DOSING IN SPECIAL POPULATIONS:

PEDIATRIC INDICATION:

- **Sponsor has not established safety or pharmacokinetics and therefore the drug is not indicated in the pediatric age group.**

~ Reviewer's comment: See comments in study 525 on dosing of patient who was 12 years old. ~ Labeling should reflect the appropriate age group (no pediatric indication).

OTHER SPECIAL POPULATION

- See below

DOSING SUMMARY: ALL STUDIES

- A total of 1684 subjects/patients (870 men, 52% and 814 women, 48%) were enrolled in this clinical development program. A total of 1309 subjects/patients (680, 52% men and 629, 48% women) were dosed with OptiMARK and 329 patients (165, 50% men and 164, 50% women) were dosed with Magnevist®. A total of 46 subjects/patients (25 males, 59% and 21 females, 46%) received a placebo.

- Since the Phase 2 program was designed as pseudo crossover studies, patients in these studies (Studies 464, 465, 466, 467, 468, and 469) received two separate and different injections of OptiMARK™. Therefore, in the entire clinical program the 1309 subjects/patients in the OptiMARK™ dosage group received a total of 1663 injections. Since the overall demographic summary and the Phase 2 demographic summary are presented by dose, 354 patients were counted twice, raising the number of exposed subjects/patients to 2038 overall (includes placebo) and to 729 in the Phase 2 studies.

- See table below:

SAFETY: OVERALL DOSING SUMMARY BY TREATMENT GROUP: NDA # 20 937 OptiMARK™										
		Treatment Group (mmol/kg)								
		OptiMARK™							Magnevist®	Placebo
		0.1	0.2	0.3	0.4	0.5	0.7	Combined	0.1	
Total Volume (mL)	N	958	201	221	22	256	4	1662	329	46
	mean	15.2	28.6	45.9	49.7	74.0	98.6	30.6	15.2	49.0
	SD	3.4	5.9	10.6	17.2	15.7	7.9	23.3	3.3	29.4
	min-max	7-35	15-46	14-80	10-80	39-118	89-109	7-118	9-28	11-108
Duration (sec)	N	948	197	221	22	256	4	1648	324	46
	mean	23.9	20.8	96.1	74.7	126.3	83.8	49.9	16.6	67.8
	SD	31.1	21.0	91.5	59.9	104.6	0.5	71.8	13.9	54.1
	min-max	0-360	0-120	0-600	0-240	0-600	83-84	0-600	3-114	8-300
Rate (mL/sec)	N	882	170	206	20	252	4	1534	324	46
	Mean	1.2	1.7	0.9	1.1	1.0	1.2	1.2	1.3	0.9
	SD	0.8	0.8	0.8	1.2	0.7	0.1	0.8	0.7	0.3
	min-max	0-13	0-5	0-4	0-5	0-4	1-1	0-13	0-5	0-2

DOSING SUMMARY (BY PHASES):

Dosing: Phase 1 Studies

- A total of 245 subjects/patients were enrolled in the OptiMARK™ Phase 1 program. A total of 199 subjects/patients received OptiMARK™ at 0.1, 0.3, 0.5, or 0.7 mmol/kg and 46 subjects/patients received placebo.

Dosing: Phase 2 studies

- A total of 354 patients were enrolled in the OptiMARK™ Phase 2 program. Due to the crossover nature of the Phase 2 studies, each patient was scheduled to receive 2 separate and different doses of OptiMARK™. For reporting purposes, patients were tabulated in the demographic and dosing tables for each dose they received. Therefore, a total of 729 injections of OptiMARK™ were given in the Phase 2 program.

Dosing: All Phase 3 Studies (Open-Label and Pivotal)

- A total of 608 patients received OptiMARK™ and 329 patients received Magnevist®. The mean (SD) volume of OptiMARK™ administered was 15.1 (3.3) mL and 15.2 (3.3) mL was the mean volume of Magnevist® administered. The mean (SD) total injection duration was 17.1 (16.3) and 16.6(13.9) seconds for the OptiMARK™ and Magnevist® treatment groups, respectively.
- There were no statistically significant differences between treatment groups with respect to mean volume, duration, rate and dose.

Dosing: Phase 3 Pivotal Studies (488, 490, 525 and 526)

- A total of 461 patients received OptiMARK™ and 329 patients received Magnevist®. The mean (SD) total volume of OptiMARK™ and Magnevist®

administered was 15.11 (3.25) mL and 15.22 (3.33) mL, respectively. The mean (SD) dose administered was 0.100(0.003) mmol/kg and 0.100(0.005) mmol/kg for the OptiMARK™ and Magnevist® treatment groups, respectively.

- There were no statistically significant differences between OptiMARK™ and Magnevist® for the mean total volume administered or for the mean dose administered or for the mean duration of injection or the mean rate of injection.

Dosing: Phase 3 Pivotal CNS Studies (Studies 488 and 525)

- A total of 262 patients received OptiMARK™ and 133 patients received Magnevist®. The mean (SD) total volume of OptiMARK™ and Magnevist® administered was 15.4 (3.3) mL and 15.5 (3.1) mL, respectively. The mean (SD) dose administered was 0.100 (0.004) mmol/kg and 0.100 (0.005) mmol/kg for the OptiMARK™ and Magnevist® treatment groups, respectively.
- There were no statistically significant differences between OptiMARK™ and Magnevist® for the mean total volume administered or the mean dose administered or the mean duration of injection or the mean rate of injection.

Dosing: Phase 3 Pivotal Liver Studies (Studies 490 and 526)

- A total of 199 patients received OptiMARK™ and 196 patients received Magnevist®. The mean (SD) total volume of OptiMARK™ and Magnevist® administered was 14.8 (3.2) mL and 15.1 (3.5) mL, respectively. The mean (SD) dose administered was 0.100 (0.002) mmol/kg and 0.100 (0.004) mmol/kg for the OptiMARK™ and Magnevist® treatment groups, respectively.
- There were no statistically significant differences between OptiMARK™ and Magnevist® for the mean total volume administered, mean dose administered, mean duration of injection or mean rate of injection.
- The table below summarizes the treatment groups by phases:

SAFETY: OVERALL DOSING SUMMARY BY TREATMENT GROUP & PHASE*: NDA # 20 937 OptiMARK™

	Treatment Group (mmol/kg)								
	OptiMARK™							Magnevist®	Placebo
	0.1	0.2	0.3	0.4	0.5	0.7	Combined	0.1	
Phase 1 (N)	106	-	46	-	43	4	199	-	46
Phase 2 (N)	244	80	170	22	213	-	729	-	-
All Phase 3 (N)	608	121	5	-	-	-	734	329	-
All Phase 3 Pivotal (N)	461	-	-	-	-	-	461	329	-
All Phase 3 CNS (N)	262	-	-	-	-	-	262	133	-
All Phase 3 Liver (N)	198	-	-	-	-	-	198	196	-

*This table was formulated using information provided by the Sponsor (Vol. 2.26A, pp. 26.0076-26.0087). The tabulation here is different due to the crossover type in the phase 2 studies. Additionally, the Sponsor states (p. 26.0077, Vol. 2.26), some patients were enrolled in more than one study. (See note below)

~ Reviewer's comment:

~ Whether the same patient can be enrolled in more than one study (per Sponsor, this may be a disqualification as mentioned in the inclusion criteria in several studies), constitutes a study/protocol violation is a concern. Additionally, whether, this is also

a regulatory violation (per agency) needs to be verified. The Sponsor has not provided the total number of such patients who were enrolled in more than one study.

SAFETY MONITORING:

The following general comments in this over-view are applicable to the individual trials where comments on safety have been made in those trials assigned to the reviewer.

- The following parameters were used to monitor safety in this clinical program across the trials:
  1. **Laboratory Testing**
  2. **Electrocardiograms**
  3. **Vital signs**
  4. **Physical Examination**
  5. **Adverse Event Monitoring**
- Respective (for the study and for the each parameter) Case Report Forms (see individual study reports) were provided to the principal site investigators for completion.
- The set parameters for abnormal/extreme values (for EKGs, Vital Signs) and the definitions used to designate adverse events were similar across the trials as noted and commented in the individual study reports (see below for comments on each of these parameters).
- The bulk of the data has been presented in a form of shifts from baseline (without the actual baseline reading) with ranges, means and standard deviations. Scatter plots are not provided for all the parameters. Clinical interpretation is therefore restricted without a formal statistical opinion.

LABORATORY TESTING:

The following general comments in this over-view are applicable to the individual trials where comments on safety have been made in those trials assigned to the reviewer.

1. As with the data on vital signs, EKGs, etc., the Sponsor has "re-formatted" the values using means and standard deviations without providing the baseline values. Additionally, several labs (each with a different set of normal ranges) were used by the Sponsor. The actual values for these normal ranges and baselines values and related information were requested by the agency. Some of this information was provided to the agency in a laptop on October 7, 1998. At this time, the reviewer has not been able to review the information provided in the laptop. Comments are directed to the information obtained from the submitted volumes as indicated above.

2. The lab parameters that were assessed were generally similar across the trials and appropriately indicated (included standard: hematology including coagulation profiles; electrolytes; hepatic panel; iron studies including iron, TIBC, ferritin, % saturation; urinalysis) for these trials. These also included special tests (e.g. serum

gadolinium levels, pregnancy testing, copper levels, zinc levels, etc.) when indicated. The 'outside the normal range' value/s were appraised 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

3. Conspicuously missing were bicarbonate levels and glucose levels in some of the trials.
4. Urinalysis did not indicate whether microscopic examinations were performed on centrifuged or un-centrifuged specimens. Also, the extreme values were lacking demarcation between male and females with respect to the number of WBCs and RBCs. Specifically, the Sponsor allowed for >10WBC/HPF and >100 RBC/HPF as "extreme" values without allowance for demographic variability. Such a distinction is clearly required in clinical practice. Also urobilinogen, which is a normal component of urine in normal people (up to a certain level), is listed as an extreme value. These have been commented in the respective trials.
5. History of hemoglobinopathies was an exclusion criterion in this clinical program and has been listed among the warnings in the proposed labeling. However, besides medical history, no clinical lab testing was performed to rule it out. Many of the hemoglobinopathies may be asymptomatic (mild) so the patients may not be aware of the condition. If this was a concern to the degree that it was an exclusion criterion, appropriate lab testing should have been performed to exclude such patients definitively.

- The timings of the labs for the combined trials were:

SAFETY: TIMING OF LABORATORY TESTING: OptiMARK™ : NDA # 20937							
Study Number	Pre-Dose	0 to < 2 hrs	2 hrs to < 4 hrs	4 hrs to 8 hrs	24 hrs to 48 hrs	72 hrs	>72hrs
Phase 1 – Dose Ranging, Pharmacokinetic Studies							
433	X	X	X		X		
489	X		X	X	X	X	X
538	X		X		X	X	
543	X		X		X		X
Phase 2 – Pseudo Cross Over Dose Ranging Studies							
464	X				X		
465	X				X		
466	X				X		
467	X				X		
468	X				X		
469	X				X		
Phase 3 – Open-Label Studies							
484	X		X		X	X	
485	X		X		X	X	
486	X		X		X	X	
487	X		X		X	X	
Phase 3 – Comparative Pivotal Comparative Studies							
488	X		X		X	X	
490	X		X		X	X	
525	X		X		X	X	
526	X		X		X	X	

Labs: All Studies

- A total of 2038 subjects/patients were dosed in the combined studies; 1663 subjects/patients received OptiMARK™ (all doses combined) and 329 patients received 0.1 mmol/kg Magnevist® and 46 subjects/patients received placebo.
- The largest fluctuations in laboratory parameters were noted for glucose and are likely related to the uncontrolled, i.e., non-fasted, manner in which samples were obtained. It is also possible that the ~ 30% of the patients who were on steroids as concomitant medications had some contribution for these glucose levels.
- According to the Sponsor, for both OptiMARK™ and Magnevist®, the majority of changes in laboratory parameters were no more than 40% of the span of the reference range. Comments have been made regarding this "span" and its worthlessness clinically. It is more important to note that none of the observed changes in either treatment group were considered by the Sponsor to be clinically significant and the observed changes between treatment groups appeared to be similar. The laboratory parameters had changes from baseline greater than 40% of the span of the reference range that occurred in more than 10% of the subjects/patients. These were:

