	39
N (PATIENTS WITH AE)	26	29	33
N (ADVERSE EVENTS)	74	81	95
INTENSITY OF AE	**+ Dose related**		
MILD (N) MODERATE (N) SEVERE (N)	The majority of adverse events in the OptiMark™ group were in the mild category and similar in profile to the placebo group		
	0	1	0
LABORATORY EVENTS:			
Parameters affected	Phosphorus, TIBC, Total proteins, Zinc		
Dose related	No		
Time related	No		
Clinically significant (symptomatic)	No		
Duration (how long)	Transitory		

APPEARS THIS WAY
ON ORIGINAL

Serious Adverse Event:

- Patient 489-D-012 developed a serious (listed as serious in the integrated summary of safety – p. 26.0093, Vol. 2.147) adverse event (experienced mild heat upon 0.3mmol/kg dose of OptiMARK™ following/during administration, and ~ five days later presented with signs and symptoms of meningitis- see below).
- Description of the patient with the serious adverse event:

SAFETY: SERIOUS ADVERSE EVENT: STUDY # 489 - PHASE 1:OptiMARK™	
	Patient
Parameters	**489-D-012**
Dose received	0.3mmol/kg
Immediate Events	Mild heat
Onset of symptoms	~ 5 days post drug exposure
Presenting symptoms	Progressive headache, photophobia, stiff neck, nausea, fatigue, fever
When evaluated	Same day as onset-5 days post-drug exposure
Findings	Exam findings-none mentioned Possible clinical suspicion of recurrent meningitis
Actions, treatment, investigations, disposition	Admission Normal saline iv and pain medication Lumbar puncture (CSF: no change from baseline-hx of coccidioidal mengitis)
Resolution of symptoms/Outcome	None mentioned
Reviewer's Comments: ***Probably not related to study drug, most likely due to underlying pathology.***	

Final Comments:

1. The pharmacokinetic data established the relationship between the drug and the kidneys (and not the liver or other pathology in the absence of associated renal insufficiency) and in patients with renal insufficiency. The Sponsor has demonstrated potential usefulness, a better understanding of the PK of OptiMARK™, and potentially established the stage for phase 2 studies.
2. No imaging was performed.
3. Safety concerns were:

a) Larger incidence of adverse reactions/events than in other studies (also noted to be high in the placebo group); one patient with serious adverse event probably not drug related; and dose related adverse events
b) Minor deficiencies in obtaining some lab parameters – some as noted in the other studies.
c) One of the trials with better EKG monitoring in terms of completeness. However, the concerns are the background of the readers; the wide set parameters and data presentation.
d) Minor lab abnormalities that were transient.
e) Lesser patients on steroids or antihistamines as concomitant medications than in some of the other studies, but still a concern.
f) A 100% association between history of allergy to an iodinated or other contrast agent and development of an adverse event to OptiMARK™.
g) Regulatory concerns.

END OF STUDY REPORT 489

NDA # 20 937 **OptiMARK™** **Report # 464 /Phase 2**
IND# **Protocol # 1101-02.02**

- Volumes Reviewed: NDA # 20 937 Volumes # 2.1 - 2.168 and additional information from Sponsor with letter dates 24 April 1998 (Volumes # M7.1 - M7.3), 11 September 1998 (BM), September 23, 1998 (letter correspondence to CSO)
- Primary Volumes for this study: 2.95-2.101

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

OVERVIEW: 464*-PHASE 2 STUDY: OptiMARK™ : NDA # 20937					
Phase Start * End @	**Study # Protocol #**	**Title**	**Study Design**	**Objective**	**Population Exposed (N)=83**
2 11/18/93 12/15/94	464 1101-02	"Multicenter, Double-Blind, Multidose, Within-Patient Study to Evaluate the Safety, Tolerance, and Efficacy of MP-1177/10 Injection in MRI of the Brain"	Double-blind, Randomized, Multi-center, Pseudo-crossover (1-7 days between first and second dose)	Safety, Tolerance, Efficacy + Imaging	Adults with known or suspected CNS pathology
Centers = 6 US centers = 3 Outside US = 3 (one without patient)					

*Study proposed August 1993
Second revision April 1994

TITLE:

- This was Multicenter, Double-Blind, Multidose, Within-Patient Study to Evaluate the Safety, Tolerance, Efficacy of MP-1177/10 Injection in MRI of the Brain.

STUDY PERIOD:

- First patient dosed November 18, 1993. Last patient dosed December 15, 1994

OBJECTIVE: (Vol. 2.97, p. 17.0485)

- The main objective of this phase 2 study was to determine the dose-related safety, tolerance, and efficacy of intravenously administered OptiMARK™ (gadoversetamide injection) in patients with known or suspected brain pathology (previously detected by computed tomography or ultrasound).

METHODOLOGY/STUDY DESIGN: (Vol. 2.97, p. 17.0486)

- This study was a multicenter, double-blind, multidose within-patient clinical trial. Patients were randomly assigned to one of three pairs of OptiMARK™ doses (0.1, 0.3 mmol/kg; 0.1, 0.5 mmol/kg; and 0.3, 0.5 mmol/kg) as one of two dosing sequences (low dose followed by high dose or vice versa). Each patient received two sets of images during two sessions.

- Safety evaluations included changes in laboratory parameters and vital signs as well as the incidence of adverse events. The table below summarizes the parameters and times of collection:

SAFETY: TIMINGS OF EVENTS: PHASE 2: STUDY 464 – OptiMARK™							
Times	Pre-Dose	0 to < 2 hrs	2 hrs to < 4 hrs	4 hrs to 8 hrs	24 hrs to 48 hrs	72 hrs	>72hrs
LABS	X				X		
EKG	NONE						
PE	NONE						
VITALS	X	X	X		X		

- The comments on values to designate the normal ranges and the abnormal ranges for these parameters have been made in the over-all safety review and in the pivotal phase 3 CNS reviews. The Sponsor set criteria to designate extreme values and significant changes etc. for vitals, labs, physical exam, adverse events are similar to the other studies. Refer to comments made in the overall safety section. The case report forms are noted (Vol. 2.101, p. 17.2305)