SAFETY: CLINICAL LABORATORY PARAMETERS: ALL STUDIES: OptiMARK™ : NDA # 20937		
Dosage: mmol/kg		Comments
OptiMARK™	0.1	Increase: albumin (72 hours); bicarbonate (24 hours); creatinine clearance (24 and 72 hours); glucose (2, 24 and 72 hours); iron {AA} (72 Hours); phosphorus (72 hours); TIBC (24 and 72 hours) Decrease: creatinine clearance (24 and 72 hours); glucose (2, 24, and 72 hours); iron {AA} (24 hours); iron saturation (72 hours); monocytes (2 and 72 hours); phosphorus (72 hours)
	0.2	Increase: basophils (24 hours); glucose (2 and 24 hours); phosphorus (24 hours); TIBC (2 hours) Decrease: glucose (2 and 24 hours); hematocrit (2 hours); monocytes (2 and 24 hours)
	0.3	Increase: glucose (24 hours); phosphorus (24 hours) Decrease: glucose (24 hours)
	0.5	Increase: glucose (24 hours); phosphorus (24 hours) Decrease: glucose (24 hours); calcium {AA}
Magnevist®	0.1	Increase: glucose (2, 24, 72 Hours);iron saturation (2 hours); monocytes (24 and 72 hours); WBC (72 hours) Decrease: glucose (2, 24 ,and 72 hours); monocytes (2, 72 hours); phosphorus (72 hours)

Labs: Phase 1

- A total of 245 subjects/patients were enrolled in four Phase 1 studies. One hundred ninety-nine subjects/patients received 0.1, 0.3, 0.5, or 0.7 mmol/kg OptiMARK™ and 46 subjects/patients received placebo.
- The largest fluctuation in laboratory parameters was noted for glucose (see comments above). For both OptiMARK™ and Magnevist®, the majority of changes in laboratory parameters were no more than 40% of the span of the reference range.
- None of the observed changes in either treatment group were considered by the Sponsor to be clinically significant and the observed changes between treatment groups appeared to be similar.
- According to the Sponsor, the following laboratory parameters had changes from baseline greater than 40% of the span of the reference range that occurred in more than 10% of the subjects/patients:

SAFETY: CLINICAL LABORATORY PARAMETERS: PHASE 1: OptiMARK™ : NDA # 20937		
Dosage: mmol/kg		Comments
OptiMARK™	0.1	Increase: albumin (72 hours); calcium [AA]; creatinine clearance (24 and 72 hours); creatinine (72 hours); glucose (2, 24 and 72 hours); iron {AA} (72 Hours); phosphorus (72 hours); potassium (24 hours); TIBC (24 and 72 hours) Decrease: chloride (72hours); creatinine clearance (24 and 72 hours); creatinine (24 hours); glucose (2, 24, and 72 hours); iron {AA} (24 hours); iron saturation (72 hours)
	0.3	Increase: phosphorus (24 hours); calcium (72 hours); creatinine clearance (24 and 72 hours) Decrease: glucose (24hours and 72 hours)
	0.5	Increase: phosphorus (24 hours); creatinine clearance (24 hours) Decrease: glucose (24 and 72 hours); calcium [AA] (24 hours)
Placebo		Increase: creatinine clearance (24 hours); phosphorus (72 hours) Decrease: glucose (24 and 72 hours); creatinine clearance (24 hours); iron saturation (72 hours)

Labs: Phase 2

- A total of 729 patients were dosed in Phase 2 studies and received 0.1, 0.2, 0.3, 0.4, or 0.5 mmol/kg OptiMARK™.
- The largest fluctuations in laboratory parameters were noted for glucose (see above).

- For all OptiMARK™ dose groups, the majority of changes in laboratory parameters were no more than 40% of the span of the reference range.
- The following laboratory parameters had changes from baseline greater than 40% of the span of the reference range that occurred in more than 10% of the patients:

SAFETY: CLINICAL LABORATORY PARAMETERS: PHASE 2: OptiMARK™ : NDA # 20937		
Dosage: mmol/kg		Comments
OptiMARK™	0.1	Increase: bicarbonate (24 hours); glucose (24 hours); phosphorus (24 hours) Decrease:basophils (24 hours); glucose (24 hours0.
	0.2	Increase: basophils (24 hours); glucose (24 hours); phosphorus (24 hours) Decrease: AST/SGOT (24 hours); basophils (24 hours); chloride (24 hours); eosinophils(24 hours); glucose (24 hours); LDH (24 hours)
	0.3	Increase: glucose (24 hours); phosphorus (24 hours) Decrease: glucose (24 hours)
	0.5	Increase: glucose (24 hours); phosphorus (24 hours) Decrease: glucose (24 hours)

Labs: Phase 3 (Labs):

- A total of 790 patients were dosed in four pivotal Phase 3 studies; 461 patients received 0.1 mmol/kg OptiMARK™ and 329 patients received 0.1 mmol/kg Magnevist®.
- Only glucose had changes from baseline greater than 80% of the span of the reference range that occurred in more than 10% of the patients. With the exception of glucose, there were no clinical laboratory values for which at least 5% of the patients dosed with OptiMARK™ experienced a decrease or increase from baseline greater than 80% of the span of the reference range.
- According to the Sponsor, for both treatment groups, the majority of changes in laboratory parameters were no more than 40% of the span of the reference range.
- None of the observed changes in either treatment group were considered by the Sponsor to be clinically significant and the observed changes between treatment groups appeared to be similar.
- According to the Sponsor, the following statistically significant differences in the distribution of upward or downward shifts between OptiMARK™ and Magnevist® were observed:
  Allkaline phosphatase – 24 hours post-dosing (p= 0.018)
  Iron – 2 hours post-dosing (p=0.010)
  Iron saturation – 2 hours post-dosing (p< 0.001)
  Iron saturation – 72 hours post-dosing (p=0.013)
  PT – 24 hours post-dosing (p=0.016)
  TIBC – 2 hours post-dosing (p< 0.001)
- The observed difference in the proportion of OptiMARK™ or Magnevist® patients for these laboratory parameters was < 5% for all but iron saturation and TIBC where the differences was < 10%.
- Despite reaching statistical significance this difference in clinical laboratory parameters was not considered clinically important by the Sponsor.
- The following laboratory parameters had changes from baseline greater than 40% of the span of the reference range that occurred in more than 10% of the patients:

SAFETY: CLINICAL LABORATORY PARAMETERS: PHASE 3: OptiMARK™ : NDA # 20937		
Dosage: mmol/kg		Comments
OptiMARK™	0.1	**Increase:** glucose (2, 24 and 72 hours post-dosing), phosphorus (72 hours post-dosing) **Decrease:** glucose (2, 24 and 72 hours post-dosing), hematocrit (72 hours post-dosing), iron (72 hours post-dosing), monocytes (72 hours post-dosing), phosphorus (72 hours post-dosing)
Magnevist®	0.1	**Increase:** calcium [AA] (24 hours post-dosing), glucose (2, 24 and 72 hours post-dosing), monocytes (24 and 72 hours post-dosing), phosphorus (72 hours post-dosing), WBC (72 hours post-dosing) **Decrease:** BUN (72 hours post-dosing), calcium [AA] (72 hours post-dosing), glucose (2, 24 and 72 hours post-dosing), iron saturation (24 and 72 hours post-dosing), monocytes (2, 24 and 72 hours post-dosing), pH (2 and 24 hours post-dosing), phosphorus (72 hours post-dosing)

Labs: Overall Impression:

1. There were no particular lab abnormalities that were consistently or persistently abnormal or clinically worrisome (except for calcium-see Japanese study).
2. Calcium, iron, and zinc changes occurred particularly at higher doses (these have been incorporated in the proposed labeling).
3. Glucose changes are probably not attributable to OptiMARK™.
4. Changes in Renal Function parameters in patients without renal insufficiency (minor changes in BUN and Cr) and in patients with renal insufficiency has been well captured and documented.
   Appropriate caution for patients with renal impairment in the labeling should reflect this.
5. There were no significant differences in the profiles between Magnevist® and OpitMARK™ as for a labs were concerned. On this aspect, equivalency is probably established.
6. The bulk of the data was presented (in the original volumes) as shifts from a baseline and as a mean change without the actual values; which were all clinically meaningless.
7. Minor deficiencies noted were exclusion of serum/blood bicarbonate or glucose levels in some trials. Urine analysis methodology requires clarification for purposes of documentation only and for possible future recommendations.

ELECTROCARDIOGRAM:

The following general comments in this over-view are applicable to the individual trials where comments on safety have been made in those trials assigned to the reviewer.

- The following are the primary concerns regarding EKGs:

1. The Sponsor chose the following parameters to define "extreme" values across the trials in this clinical program. These were:

PR Interval	<60 msec	>240 msec
QRS Interval	<40 msec	>160 msec
QT Interval	<200 msec	>500 msec

These "Sponsor chosen" parameters are too liberal (wide) and unacceptable. Standard references in cardiology (Henry Marriott's Practical EKG) and internal medicine text books (Cecil's 20th edition) consider the following ranges as normal or upper limits of normal:

1. PR Interval = 0.12 secs (120msec) to 0.20 secs (200msec) with 240 msec being the maximum upper limit of normal.
2. QRS Interval = 0.05 to 0.10 secs (50 to 100 msec) with 0.11 secs (110 msec) being considered the maximum upper limit of normal
3. QT Interval = rate dependent; 0.36 secs (360 msec) to 0.39 secs (390 msec) at an average rate of ~ 75 beats per minute

2. According to the Sponsor, these EKGs were read mostly by the principal site investigators who were all/mostly radiologists.
3. It is not clear whether these were automated or manual readings. It is very important to know this specially when interpreting QT intervals when hypokalemia or hypocalcemia (known to occur with OptiMARK™- see phase 1 studies and precautions) co-exists.
4. Although a total of 1684 subjects/patients were enrolled in this clinical development program and a total of 1309 subjects/patients were dosed with OptiMARK™ and 329 patients were dosed with Magnevist®, the total number of patients who had complete meaningful EKG records were significantly fewer than what was proposed or planned. Several of these trials did not have EKG (including those in which it was proposed in the study protocol) as safety monitoring parameter (see table below). **In particular, in study 433 which was the first-in-human study (subjects received doses as high as 0.7 mmol/kg), the Sponsor did not perform any EKGs** (study 433, Vol. 2.147, p.26.0265). Additionally, those patients in the phase 2 and phase 3 studies who were on many medications and medically sick were potential targets for cardiac arrhythmias (pre-disposition). The timing and frequency in these cases were also inadequate. In those studies in which EKGs were obtained, the records were incomplete (no QT or QTc readings, etc) to a significant degree. Readings in some trials included only the interpretation as "normal" or "abnormal" without providing the intervals/values. Of the 1684 patients/subjects enrolled in this study, ~680 (40.38 %) patients had values that can be potentially interpretable (if the tracings are still available). But then again, the data was presented as means and SDs and changes were accordingly reflected without the baselines. The actual tracings have not been provided either. Then the matter of who read and interpreted these records (man or machine?; radiologist or internist or cardiologist?) remains and is unsettled at this time.
5. The best utilizable data (in terms of adequacy and timing) could potentially stem only from the phase 1 studies (489 and 538, N=163 records); because the others were inadequate in terms of frequency and completeness. Specifically, in the phase 3 studies, EKGs were obtained only at a 24-hour post-dosing interval after a pre-dose baseline. Obtaining a single 24-hour post reading (after the baseline) has no clinically meaningful significance based on the pharmacokinetics of gadolinium. The importance of this issue (correlation of the pharmacokinetics with any adverse event and its, monitoring) is highlighted in the patient in the Japanese study-phase 1, who developed a significant bradycardia with EKG changes during the 2 to 8 hour post-drug window that was also associated with hypocalcemia. All events normalized after 8 hours (all subjects were normal healthy volunteers).
6. There was no monitoring during the dosing or during imaging (when carried out).

- The table below summarizes these deficiencies:

SAFETY: DEFECIENCIES: ELECTROCARDIOGRAMS: OptiMARK™ : NDA # 20937				
Study Number	N (enrolled) =1684	Potentially useable* data (N=680)	NDA Volume Reference	COMMENTS
Phase 1 – Dose Ranging, Pharmacokinetic Studies				
433	16	0	2.10	Protocol called for EKGs, but none performed - ? violation
489	121	109	2.28	12 incomplete records
538	54	54	2.39	No specific comments (see general comments)
539	Application does not include this trial (Sponsor chose not to submit- Pediatric trial-Ongoing)			
543	8	8	2.43	No specific comments (see general comments)
Phase 2 – Pseudo Cross Over Dose Ranging Studies				
464	83	0	2.147	No planned EKG in any of these studies
465	89	0		
466	36	0		
467	86	0		
468	5	0	2.136	Although EKGs were performed, no intervals or relevant information is provided other than an overall interpretation
469	72	0	2.142	
Phase 3 – Open-Label Studies				
484	15	0	2.117	Entirely incomplete records where QT intervals were not recorded at all. Of all the parameters, QT interval is probably the most important interval that needs attention in such drug trials
485	39	0		
486	98	0	2.127	
487	122	0		
Phase 3 – Comparative Pivotal Comparative Studies				
488	201	141	2.56	~ 60 of the 201 –mostly lacking QT intervals or other parameters
490	193	96	2.76	~ 97 of the 193 patients had incomplete records as in 488
525	194	125	2.66	~ 69 of the 194 patients had incomplete records as in 488
526	202	147	2.86	~ 55 of the 202 patients had incomplete records as in 488

Note: These numbers are approximates and may or may not reflect the actual numbers; but provides as estimate.
*includes intervals (including QT); deficient in the frequency, timing and parameters.

APPEARS THIS WAY
ON ORIGINAL

- 12 lead EKGs were performed at various time points during these trials. These are summarized as shown in the table below:

SAFETY: TIMING OF ELECTROCARDIOGRAMS: OptiMARK™ : NDA # 20937							
Study Number	Pre-Dose	0 to < 2 hrs	2 hrs to < 4 hrs	4 hrs to 8 hrs	24 hrs to 48 hrs	72 hrs	>72hrs
Phase 1 – Dose Ranging, Pharmacokinetic Studies							
433	None						
489	X	X[1]	X		X		
538	X	X[1]	X		X		
1177	X	X[2]					
543	X	X[2]			X		
Phase 2 – Pseudo Cross Over Dose Ranging Studies							
464	None						
465							
466							
467							
468	X	X[3]					
469	X				X		
Phase 3 – Open-Label Studies							
484	X				X		
485	X				X		
486	X				X		
487	X				X		
Phase 3 – Comparative Pivotal Comparative Studies							
488	X				X		
490	X				X		
525	X				X		
526	X				X		

1= includes immediate post dosing, 15 minutes post dosing, 30 minutes post dosing, 1 hour post dosing, 2 hours post dosing
2= 1 hour post dosing 3= 2 hours post dosing

SUMMARY OF EKG FINDINGS: ALL STUDIES COMBINED:

- The sponsor has provided summary descriptive statistics for ECGS (PR, QRS, HR, QT_c) by dose and treatment for all patients or subjects enrolled in all studies in Tables 9.1.1-1 through 9.5.1-7 (Vol. 2.147) for baseline and 24 hours after the start of injection.
- According to the Sponsor, although these changes reached statistical significance, the overall mean change was small and were not felt to be clinically relevant or thought to represent a cardiac electrophysiological effect.
- Statistical comparisons of ECG differences from baseline by dose and treatment revealed the following findings at 24 hours post-dosing:

SAFETY: ELECTROCARDIOGRAMS BY DOSE: ALL STUDIES COMBINED: OptiMARK™ : NDA # 20937		
Dosage: mmol/kg		Comments
OptiMARK™	0.1	Statistically significant increase for heart rate Statistically significant decreases for PR and QT
	0.2	No statistically significant increases or decreases
	0.3	No statistically significant increases or decreases
	0.5	No statistically significant increases or decreases
	All doses	Statistically significant increase for heart rate Statistically significant decreases for PR, QRS, and QT
Magnevist®	0.1	Statistically significant increase for heart rate Statistically significant decreases for PR and QT
Placebo		Statistically significant decreases for QT

EKG: BY PHASES AND DOSE:

EKG BY DOSE: Phase 1 Studies

- A total of 225 subjects or patients were enrolled in three Phase 1 studies (Studies 489, 538, and 543) of OptiMARK™. *EKGs were not performed as part of Study 433.*
- According to the Sponsor, although these changes reached statistical significance, the overall mean changes were small and were felt not to be clinically relevant.
- Statistical comparison of ECG parameter differences from baseline by dose and treatment revealed the following findings at 1 hour and 24 hours post-dosing:

SAFETY: ELECTROCARDIOGRAMS BY DOSE: PHASE 1 STUDIES: OptiMARK™ : NDA # 20937		
Dosage: mmol/kg		Comments
OptiMARK™	0.1	Statistically significant decreases in heart rate 1 hour post-dosing; in PR and QT at 24 hours post-dosing Statistically significant increase in heart rate 24 hours post-dosing
	0.3	Statistically significant decrease in heart rate 1 hour post-dosing; in PR 24 hours post-dosing
	0.5	Statistically significant decreases in heart rate and QT_c 1 hour post-dosing
	All doses	Statistically significant decreases in heart rate and QT_c 1 hour post-dosing; in PR and QT 24 hours post-dosing
Placebo		Statistically significant decrease for heart rate 1 hour post-dosing; for QT 24 hours post-dosing

EKG BY DOSE: Phase 2 Studies

- A total of 938 patients were enrolled in eight Phase 3 Studies (open-label and comparative studies combined).
- According to the Sponsor, although these changes reached statistical significance, the overall mean changes were small and were not felt to be clinically relevant or different between OptiMARK™ and Magnevist®.
- According to the Sponsor, statistical comparisons of ECG differences from baseline by dose and treatment revealed the following findings at 24 hours post-dosing:

SAFETY: ELECTROCARDIOGRAMS BY DOSE: PHASE 2 STUDIES: OptiMARK™ : NDA # 20937		
Dosage: mmol/kg		Comments
OptiMARK™	0.1	No statistically significant increase or decrease
Magnevist®	0.1	Statistically significant decreases for PR and QT 24 hours post-dosing Statistically significant increase for heart rate 24 hours post-dosing

EKG BY DOSE: Phase 3 Studies

All Studies (Open-Label and Pivotal Studies)

- A total of 938 patients were enrolled in eight Phase 3 Studies (open-label and comparative studies combined).
- According to the Sponsor, although these changes reached statistical significance, the overall mean changes are small and are not felt to be clinically relevant or different between OptiMARK™ and Magnevist®.
- Statistical comparisons of ECG differences from baseline by dose and treatment revealed the following findings at 24 hours post-dosing:

SAFETY: ELECTROCARDIOGRAMS BY DOSE: PHASE 3 STUDIES: OptiMARK™ : NDA # 20937			
Dosage: mmol/kg		N	Comments
OptiMARK™	0.1	595	No statistically significant increase or decreased
Magnevist®	0.1	326	Statistically significant decreases for PR and QT 24 hours post-dosing Statistically significant increase for heart rate 24 hours post-dosing

EKG BY DOSE: Pivotal Studies

- A total of 790 patients were enrolled in the pivotal studies and received either 0.1 mmol/kg OptiMARK™ or 0.1 mmol/kg Magnevist® in the four pivotal Phase 3 studies.
- According to the Sponsor, although a few parameters attained statistically significant differences from baseline the mean ECG changes were very small with no clinically significant difference between OptiMARK™ and Magnevist® treatment groups.
- Statistically significant mean changes from baseline included:

SAFETY: ELECTROCARDIOGRAMS: PIVOTAL STUDIES: OptiMARK™ : NDA # 20937			
Dosage: mmol/kg		N	Comments
OptiMARK™	0.1	452	Statistically significant increase for heart rate 24 hours post-dosing
Magnevist®	0.1	326	Statistically significant decreases for PR and QT 24 hours post-dosing Statistically significant increase for heart rate 24 hours post-dosing

EKG: BY STUDIES

- The table below summarizes some of the EKG findings by study that were significantly different from the baseline EKG:

SAFETY: SIGNIFICANT CHANGES: ELECTROCARDIOGRAMS: OptiMARK™ : NDA # 20937					
Study Number (N exposed)	Treatment groups	COMMENTS/ABNORMALITIES (N) Significant changes form baseline	(N) Clinically Significant	All Changes	NDA Ref Vol.
Phase 1 – Dose Ranging, Pharmacokinetic Studies					
433	No EKGs performed				
489 (121)	OptiMARK™	18	5 of 18	QT, ST-T changes in 4 patients	2.28
	Placebo	6			
538 (54)	OptiMARK™	3	1 of 3	T wave inversion, QT interval changes, PVCs	2.39
539	Application not submitted by Sponsor				
543 (8)	OptiMARK™	None reported			2.43
Phase 2 – Pseudo Cross Over Dose Ranging Studies					
464	EKGs not performed				
465					
466					
467					
468 (5)	OptiMARK™	Only overall impressions in the interpretation, no intervals No reported abnormalities			2.136
469 (72)	OptiMARK™				2.142
Phase 3 – Open-Label Studies					
484/485 (15+49)	OptiMARK™	No QT or QTc intervals recorded (100%) None reported			2.117
486 (98)		8	0	2/8 received 0.1mmol dose; 6/8 received 0.2 mmol dose. Poor R wave prog, T wave inversion, ST depresiion, PVCs, Sinus bradycarida No QT/QTc measured (100%)	2.127
487 (122)	OptiMARK™	0	0	None reported No QT/QTc measured (100%)	
Phase 3 – Comparative Pivotal Comparative Studies					
488 201	OptiMARK™	2	0	QT prolongation, T wave inversion ~ 30% without QT intervals or others	2.56
	Magnevist®	0	0		
490 193	OptiMARK™	7	0	~51% without QT intervals or others Poor R wave progression, PVCs, Sinus tach, PACs, ST changes, QT prologation	2.76
	Magnevist®	3	0		
525 194	OptiMARK™	7	0	~ 35% without QT intervals or others Sinus tach, SVT, PVCs, BBB, Prolonged QRS, T wave changes, QT prolongation	2.66
	Magnevist®	4	0		
526 202	OptiMARK™	4	0	~27.22% without QT interval or others Abnormal overall	2.86
	Magnevist®	4	0		

- These numbers are approximate and do not reflect the actual numbers. They give an estimate.

The follcwing conclusions can be drawn from the 'deficiency' tables and the 'significant changes' tables above:

a) ~ 56/1063 (5.2%) EKGs were read by the Sponsor as being abnormal (significant change from baseline). This is based on the wide intervals that the Sponsor has chosen (see comments above).

b) Of these, (N) of incomplete/unusable records (those in which either all the stated intervals are not measured or incompletely commented on-the majority of which are those without QT intervals) = ~ 642 (needs to be eliminated).

c) Therefore the useable meaningful number of records is actually 1063 minus 642 = 421.

d) Therefore, standing on the same grounds as the Sponsor, 56/421 = **13%** is the approximate number of patients who had significant change/s in their EKGs compared to the baseline (when the same parameters are used and when all the abnormal readings are counted once in the useable group). Re-analysis of the records (if available and if complete) with the "accepted" range of parameters for the same number of 421 records (if the other EKG tracings are not salvageable or complete) would probably or most likely yield a larger number of abnormal EKGs post drug exposure. This is a serious safety concern, and specific recommendations need to be made to address this deficiency.

e) Silent EKG changes occurring (electrical abnormality without associated clinical signs or symptoms) should be treated with greater caution than when similar silent/asymptomatic changes occur with some of the other parameters (e.g. labs). These electrical changes may be the harbingers for a serious life threatening devastating event, and the window of opportunity to take the necessary actions is usually very small. It calls for specialists' intervention in an emergent manner. Capturing, recognizing and managing these expeditiously is the single most critical step in managing cardiac events. Uncertainties exist whether such an environment was made feasible or available or even existed in this clinical program. Study 433 is a an extreme example of this concern, in which there were no EKGs at all in this first-in-human study in which the maximum dose of 0.7mmol/kg was administered to some of the subjects, who were all healthy male subjects.

f) In retrospect, despite the inadequacies (for: frequency, timing, capturing, completeness, chosen parameters, etc.) in this program (as for as EKG is concerned), there were no deaths related to cardiac events. But there is no way of determining the actual number of electrical abnormalities as and when they occurred (or if they occurred at all) at this time.

- **Overall EKG Impressions:**

1. Although there were no deaths or serious events attributable to cardiac events by OpitMARK™, the capturing and documentation of these events were inadequate (timing, frequency, completeness, interpretation) and inappropriate (parameters too liberal, no QT intervals).
2. Whether such abnormalities occurred (although there were no mortality associated) at all is unknown.
3. Of the captured data, a significant number of records are incomplete.
4. Uncertainties regarding the appropriateness of background of EKG readers exist (including automated v/s manual readings).
5. The observations noted by the Sponsor are meaningless. Presented data is in a form that is largely clinically meaningless.
6. If approved, the case/s described in the Japanese study necessitates appropriate labeling for bradycardia/EKG changes.

PHYSICAL EXAMINATION

The following general comments in this over-view are applicable to the individual trials where comments on safety have been made in those trials assigned to the reviewer.

- Physical examinations were performed by "medically-certified" individual according to the Sponsor (Medical Doctor, doctor in training, physician's assistant or nurse practitioner). The Sponsor defines a clinically significant change as "any variation in physical findings which has medical relevance resulting in alteration in medical care"
- Findings were recorded in the CRFs accordingly (comments have been made in the study reports).
- Few of the patients enrolled in some of the studies across the trials were medically ill and were complicated cases. Those in the CNS studies in particular, had complicated history and findings. Appropriate physical examination for a given condition is best delivered by individuals in that field. This clarification at this time has no significance except to reflect good medical practice if such considerations were made in this clinical program.
- Physical examinations are very subjective with respect to- the examiner, the patient, the situation, the problem, the circumstances, background, etc. Therefore, comments are abbreviated.
- The timings of physical examinations are summarized in the table below:

SAFETY: TIMING OF PHYSICAL EXAMINATIONS: OptiMARK™ : NDA # 20937							
Study Number	Pre-Dose	0 to < 2 hrs	2 hrs to < 4 hrs	4 hrs to 8 hrs	24 hrs to 48 hrs	72 hrs	>72hrs
Phase 1 – Dose Ranging, Pharmacokinetic Studies							
433	X			X	X	X	
489	X	X			X	X	
538	X				X	X	
539	X				X	X	
543	X				X		X
Phase 2 – Pseudo Cross Over Dose Ranging Studies							
464							
465							
466							
467							
468	X				X		
469	X				X		
Phase 3 – Open-Label Studies							
484	X				X		
485	X				X		
486	X				X		
487	X				X		
Phase 3 – Comparative Pivotal Comparative Studies							
488	X				X		
490	X				X		
525	X				X		
526	X				X		

ADVERSE EVENTS:

The general comments in this over-view are applicable to the individual trials where comments on safety have been made in those trials assigned to the reviewer.

- Adverse Events (AE) was defined by the Sponsor is as follows- "An adverse event is defined as any undesirable experience occurring to the patient following drug administration, regardless of attribution".
- 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".
- Similar definitions are mentioned across the clinical trials in this program. As stated in the individual trials and in the 'Tolerance' section, 'severe' and 'serious' have been used interchangeably, causing confusion and therefore requiring clarification.

AE: ALL STUDIES

- Of the 2038 subjects/patients exposed to a study drug or placebo in the OptiMARK™ clinical development program, 646 subjects/patients experienced an adverse event; 1293 adverse events were reported.
  For all OptiMARK™ subjects/patients, regardless of dose, 510 of the 1663 patients (30.7%) reported a total of 997 adverse events.
  For patients dosed with Magnevist®, 114 of the 329 patients (34.7%) reported a total of 215 adverse events.
  For subjects/patients dosed with placebo, 22 of the 46 subjects/patients (47.8%) reported a total of 81 adverse events.
  Overall there was no difference between the OptiMARK™ and Magnevist® treatment groups with respect to the adverse event rate for subjects/patients dosed with either study contrast agent.
- For all treatment groups, i.e., OptiMARK™, Magnevist®, or placebo, the body system in which adverse events were reported more frequently were body as a whole, nervous system, special senses and digestive system.
  For OptiMARK™ patient regardless of whether the subject/patient received 0.1 mmol/kg or any higher dose the most common adverse event types reported were headache, taste perversion, vasodilation, dizziness, nausea and paresthesia.
  For patients who received Magnevist®, the most common adverse event types were headache, taste perversion, pain asthenia, vasodilation, injection site reaction, nausea, dizziness, paresthesia and rash.

AE: PHASE 1

- A total of 245 subjects/patients were enrolled in four U.S. Phase 1 studies and received 0.1, 0.3, 0.5, 0.7 mmol/kg OptiMARK™ or placebo.
  Adverse events were reported by 136 of the OptiMARK™ subjects/patients (136/199, 68.3%) and by 22 placebo subjects/patients (22/46, 47.8%).
  For both treatment groups, i.e., placebo and OptiMARK™ (all doses combined), the most common body systems in which adverse events were reported were body as a whole, nervous system, and digestive system.
- For all of the OptiMARK™ dose groups combined, the most frequently reported adverse events were headache (48/199, 24.1%), vasodilation (29/199, 13.1%), dizziness (18/199, 9.0%), taste perversion (17/199, 8.5%), and nausea (13/199, 6.5%). For subjects/patients who received placebo, the most frequently reported adverse events were headache (8/46, 17.4%), dizziness (7/46, 15.2%), nausea (4/46, 8.7%), dyspepsia (3/46, 6.5%), and rash (3/46, 6.5%).
- A statistically significant difference in the incidence of adverse events across doses was observed.

AE: PHASE 2

Since the Phase 2 program was designed as pseudo crossover studies, patients in these studies (464, 465, 466, 467, 468, and 469) received one or two separate and different injections of OptiMARK™. Since this summary of adverse events is presented by dose, 354 patients are counted twice, raising the number of exposed patients to 729 in Phase 2 studies. Of these patients, 172 (172/729, 23.6%) experienced a total of 251 adverse events.

- Studies 464 and 465 suggested that the number and the severity of adverse events were greater with increasing doses. This finding and the fact that the other approved agents have proven efficacy at a 0.1mmol/kg dose lead to the dose selection of 0.1mmol for the phase three studies and for the requested dosage for labeling.
- For all OptiMARK™ dose groups combined, the body systems in which adverse events were most frequently reported were special senses, cardiovascular, body as a whole, digestive and nervous system.
  For all of the OptiMARK™ dose groups combined, the most frequent adverse event types include taste perversion (52/729, 7.1%), vasodilation (43/729, 5.9%), headache (22/729, 3.0%), diarrhea (13/729, 1.8%), and nausea (11/729, 1.5%).
  There was a significant and linear dose relationship among the five OptiMARK™ dose groups for the proportion of patients experiencing one or more adverse events.

AE: ALL PHASE 3 STUDIES (OPEN LABEL AND PIVOTAL STUDIES)

- A total of 938 patients were enrolled in eight Phase 3 clinical studies (open-label and pivotal studies combined). Six hundred nine patients received 0.1 mmol/kg OptiMARK™ and 329 patients received 0.1 mmol/kg Magnevist®.

Of the 609 patients who received OptiMARK™, 174 (174/609, 28.6%) reported 322 adverse events.
Of the 329 patients who received Magnevist®, 114 (114/329, 34.7%) reported 215 adverse events.

- For both treatment groups the most frequent body systems in which adverse events were reported were body as a whole, digestive system, nervous system, and special senses.
  For OptiMARK™ patients the most common adverse event types reported were headache (48/609, 7.9%), taste perversion (22/609, 3.6%), and nausea (18/609, 3.0%).
  The most common adverse event types reported in the Magnevist® treatment group were headache (31/329, 9.4%), taste perversion (16/329, 4.9%), pain (12/329, 4.9%), and nausea (8/329, 2.4%).
  There were no statistically significant differences between OptiMARK™ and Magnevist® in the reporting of adverse events.

AE: PIVOTAL STUDIES

- A total of 790 patients were enrolled in four comparative pivotal Phase 3 clinical studies (two CNS and two liver studies; 461 patients received 0.1 mmol/kg OptiMARK™ and 329 patients received 0.1 mmol/kg Magnevist®.
  Of the 461 patients who received OptiMARK™, 145 (145/461, 31.5%) reported 283 adverse events.
  Of the 329 patients who received Magnevist®, 114 (114/329, 34.7%) reported 215 adverse events.
- For OptiMARK™ patients, the body systems in which adverse events were most frequently reported were body as a whole, nervous system, digestive system, and special senses.
  The most common adverse events reported by patients who received OptiMARK™ were headache (40/461, 8.7%), taste perversion (17/461, 3.7%), dizziness (19/461, 4.1%), nausea (16/461, 3.5%), paresthesia (12/461, 2.6%), pain abdomen (11/461, 2.4%) and asthenia (9/461, 2.0%).
  For Magnevist® patients, the body systems in which adverse events were most frequently reported were body as a whole, nervous, digestive, and special senses.
  The most common adverse events reported in the Magnevist® treatment group were headache (31/329, 9.4%), taste perversion (16/329, 4.9%), asthenia (8/329, 2.4%), nausea (8/329, 2.4%), dizziness (7/329, 2.1%), paresthesia (7/329, 2.1%) and rash (7/329, 2.1%).
- For all Phase 3 studies combined, as well as by indication, there were no statistically significant differences between OptiMARK™ and Magnevist® treatment groups with respect to the proportion of patients reporting adverse experiences.
- The table below provides adverse events by the body systems (with subjects, COSTART terms and doses for all drugs including placebo).
  Note: this table has been modified from the application – the incidence is shown in a descending order (most frequent to less frequent), >0.5% events have been emphasized, and <0.5% events when relevant have been included. Additionally, the

0.1mmol/kg dose has been given emphasis, as this is the indicated dosage for this application.

- **Overall AE Impression**:

1. Generally, when comparisons are made between the adverse event profile of OptiMARK™ and the other approved gadolinium agents including Magnevist®, OptiMARK™ appears to fall along the same lines with no significant differences.
2. But it is important to refresh that, a significant number of patients in this clinical program were on steroids and/or anti-histamines (see drug-dose-concomitant medications above) during the study period. Therefore, the true intensity, frequency, incidence and occurrence of AEs could all be potentially higher than these noted observations.
3. 6 patients (0.4%) in the entire OptiMARK™ group were reported to have seizures as an adverse event by the Sponsor (see table below). This number is probably slightly larger when one cannot exclude seizures in a few of the cases that had a serious adverse event or dropped out due to an adverse event (these were not considered to be an ictal phenomenon by the Sponsor). Gadolinium compounds are known to increase or trigger pre-existing seizures. Magnevist®, the comparator in this study has this in its labeling. Similar warning or a precaution is recommended.
4. Symptomatic bradycardia lasting between 2hrs post to 8 hours post associated with EKG changes and hypocalcemia during the same period has been noted in the Japanese Study. Cautioning is recommended in labeling.

SAFETY: ADVERSE EVENTS*: OptiMARK™ : NDA # 20937
Subjects/Patients with an Adverse Event by Body System & COSTART TERM - N (%)

		Treatment Group								
		OptiMARK™ (mmol/kg)							Magnevist® (mmol/kg)	Placebo
		0.1	0.2	0.3	0.4	0.5	0.7	All	0.1	
Body System	Term	N=959	N=201	N=221	N=22	N=256	N=4	N=1663	N=329	N=46
Event	None	678 [70.7]	159 [79]	144 [65]	16 [73]	155 [61]	1-25	1153 [70]	215 [65]	24 [52]
	Any event	281 [30]	42 [21]	77 [35]	6 [27]	101 [40]	3-75	510 [31]	114 [35]	22 [48]
Number of patients with one or more AEs	One event	147 [16]	25 [12]	47 [21]	4 [18]	58 [23]	1-25		62 [19]	6 [13]
	Two events	66 [7]	8 [4]	10 [5]	2 [9]	21 [8]	1-25		30 [9.1]	4 [8.7]
	> two events	68 [7.1]	9 [4.5]	20 [9]	0	22 [8.6]	1-25		22 [6.7]	12 [26.1]
Body as a whole	Any event	141[(14.7]	11 (5.5)	32 (14.5)	2 (9.1)	31 (12.1)	0	217 (13.1)	63 (19.1)	12 (26.1)
	Headache	81 (8.4)	5 (2.5)	19 (8.6)	1 (4.5)	18 (7.0)	0	124 (7.5)	31 (9.4)	8 (17.4)
	Pain Abdomen	17 (1.8)	3 (1.5)	0	0	4 (1.6)	0	24 (1.4)	4 (1.2)	2 (4.3)
	Asthenia	13 (1.4)	1 (0.5)	2 (0.9)	0	4 (1.6)	0	20 (1.2)	8 (2.4)	2 (4.3)
	Inj. site reaction	16 (1.7)	0	3 (1.4)	0	1 (0.4)	0	20 (1.2)	10 (3.0)	2 (4.3)
	Pain - Back	9 (0.9)	0	5 (2.3)	0	2 (0.8)	0	16 (1.0)	3 (0.9)	0
	Pain	8 (0.8)	1 (0.5)	2 (0.9)	1 (4.5)	1 (0.4)	0	13 (0.8)	12 (3.6)	1 (2.2)
	Pain - Chest	7 (0.7)	0	2 (0.9)	0	2 (0.8)	0	11 (0.7)	1 (0.3)	0
	Chills	5 (0.5)	0	0	0	3 [1.2]	0	8 [0.5]	3 [0.9]	2 [4.3]
	Fever	4 [0.4]	2 [1.0]	0	0	2 [0.8]	0	8 [0.5]	2 [0.6]	0
	Inflam. Inj. Site	2 [0.2]	0	0	0	0	0	2 [0.1]	0	0
	Muc. Mem. Dis.	1 [0.1]	0	0	0	0	0	1 [0.1]	0	0
	Abnormal labs	1 [0.1]	0	0	0	0	0	1 [0.1]	0	0
	Pain – Substernal	0	0	0	0	1 [0.4]	0	1 [0.1]	0	0
	Lab test abnorm	1 [0.1]	0	0	0	0	0	1 [0.1]	0	0
	Flu syndrome	1 [0.1]	0	0	0	0	0	1 [0.1]	0	0
	Edema inj. Site	1 [0.1]	0	0	0	0	0	1 [0.1]	0	0
	Edema face	1 [0.1]	0	0	0	0	0	1 [0.1]	0	0
	Allergic reaction	0	0	0	0	1 [0.4]	0	1 [0.1]	0	0
Cardiovascular	Any event	38 [4.0]	17 [8.5]	21 [9.5]	3[13.6]	27 [10.5]	3-75	109 [6.6]	10 [3.3]	4 [8.7]
	Palpitation	6 [0.6]	0	0	0	1 [0.4]	0	7 [0.4]	1 [0.3]	0
	Hypertension	3 [0.3]	0	1 [0.5]	0	0	0	4 [0.2]	0	1 [2.2]
	Postural hypotension	3 [0.3]	0	0	0	0	0	3 [0.2][a]	0	0
	Pallor	1 [0.1]	0	1 [0.5]	0	0	0	2 [0.1]	0	0
	Tachycardia	2 [0.2]	0	0	0	0	0	2 [0.1][a]	1 [0.3]	0
	Hypotension	1 [0.1]	0	0	0	0	0	1 [0.1]	0	0
	Syncope	1 [0.1]	0	0	0	0	0	1 [0.1]	0	0
	Arrhythmia	1 [0.1]	0	0	0	0	0	1 [0.1]	0	0
Digestive	Any event	58 [6.0]	10 [5.0]	15 [6.8]	0	23 [9.0]	0	106 [6.4]	20 [6.1]	7 [15.2]
	Nausea	29 [3.0]	2 [1.0]	6 [2.7]	0	6 [2.3]	0	43 [2.6]	8 [2.4]	4 [8.7]
	Diarrhea	12 [1.3]	5 [2.5]	3 [1.4]	0	9 [3.5]	0	29 [1.7]	3 [0.9]	1 [2.2]
	Dyspepsia	7 [0.7]	2 [1.0]	3 [1.4]	0	4 [1.6]	0	16 [1.0]	2 [0.6]	3 [6.5]
	Vomit	7 [0.7]	2 [1.0]	1 [0.5]	0	2 [0.8]	0	12 [0.7]	3 [0.9]	1 [2.2]
Hemic & Lymphatic	Any event	5 [0.5]	1 [0.5]	4 [1.8]	0	3 [1.2]	0	13 [0.8]	5 [1.5]	0
	Ecchymosis	5 [0.5]	0	4 [1.8]	0	2 [0.8]	0	11 [0.7]	5 [1.5]	0
	Thromb.penia	0	1 [0.5]	0	0	0	0	1 [0.1]	0	0
Metabolic & Nutritional	Any event	6 [0.6]	1 [0.5]	4 [1.8]	0	4 [1.6]	0	15 [0.9]	0	0
	Edema	2 [0.2]	0	2 [0.9]	0	2 [0.8]	0	6 [0.4]	0	0
	Edema – periph.	1 [0.1]	0	2 [0.9]	0	1 [0.4]	0	4 [0.2]	0	0
	Hypercalcemia	1 [0.1]	0	0	0	0	0	1 [0.1]	0	0
	Hyperglycemia	1 [0.1]	0	0	0	0	0	1 [0.1]	0	0
	Hypoglycemia	0	0	0	0	1 [0.4]	0	1 [0.1]	0	0
	Hyponatremia	1 [0.1]	0	0	0	0	0	1 [0.1]	0	0
	Creatinine	0	1 [0.5]	0	0	0	0	1 [0.1]	0	0
Musculoskeletal	Any event	14 [1.5]	1 [0.5]	0	0	4 [1.6]	0	9 [1.1]	3 [0.9]	2 [4.3]
	Myalgia	5 [0.5]	1 [0.5]	0	0	1 [0.4]	0	7 [0.4]	1 [0.3]	1 [2.2]
	Arthralgia	3 [0.3]	0	0	0	2 [0.8]	0	5 [0.3]	1 [0.3]	0
	Cramps – leg	4 [0.4]	0	0	0	0	0	4 [0.2]	1 [0.3]	0

SAFETY: ADVERSE EVENTS*: OptiMARK™ : NDA # 20937
Subjects/Patients with an Adverse Event by Body System & COSTART TERM - N (%)

		Treatment Group								
		OptiMARK™ (mmol/kg)							Magnevist® (mmol/kg)	Placebo
		0.1	0.2	0.3	0.4	0.5	0.7	All	0.1	
Body System	Term	N=959	N=201	N=221	N=22	N=256	N=4	N=1663	N=329	N=46
Event#	None	678 [70.7]	159 [79]	144 [65]	16 [73]	155 [61]	1-25	1153 [70]	215 [65]	24 [52]
	Any event	281 [30]	42 [21]	77 [35]	6 [27]	101 [40]	3-75	510 [31]	114 [35]	22 [48]
Number of patients with one or more AEs	One event	147 [16]	25 [12]	47 [21]	4 [18]	58 [23]	1-25		62 [19]	6 [13]
	Two events	66 [7]	8 [4]	10 [5]	2 [9]	21 [8]	1-25		30 [9.1]	4 [8.7]
	> two events	68 [7.1]	9 [4.5]	20 [9]	0	22 [8.6]	1-25		22 [6.7]	12 [26.1]
Nervous	Any event	66 [6.9]	4 [2.0]	18 [8.1]	2 [9.1]	22 [8.6]	2-50	114 [6.9]	20 [6.1]	11 [23.9]
	Dizziness	30 [3.1]	1 [0.5]	9 [4.1]	0	10 [3.9]	0	50 [3.0]	7 [2.1]	7 [15.2]
	Paresthesia	20 [2.1]	1 [0.5]	2 [0.9]	0	6 [2.3]	1-25	30 [1.8]	7 [2.1]	2 [4.3]
	Convulsion	3 [0.3]	0	2 [0.9]	0	1 [0.4]	0	6 [0.4]	0	0
	Hypesthesia	2 [0.2]	1 [0.5]	1 [0.5]	0	0	0	4 [0.2]	0	0
	Hypertonia	2 [0.2]	0	1 [0.5]	0	0	0	3 [0.2]	1 [0.3]	0
	Depersonal.	0	0	1 [0.5]	0	0	0	1 [0.1]	0	0
	Confusion	1 [0.1]	0	0	0	0	0	1 [0.1]	0	0
	Tremor	1 [0.1]	0	1 [0.5]	0	0	0	2 [0.1]	0	1 [2.2]
Respiratory	Any event	29 [3.0]	2 [1.0]	7 [3.2]	0	9 [3.5]	0	47 [2.8]	10 [3.0]	3 [6.5]
	Rhinitis	16 [1.7]	2 [1.0]	2 [0.9]	0	0	0	20 [1.2]	4 [1.2]	1 [2.2]
	Pharyngitis	7 [0.7]	0	0	0	2 [0.8]	0	9 [0.5]	2 [0.6]	0
	Cough	5 [0.5]	1 [0.5]	2 [0.9]	0	1 [0.4]	0	9 [0.5]	2 [0.6]	0
	Asthma	3 [0.3]	0	1 [0.5]	0	2 [0.8]	0	6 [0.4]	0	0
	Dyspnea	2 [0.2]	0	2 [0.9]	0	1 [0.4]	0	5 [0.3]	2 [0.6]	1 [2.2]
Skin & Appendages	Any event	20 [2.1]	3 [1.5]	9 [4.1]	0	7 [2.7]	0	39 [2.3]	13 [4.0]	3 [6.5]
	Rash	6 [0.6]	1 [0.5]	4 [1.8]	0	4 [1.6]	0	15 [0.9]	7 [2.1]	3 [6.5]
	Pruritus	4 [0.4]	1 [0.5]	1 [0.5]	0	3 [1.2]	0	9 [0.5]	3 [0.9]	0
	Sweat	5 [0.5]	1 [0.5]	1 [0.5]	0	0	0	7 [0.4]	2 [0.6]	0
	Rash vesic bull	1 [0.1]	0	2 [0.9]	0	0	0	3 [0.2]	0	0
	Urticaria	2 [0.2]	1 [0.5]	0	0	0	0	3 [0.2]	2 [0.6]	0
	App. Site React.	0	0	1 [0.5]	0	1 [0.4]	0	2 [0.1]	0	0
	Eryth. Multiform	1 [0.1]	1 [0.5]	0	0	0	0	2 [0.1]	0	0
Special Senses	Any event	53 [5.5]	12 [6.0]	13 [5.9]	1 [4.5]	31 [12.1]	1-25	111 [6.7]	20 [6.1]	5 [10.9]
	Taste perversion	42 [4.4]	12 [6.0]	12 [5.4]	1 [4.5]	28 [10.9]	0	95 [5.7]	16 [4.9]	2 [4.3]
	Parosmia	6 [0.6]	0	2 [0.9]	0	4 [1.6]	1-25	13 [0.8]	3 [0.9]	1[2.2]
Urogenital	Any event	8 [0.8]	0	1 [0.5]	0	2 [0.8]	0	11 [0.7]	2 [0.6]	1 [2.2]
	Urin. Abnorm.	0	0	1 [0.5]	0	1 [0.4]	0	2 [0.1]	0	0

*~ Reviewer's comment: The order of the adverse events has been shown from the most common to the least common. Adverse events if less than 0.5% (unless felt relevant or important) have not been tabulated. @ This does not concur given that there were three patients who expericnced this AE only in the 0.1 mmol/kg dose group.
Some of the values have been rounded off to the next higher tenth decimal

VITAL SIGNS:

The following general comments in this over-view are applicable to the individual trials where comments on safety have been made in those trials assigned to the reviewer.

- Vital signs were obtained at various time points for all the trials (phase I, phase 2 and the phase 3 open-label and pivotal) as summarized in the table below:

SAFETY: TIMING OF SAFETY PARAMETERS: VITAL SIGNS: OptiMARK™ NDA # 20937							
Study Number	Pre-Dose	0 to < 2 hrs	2 hrs to < 4 hrs	4 hrs to 8 hrs	24 hrs to 48 hrs	72 hrs	>72hrs
Phase 1 – Dose Ranging, Pharmacokinetic Studies							
433	X	X	X		X	X	
489	X	X	X	X	X	X	
538	X	X			X	X	
543	X	X	X	X	X		X
Phase 2 – Pseudo Cross Over Dose Ranging Studies							
464	X	X	X		X		
465	X	X	X		X		
466	X	X	X		X		
467	X	X	X		X		
468	X	X	X		X		
469	X	X	X		X		
Phase 3 – Open-Label Studies							
484	X	X	X		X		
485	X	X	X		X		
486	X	X	X		X		
487	X	X	X		X		
Phase 3 – Comparative Pivotal Comparative Studies							
488	X	X	X		X	X	
490	X	X	X		X	X	
525	X	X	X		X	X	
526	X	X	X		X	X	

VITALS: ALL STUDIES COMBINED

- A total of 2038* (includes OptiMARK™, Magnevist®, and Placebo group, and the multiple dosing patients-counted twice) exposures (subjects = 1684) were enrolled in the entire clinical program.
  * *Reviewer's note*: See comments in the regulatory section for the break down of the actual numbers.
- Overall, the mean changes from baseline in vital sign parameters were small and considered to be clinically insignificant.
- No clinically significant trend or change occurred in vital signs by treatment or dose group.
- There was no statistically significant difference between OptiMARK™ and Magnevist® in the proportion of OptiMARK™ and Magnevist® patients experiencing upward and downward shifts in vital signs (analysis performed by Pearson's χ^2 – Vol. 2.147, p. 26.0222).
- Statistical comparisons of vital sign differences from baseline by dose and treatment revealed the following findings:

SAFETY: VITAL SIGN CHANGES: ALL STUDIES COMBINED: OptiMARK™ : NDA # 20937			
Dosage: mmol/kg		N	Comments
OptiMARK™	0.1	957	Statistically significant decreases from baseline values for pulse rate immediately post-dosing; for systolic and diastolic blood pressure 2 hours post-dosing; for diastolic blood pressure 24 hours post-dosing; and for diastolic blood pressure 72 hours post-dosing. Statistically significant increases from baseline values for pulse rate 2, 24 and 72 hours post-dosing; for respirations 2 hours post-dosing.
	0.2	200	Statistically significant decreases from baseline values for diastolic blood pressure at 2 hours post-dosing
	0.3	221	Statistically significant decreases from baseline values for systolic blood pressure immediately post-dosing, 2 and 24 hours post-dosing; for diastolic blood pressure immediately post-dosing and 24 hours post-dosing
	0.4	22	No statistically significant increases or decreases
	0.5	256	Statistically significant decreases from baseline values for systolic blood pressure at 2 hours post-dosing
	0.7	4	No statistically significant increases or decreases
	All doses	1663	Statistically significant decreases from baseline values for systolic blood pressure at 2 and 24 hours post-dosing; for diastolic blood pressure immediately post-dosing, 2, 24 and 72 hours post-dosing; for pulse rate immediately post-dosing Statistically significant increases from baseline values for pulse rate 24 and 72 hours post-dosing; for respiration rate immediately post-dosing and 2 hours post-dosing
Magnevist®	0.1	329	Statistically significant decreases from baseline values for diastolic blood pressure 2 hours post-dosing
			Statistically significant increases from baseline values for pulse rate 2, 24 and 72 hours post-dosing
Placebo		46	No statistically significant increases or decreases

- Most protocols specified changes in vital signs to be of medical relevance as assessed by the principal investigator if the following occurred:
  - 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 table below summarizes vital sign changes > Specified Magnitudes for all 0.1 mmol/kg OptiMARK™ subjects/patients by time point:

SAFETY: VITAL SIGN CHANGES > SPECIFIED MAGNITUDE: OptiMARK™ All 0.1 mmol/kg (N=957)										
			Immediately post		2 Hours		24 Hours		72 Hours	
Parameter	Magnitude	Direction	N	%	N	%	N	%	N	%
SBP	20 mmHg	▼	29	3.0	37	4.2	42	4.8	22	5.6
		▲	36	3.8	24	2.7	41	4.7	14	3.6
DBP	20 mmHg	▼	9	0.9	13	1.5	15	1.7	6	1.5
		▲	5	0.5	8	0.9	5	0.6	5	1.3
Pulse Rate	15 bpm	▼	33	3.5	26	2.9	31	3.6	14	3.6
		▲	13	1.4	35	3.9	47	5.4	31	7.9
Respiration Rate/min	10 bpm	▼			2	0.2	3	0.3	2	0.5
		▲	2	0.2	1	0.1	2	0.2		

Note: baseline line values are not available

VITALS: Phase 1 Trials

- A total of 245 subjects/patients were enrolled in four Phase 1 studies. One hundred ninety-nine subjects/patients received 0.1, 0.3, 0.5, 0.7 mmol/kg OptiMARK™ and 46 subjects/patients received placebo.
  Overall, the mean changes from baseline in vital sign parameters were small and considered to be clinically insignificant.
  The changes observed were similar between OptiMARK™ doses and between treatment groups with no apparent dose-related trend.
  There was no statistically significant difference between OptiMARK™ and Magnevist® in the proportion of OptiMARK™ and Magnevist® patients experiencing upward and downward shifts in vital signs.
  According to the Sponsor, statistical comparisons of vital sign differences from baseline by dose and treatment revealed the following findings:

SAFETY: VITAL SIGN CHANGES: PHASE 1: OptiMARK™ : NDA # 20937			
Dosage: mmol/kg		N=245	Comments
OptiMARK™	0.1	106	Statistically significant decreases from baseline values for diastolic blood pressure immediately post-dosing and 24 hours; for pulse rate at 1 hour post-dosing; and for respiration rate at 24 hours post-dosing Statistically significant increases from baseline values for pulse rate at 72 hours post-dosing
	0.3	46	Statistically significant decreases from baseline values for pulse rate at 1 hour post dosing
	0.5	43	Statistically significant decreases from baseline values for pulse rate at 2 hours post-dosing Statistically significant increases from baseline values for pulse rate at 48 and 72 hours post-dosing
	0.7	4	No statistically significant increases or decreases
Placebo		46	Statistically significant decreases from baseline values for systolic and diastolic blood pressure immediately post-dosing Statistically significant increases from baseline values for pulse rate at 72 hours post-dosing

VITALS: Phase 2 trials

- A total of 729 patients were dosed in Phase 2 studies and received either 0.1, 0.2, 0.3, 0.4, or 0.5 mmol/kg OptiMARK™.
  Overall, the mean change from baseline in vital sign parameters were small and considered to be clinically insignificant.
  The changes observed were similar between OptiMARK™ doses with no apparent dose related trend.
  There was no statistically significant difference between OptiMARK™ and Magnevist® in the proportion of OptiMARK™ and Magnevist® patients experiencing upward and downward shifts in vital signs.
  According to the Sponsor, statistical comparisons of vital sign differences from baseline by dose and treatment revealed the following findings:

SAFETY: VITAL SIGN CHANGES:PHASE 2: OptiMARK™ : NDA # 20937			
Dosage: mmol/kg		N	Comments
OptiMARK™	0.1	243	Statistically significant decreases from baseline values for pulse rate immediately post-dosing
	0.2	80	Statistically significant decreases from baseline values for pulse rate at 2 hours post-dosing
	0.3	170	Statistically significant decreases from baseline values for systolic pressure immediately post-dosing, 1, 2, and 24 hours post-dosing; for diastolic blood pressure immediately post-dosing and 24 hours post-dosing
	0.4	22	No statistically significant increases or decreases
	0.5	213	Statistically significant decreases from baseline values for systolic blood pressure at 2 hours post-dosing

VITALS: Phase 3 trials

- A total of 938 patients were enrolled in eight Phase 3 clinical studies (open-label and comparative studies combined). Six hundred nine patients received 0.1 mmol/kg OptiMARK™ and 329 patients received 0.1 mmol/kg Magnevist®.
  Overall, the mean changes from baseline in vital sign parameters were small and considered to be clinically insignificant.
  The changes observed were similar between OptiMARK™ doses with no apparent dose related trend.
  There was no statistically significant difference between OptiMARK™ and Magnivest® in the proportion of OptiMARK™ and Magnevist® patients experiencing upward and downward shifts in vital signs.
  Statistically comparisons of vital sign differences from baseline by dose and treatment revealed the following findings:

SAFETY: VITAL SIGN CHANGES:PHASE 3: OptiMARK™ : NDA # 20937			
Dosage: mmol/kg		N	Comments
OptiMARK™	0.1	596	Statistically significant decreases from baseline values for systolic blood pressure at 2 hours post-dosing; for diastolic blood pressure at 2 and 72 hours post-dosing; and for pulse rate immediately post-dosing Statistically significant increases from baseline values for pulse rate at 2, 24 and 72 hours post-dosing
Magnevist®	0.1	329	Statistically significant decreases from baseline values for diastolic blood pressure at 2 hours post-dosing Statistically significant increases from baseline values for pulse rate at 2, 24 and 72 hours post-dosing

VITALS: Pivotal trials

- A total of 790 patients were enrolled in the pivotal studies and received either 0.1 mmol/kg OptiMARK™ or 0.1mmol/kg Magnevist® in the four pivotal Phase 3 studies.
- None of these small but significant changes from baseline in vital signs parameters was considered indicative of a post-dosing trend or considered clinically meaningful. Similar observations were reported for CNS and liver studies combined and there were no treatment-related effects by indication. Statistically significant mean changes from baseline included:

SAFETY: VITAL SIGN CHANGES:PIVOTAL: OptiMARK™ : NDA # 20937			
Dosage: mmol/kg		N	Comments
OptiMARK™	0.1	461	Statistically significant decreases for systolic blood pressure at 2 hours post-dosing; for diastolic blood pressure at 2 and 72 hours post-dosing; and for pulse rate immediately post-dosing Statistically significant increases for pulse rate at 2, 24 and 72 hours post-dosing
Magnevist®	0.1	329	Statistically significant decreases for diastolic blood pressure at 2 hours post-dosing Statistically significant increases for pulse rate at 2, 24 and 72 hours post-dosing

Vital Signs: Impressions

1. The Sponsor has presented vital sign changes as a mean and standard deviation without giving the actual values (baseline). Analyses and interpretations of changes are also presented as a mean change from the baseline (Vol. 2.147, pp. 26.0214-26.0261). Interpretation of this information without a given baseline value is clinically meaningless (for example: a decrease of 30 mm Hg in SBP in a patient with a baseline SBP of 80mm Hg might be highly clinically significant, where as, a similar drop in a different patient with a baseline SBP of 160 mm Hg may have no clinical importance. Like wise an increase in the SBP/DBP in a patient whose "thermostat" is set for a lower baseline is at a very high risk to suffer the consequences of such a rise, specially if rapid, where as a different patient with a higher set baseline may handle this change without any deleterious effects). The rapidity of this change is as important as the magnitude. The information contained in the 'magnitude of change' is clinically meaningful to a certain extent, but then again, the baseline value is not provided.
2. Additionally, whether a change was significant or not was left to the site investigators' discretion. This may be very subjective. The guidelines or the rationale to make such decisions is not explained. Therefore, the data so presented as "statistically significant or insignificant" has very little clinical meaning based on how it was derived. Interpretation of this information is therefore restricted without a statistical analysis.
3. The chosen parameters are acceptable (the reviewer has noted that these were narrowed from a previously proposed values of SBP of >35m Hg, DBP of >25 mm Hg, Radial pulse of >20 beats in several trials).
4. Temperature recording, a critical vital sign parameter was not recorded in any of the trials. This deficiency is too late to be corrected at this time, nonetheless, retrospectively; a big part of the vital signs was not recorded.
5. There was no monitoring when the drug was being administered or during imaging (when performed). This was a critical period that called for monitoring. This deficiency, again, may be too late to be corrected, but should have been performed during the trials.

INJECTION-ASSOCIATED DISCOMFORT OR TOLERANCE

The following general comments in this over-view are applicable to the individual trials where comments on safety have been made in those trials assigned to the reviewer.

- Tolerability Assessments (Tol) - sensations or discomfort (heat, cold, and/or pain) that the patient experienced at the injection site were recorded on the Case Report

Forms and were graded as: mild (slight sensation/discomfort), moderate (definite but tolerable sensation/discomfort), or severe (excruciating sensation/discomfort). These have all been reviewed and commented in the individual review sections. Two brief comments worth noting are:

1. These scales were subjective in nature.
2. Clarification on the terminology between "severe" and "serious" is necessary. During the review of the individual trials (detailed comments have been made there), it is noted that these categories have been used interchangeably at times. Additionally, it is important that these are compliant with the regulatory policies.

Summary of Tolerance: All Subject/Patients: All Studies

- Overall, 382 of the 1663 (23.0%) OptiMARK™ subjects/patients (all dosed) reported 409 incidences of injection-associated discomfort defined as cold, heat or pain associated with administration of the study drug. A total of 75 of the 329 Magnevist® patients (22.8%) and 19 of the 46 placebo subjects/patients (41.3%) reported 80 and 20 incidents of any injection-associated discomfort, respectively.
- For all treatment groups, i.e., OptiMARK™, Magnevist®, or placebo, the most commonly reported injection-associated discomfort was cold.
  Overall, there was no difference in the incidence of injection-associated discomfort, i.e., cold, heat or pain, between the 0.1 mmol/kg OptiMARK™ and Magnevist® treatment groups. With increasing doses, there were slightly increase reports of heat.
- The majority of subject/patient tolerance/injection-associated discomforts were of mild or moderate intensity with the exception of 7 incidents of discomfort, which were considered by the investigator to be of severe intensity.
  The severe intensity discomforts included 2 episodes of severe heat (1 report each in the OptiMARK™ and Magnevist® group), 3 episodes of severe cold in the combined OptiMARK™ group and 2 episodes of severe pain in the combined OptiMARK™ group.

Summary of Tolerance: Phase 1 Studies (Studies 433,489, 538, and 543)

Note: Study 539 (pediatric indication) is on going and is not submitted for review; and in study 1177 (Japanese study), there were no reported events.

- A total or 245 subjects/patients were enrolled in four Phase 1 studies and received 0.1, 0.3, 0.5, or 0.7 mmol/kg OptiMARK™ or placebo. Twenty of the 199 (20/199, 10.1%) OptiMARK™ subjects/patients (all doses) reported injection-associated discomfort defined as cold, heat, or pain associated with administration of the study drug. A total of 2 placebo subjects/patients (2/46, 4.3%) reported injection-associated discomfort.
- For either treatment groups, i.e., OptiMARK™ or placebo, the most commonly reported injection-associated discomfort was cold.
  For both treatment groups, all of the injection-associated discomforts were of mild or moderate intensity.

There were no statistically significant differences in the incidence of injection-associated discomfort, i.e., cold, heat or pain between the OptiMARK™ (all dosed) and placebo treatment groups.
There were no dose- related trends.

Summary of Tolerance: Phase 2 Studies (Studies 464, 465, 466, 467, 468 and 469)

Note: Study 466 (breast indication, N=36), Study 468 (MRA, N=5), and Study 469 (bone or soft tissue, N=76) are not being pursued for efficacy by the Sponsor. These have been reviewed only for safety. Study 467 (liver indication, N=86) has been reviewed fully by another medical reviewer.

- A total of 729 patients in Phase 2 studies received 0.1, 0.2, 0.3, 0.4, or 0.5 mmol/kg OptiMARK™. One hundred sixty (160/729, 21.9%) patients (all doses combined) reported injection-associated discomfort defined as cold, heat or pain associated with administration of the study drug.
- The most commonly reported injection-associated discomfort, regardless of dose group, was cold.
  The majority of the patients reporting injection-associated discomfort were of mild or moderate intensity (156/176, 91.8%).
  Only 4 patients reported severe intensity discomfort, 3 incidences of cold and one incidence of heat upon injection.
- There were no statistically significant differences in the incidence of injection-associated discomfort, i.e., cold, heat or pain between OptiMARK™ doses and there were no dose-related trends.

Summary of Tolerance: All Subjects/Patients (Phase 1, Phase 2 and Phase 3) Who Received Either OptiMARK™ 0.1 mmol/kg or Magnevist® 0.1 mmol/kg

- One hundred ninety-nine of the 959 subjects/patients (20.8%) who received a dose of 0.1 mmol/kg OptiMARK™ in Phase 1, 2, or 3 studies experienced at least one event of injection-associated discomfort. Fifty-six subjects/patients (5.8%) experienced heat, 124 subjects/patients (12.9%) experienced cold, and 135 subjects/patients (3.6%) experienced pain. Among the subjects/patients experiencing discomfort, the majority of the events per patient were mild to moderate in intensity (179/199, 99.0%). Two subjects/patients reported 3 severe events, 1 episode each of severe pain, heat or cold.
- Seventy-five of the 329 patients (22.8%) who received 0.1 mmol/kg Magnevist® in the pivotal Phase 3 studies experienced at least one event of injection- associated discomfort. Sixteen patients (4.9%) experienced heat, 53 patients (16.1%) experienced cold and 11 patients (3.3%) experienced pain. Among the patients experiencing discomfort, the majority of the events per patient were mild to moderate in intensity (74/75, 98.7%). One subject/patient reported 1 episode of severe pain. The duration of injection-associated discomfort was not recorded during this study.
- There was no significant difference between OptiMARK™ and Magnevist® treatment groups for heat, cold, and pain.

Summary of Tolerance: All Phase 3 Trials (Open-Label and Pivotal) Who Received 0.1 mmol/kg OptiMARK™ or 0.1 mmol/kg Magnevist®

- A total of 938 patients were enrolled in eight Phase 3 studies (open-label and pivotal) combined. Six hundred nine patients received 0.1 mmol/kg OptiMARK™ and 329 patients received 0.1 mmol/kg Magnevist®. One hundred thirty-one (131/609, 21.5%) OptiMARK™ patients and 75 (75/329, 22.8%) Magnevist® patients reported injection associated discomfort defined as cold, heat, or pain upon administration of either study drug.
- For either treatment group, the most commonly reported injection-associated discomfort was cold. The majority of the patients reporting injection-associated discomfort were of mild or moderate intensity for OptiMARK™ (130/131, 99.2%) and Magnevist® (74/75, 98.7%). Only 2 incidents of severe discomfort were reported; one incident of pain following OptiMARK™ dosing and 1 incident of heat following Magnevist® dosing.
- There were no statistically significant differences in the incidence of injection-associated discomfort, i.e., cold, heat, or pain between OptiMARK™ doses and there were no dose-related trends.

Summary of Tolerance: Pivotal Phase 3 Studies (Studies 488, 490, 525, and 526)

- Overall in the combined Phase 3 CNS and liver pivotal studies, 108 of the 461 OptiMARK™ patients (23.4%) experienced at least one event of injection-associated discomfort. Thirty-one patients (6.7%) experienced heat, 63 patients (13.7%) experienced cold and 21 patients (4.6%) experienced pain. Among the patients experiencing discomfort, the majority of the events per patient were mild to moderate in intensity (99.1%, 107/108). One patient reported severe pain.
- For patients who received Magnevist®, 75 of the 329 patients (22.8%) experienced at least one event of injection-associated discomfort. Sixteen patients (4.9%) experienced heat, 53 patients (16.1%) experienced cold, and 11 patients (3.3%) experienced pain. Among the patients experiencing discomfort, the majority of the events per patient were mild to moderate in intensity (98.7%, 74/75). One subject reported severe heat.
- There was no significant difference between OptiMARK™ and Magnevist® treatment groups with respect to injection-associated discomfort/tolerance or intensity defined as heat, cold, and pain.

Summary of Tolerance: CNS Pivotal Phase 3 Studies (Studies 488 and 525)

- Thirty-nine of the 262 patients (14.9%) dosed with 0.1 mmol/kg OptiMARK™ in the combined pivotal Phase 3 CNS studies experienced at least one event of injection-associated discomfort. Six patients (2.3%) experienced heat, 27 patients (10.3%) experienced cold and 7 patients (2.7%) experienced pain. Among the patients experiencing discomfort, all of the events were mild to moderate in intensity (100%, 39/39). No patients reported severe intensity events.

- Twenty-four of the 133 patients (18.0%) dosed with 0.1 mmol/kg Magnevist® experienced at least one event of injection-associated discomfort. Six patients (4.5%) experienced heat, 18 patients (13.5%) experienced cold and 2 patients (1.5%) experienced pain. Among the patients experiencing discomfort, majority of the events per patient was mild to moderate in intensity (95.8%, 23/24). One patient reported severe heat.
- There was a significant difference (p=0.011) between treatment groups with respect to the number of patients experiencing a sensation of heat upon injection. The difference is related to 6 OptiMARK™ patients and 1 Magnevist® patient reporting mild intensity heat discomfort in comparison to no Optimark™ and 5 Magnevist® patients reporting moderate or severe intensity pain. There were no other statistically significant differences between treatment groups with respect to injection-associated discomfort of cold and pain.

Summary of Tolerance: Liver Pivotal Phase 3 Studies (Studies 490 and 526)

- Overall, in the combined pivotal Phase 3 liver studies, 69 of the 199 patients (34.7%) who received OptiMARK™ experienced at least one event of injection-associated discomfort. Twenty-five patients (12.6%) experienced heat, 36 patients (18.1%) experienced cold and 14 patients (7.0%) experienced pain. Among the patients experiencing discomfort, the majority of the events per patient were mild to moderate in intensity (98.6%, 68/69). One patient reported severe pain.
- Fifty-one of the 196 patients (26.0%) who received Magnevist® experienced at least one event of injection-associated discomfort. Ten patients (5.1%) experienced heat, 35 patients (17.9%) experienced cold and 9 patients (4.6%) experienced pain. Among the patients experiencing discomfort, all of the events were mild to moderate in intensity. No patient experienced a severe intensity event.
- Overall, there was no statistically significant difference between OptiMARK™ and Magnevist® treatment groups with respect to cold or pain. A statistically significant difference between treatment groups was observed for injection-associated heat (p=0.019), i.e., more OptiMARK™ patients reported experiencing mild or moderate heat upon injection when compared to the Magnevist® treatment group.

TOLERANCE: Summary:

1. There were no significant differences between OptiMARK™ and Magnevist® on this subjective assessment.
2. Majority experienced a sensation of cold. Heat sensation was noted at higher doses.
3. There were no significant injection site associated phenomena such as severe phlebitis or necrosis.

DEMOGRAPHICS AND SPECIAL POPULATIONS

- The difference between OptiMARK™ and Magnevist® with regard to safety parameters was examined for demographic factors, sex, age category, and race. Differences between OptiMARK™ and Magnevist® were also tested for the risk

groups of renal impairment and hepatic impairment. The safety variables examined were adverse events, laboratory parameters, and vital signs.

- Overall there was no statistically significant difference between OptiMARK™ and Magnevist® groups in the rate of adverse events experienced by gender, race or age.

Laboratory Parameters:

- There were isolated statistically significant differences for several demographic factors. There were no time-related trends observed in these differences. The differences were small and are felt by the Sponsor to be of no clinical significance and could be considered to be within the normal physiological variability of a patient population.

Vital Signs:

- There were isolated statistically significant differences for several demographic factors. There were no time-related trends observed in these differences. The differences were small and are felt by the Sponsor to be of no clinical significance and could be considered to be within the normal physiological variability of a patient population.

RENAL IMPAIRMENT:

- Three phase one PK studies (538, 489 and 543) established the relationship between OptiMARK™ and renal function. It is worthwhile at this time to summarize these:

  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 was dependent on the severity of the renal insufficiency. This resulted in a prolongation of the half-life ($t_{½}$), a decrease in renal clearance (CL_T) and a slight increase in V_{DSS}. Serum clearances 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 was prolonged leading to increased exposure that was dependent on the degree of renal impairment.
  3. Renal impairment emerged as a significant factor, and not the other associated disease processes (CNS pathology, Liver pathology).
  4. Serum iron changes as noted in the phase 1 #433 PK study were attributable to diurnal variability.
  5. 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.

6. Renal impairment affected only the rate of excretion of the drug, and not the extent of excretion.
7. There was no metabolic breakdown of the drug.

- See pharmacokinetics section above for additional information.
- Of the 69 renally impaired OptiMARK™ patients, 31 (31/69, 44.9%) patients experienced one or more adverse events. For the 17 patients who received Magnevist® that were considered renally impaired, 7 (7/17, 41.2%) patients experienced one or more adverse events.
  For both OptiMARK™ and Magnevist® treatment groups, the proportion of patients with renal impairment experiencing an adverse event was slightly greater than the rate for patients with normal renal function.
- For the OptiMARK™ renal impaired group, the body systems in which adverse events were reported more frequently were body as a whole, nervous system, cardiovascular system, respiratory system and digestive system and is similar to the non-impaired OptiMARK™ treatment group.
  For impaired Magnevist® patients, the body as a whole and digestive system were the most frequently involved body systems however the overall number of patients in this group is small.
- For both OptiMARK™ subgroups (normal renal function and impaired function), headache was the most common adverse event reported in 72 (8.1%) and 9 (13.0%) subjects/patients, respectively. Other common adverse events that occurred in the impaired renal OptiMARK™ treatment group include dizziness, nausea, vomiting and vasodilation.
- There were no statistically significant differences observed between OptiMARK™ and Magnevist® for any of the laboratory parameters for the subgroup of patients who had impaired renal function.

HEPATIC IMPAIRMENT SUBGROUP:

- A total of 96 OptiMARK™ patients (96/959, 10.0%) and 47 Magnevist® patients (47/329, 14.3%) were identified as having hepatic impairment.
  Of these 96 hepatic impaired OptiMARK™ patients, 27 (27/96, 28.1%) patients experienced one or more adverse events.
  For the forty-seven patients dosed with Magnevist® that were categorized as hepatic impairment, 20 (20/47, 42.6%) patients experienced one or more adverse events.
- For patients with normal or impaired hepatic function in either treatment group, the body systems in which adverse events were reported more frequently were body as a whole, digestive system and special senses. Within the OptiMARK™ treatment group, the frequency of adverse events were similar. Slightly more impaired patients that were dosed with Magnevist® experienced an adverse event.
- For OptiMARK™ patients, regardless of hepatic status, the most frequent adverse events were headache, and taste perversion.
  For Magnevist® patients, the most common adverse event in both hepatic status groups was headache.

Other common adverse events that occurred after dosing with Magnevist® include vomit, taste perversion, paresthesia and injection site reaction.

- There were no statistically significant differences observed between OptiMARK™ and Magnevist® for vital signs or any or the laboratory parameters for the subgroup of patients who had impaired hepatic function.

SAFETY SUMMARY & CONCLUSIONS

Gadolinium is a diagnostic agent that might be helpful in gaining additional information when used appropriately to manage patients better.
There are three other approved gadolinium diagnostic agents in the market (see comparators in the safety review section) subservient to the needs of MR imaging and diagnosis when a contrast agent is necessary. The Sponsor is neither claiming superiority nor has shown OptiMARK™ to be superior to Magnevist® or placebo. OptiMARK™ claims to be equivalent in safety (and efficacy) to another approved agent, Magnevist®.
As noted and commented in the overall safety review section, OptiMARK™ blends well with the other comparable agents in the 'over-all' picture and 'appears' to be made of the 'same fabric' on a gross level on the following profiles: physio-chemical properties, chemical properties, PK profile, and in the safety profile as well to a large extent.
Whether the Sponsor was able to accomplish and demonstrate an unequivocal beneficial profile without compromising the safety is the ultimate determination that will be discussed in these conclusions.

Studies Reviewed:
This safety review encompassed 19 clinical trials (5 in phase 1 - 433, 489, 538, 543 & 1177 (Japanese); 6 in phase 2 – 464, 465, 466, 467, 468 & 469; 4 in non-pivotal phase 3 – 484, 485, 486 & 487; 4 in pivotal phase 3 – 488, 525, 490 & 526). Study 539 phase 1 - pediatric indication was not submitted. Those studies with CNS/Spine indication have also been reviewed separately; and a second medical reviewer has commented on the liver studies.
Phase 1 studies:
These studies (all PK studies) established the pharmacokinetic properties of OptiMARK™ in humans in terms of metabolism, excretion, effect of kidney and liver disease, demographics, dialysability, etc. Findings from these studies suggested the following:

a) The frequency and severity of the adverse events were directly proportional to dose increase.
b) There was no demographic variability of AEs.
c) Patients with renal disease reported more AEs than those without renal disease.
d) There were no significant differences between OptiMARK™ and placebo.

The primary targeted population for these phase 1 studies included normal adults, adults with CNS or liver disease with or without associated renal disease, and adults on hemodialysis.

Protocol deviations and violations:

There were a few deviations in several of the clinical trials. Amongst others, these included missed lab/s and incomplete labs; treatment non-compliance (exceeding the recommended dose or volume-e.g. study 525); dosing a pediatric patient (525J012) when dosing for this age group was not proposed.

Perhaps the most significant of these violations was the lack of EKG monitoring in all the enrolled subjects in study 433, risking this entire population by exposing them to the highest dose studied in this clinical program (of 0.7mmol/kg).

Regulatory Concerns:

The description of the same patients (in particular, all the ones with serious adverse events) are different in different sections of the application (includes typographical changes, presentation of the events, sequence of events, reporting), for e.g. description in the actual study volume differs from the ISS.
Disparity between the stated definition and intended implementation differs from the actual implementation (e.g. adverse event v/s severe reaction).
Incomplete data submission (e.g. line listing on patients does not list all patients; medical history is incomplete-e.g. history of allergy is not obtained for patients in study 464 and 465).

The demographics and extent of exposure were:

- There was a total of 1684 patients/subjects enrolled in all studies of which 1309 were given OptiMARK™ (total of 1663 injections as 354 patients received two doses), 329 were given Magnevist®, and 46 received placebo.
- Of the total 1684 patients/subjects, 870 (52%) were men and 814 (48%) were women; 1718 (84.3%) were White, 183 (9%) were Black, 48 (2.4%) were Asian, and 89 (4.4%) were Others.
- In the OptiMARK™ group, 680 (52%) were men and 629 (48%) were women; the average age was 49.4 years. In the Magnevist® group, 165 (50%) were men and 164 (50%) were women; the average age was 51.4 years. In the placebo group, 25 (53%) were men and 21 (47%) were women; the average age was 44.4 years.
- Since the Phase 2 program was designed as pseudo crossover studies, patients in these studies (Studies 464, 465, 466, 467, 468, and 469) received two separate and different injections of OptiMARK™. Therefore, in the entire clinical program the 1309 subjects/patients in the OptiMARK™ dosage group received a total of 1663 injections. Additional information is provided in the overview safety section.

Deaths:
There was one death (468A027) in a patient during the study period, who died ~ 72 hours after drug exposure (probably not attributable to OptiMARK™; + autopsy). There were deaths in seven others who had participated in one of these trials at some point, but outside the study period. These have been discussed in the overview of safety. None of these deaths are attributable to OpitMARK™. If any, there may be associated morbidity with patient 525E015, in whom one cannot completely rule out the possibility if OptiMARK™ made the seizures worse.

Serious Adverse Events:

8 patients experienced serious adverse events while enrolled in this clinical OptiMARK™ program. These are discussed in the safety overview section. The Sponsor has not attributed any of these serious adverse events to OptiMARK™. In 4 of these events, the possibility that OptiMARK™ could have made pre-existing conditions worse (including seizures) cannot be fully ruled out. In one patient (543A003-renal patient), OptiMARK™ related symptomatic cardiac arrhythmia cannot be fully ruled out.

Discontinuation for Adverse events:
4 patients discontinued after exposure due to adverse events. These are discussed in the overview of safety. Three discontinued due to rash and the fourth due to seizures.

Pre-Clinical studies:
The following useful safety information was extractable from these pre-clinical studies:

i) The association between OptiMARK™ and the kidney toxicity/excretion was made.
j) Pregnancy Category C precautions and caution in nursing mothers was proposed.
k) The warning "Carcinogenic potential has not been evaluated" (with long-term studies in animals or humans).
l) Irreversible loss of germinal epithelium was observed in reproductive toxicity studies in male rats. This was incorporated in the Phase 1 studies and called for sperm count assessments (study 433).

Phase 1 studies:

These studies (all PK studies) established the pharmacokinetic properties of OptiMARK™ in humans in terms of metabolism, excretion, effect of kidney and liver disease, demographics, dialysability, etc. Findings from these studies suggested the following:

e) The frequency and severity of the adverse events were directly proportional to dose increase.
f) There was no demographic variability of AEs.
g) Patients with renal disease reported more AEs than those without renal disease.
h) There were no significant differences between OptiMARK™ and placebo.

The primary targeted population for these phase 1 studies included normal adults, adults with CNS or liver disease with or without associated renal disease, and adults on hemodialysis.

Safety monitoring:

Safety monitoring included vital signs, physical examination, laboratory evaluation including urinalysis and special labs, EKG, Adverse Event monitoring and Tolerance. Similar parameters were set to define these across the clinical trials and these were obtained at specific time points as proposed in the respective protocols. These have been discussed in the overview of safety in detail.
The deficiencies and concerns noted are as follows:

1. **Enrollment:**

a) Hemoglobinopathies was ruled out based only on a history. This importance was a self-infliction on the part of the Sponsor by making this as an exclusion criterion. Additional confirmatory lab testing probably was necessary.
b) Large populations of patients across these trials were on steroids and or antihistamines as concomitant medications. The masking effect on adverse events is of considerable concern.
c) Many of the enrolled patients were too sick or ill and therefore medically unstable. Rationalization for such enrollment was uncalled for studying OptiMARK™.
d) Demographically, across the studies, the majority of the patients were white.

2. **Monitoring**

- **LABS:**

a) There were no particular lab abnormalities that were consistently abnormal or persistent or clinically worrisome (except for calcium-see Japanese study).
b) Calcium, iron, and zinc changes occurred particularly at higher doses (these have been incorporated in the proposed labeling).
c) Glucose changes are probably not attributable to OptiMARK™.
d) Changes in Renal Function parameters in patients without renal insufficiency (minor changes in BUN and Cr levels) and in patients with renal insufficiency has been well captured and documented.
Appropriate caution for patients with renal impairment in the labeling should reflect this.
e) There were no significant differences in the profiles between Magnevist® and OpitMARK™ as for labs were concerned. On this aspect, equivalency is probably established.
f) The bulk of the data was presented (in the original volumes) as shifts from a baseline and as a mean change without the actual values; which were all clinically meaningless.
g) Minor deficiencies noted were exclusion of serum/blood bicarbonate or glucose levels in some trials. Urine analysis methodology (demographic parameter verification; centrifuged v/s uncentrifuged) requires clarification for purposes of documentation only and for possible future recommendations.

- **EKG: A major concern**

a) Although there were no deaths or serious events attributable to cardiac events by OpitMARK™, the capturing and documentation of these events were inadequate (timing, frequency, completeness, interpretation) and inappropriate (parameters too liberal, no QT intervals).
b) Whether such abnormalities occurred (although there were no mortality associated) at all is unknown.
c) Of the captured data, a significant number of records are incomplete.

d) Uncertainties regarding the appropriateness of background of EKG readers exist (including automated v/s manual readings).
e) The observations noted by the Sponsor are meaningless. Presented data is in a form that is largely clinically meaningless.
f) If approved, the case/s described in the Japanese study and in study 543 (serious adverse event) necessitates appropriate labeling for bradycardia/EKG changes.
g) Re-evaluation (by appropriate readers with appropriate parameters) of the existing records (if available) in terms of completeness and accuracy may strengthen this inadequacy to a certain degree. But the issues of the infrequency, lack of appropriate timeliness, and incompleteness, etc., (no EKG or no measurement of proper parameters or reading by non-qualified individuals) can never be mended.

- **PHYSICAL EXAMINATION:**

No specific problems or concerns or recommendations except:
a) This is a very subjective area.
b) Given that some of the patients enrolled were very sick with complicated medical problems encompassing CNS, Liver, etc., it would be commendable if the appropriately trained individuals in these areas made this assessment.

- **ADVERSE EVENTS:**

a) Generally, when comparisons are made between the adverse event profile of OptiMARK™ and the other approved gadolinium agents including Magnevist®, OpitMARK™ appears to fall along the same lines with no significant differences. Equivalence on this claim is probably demonstrated.
b) But it is important to re-capitulate that, a significant number of patients in this clinical program were on steroids and/or anti-histamines (see drug-dose-concomitant medications above) during the study period. Therefore, the true intensity, frequency, incidence and occurrence of AEs could all be potentially higher than these noted observations.
c) 6 patients (0.4%) in the entire OptiMARK™ group were reported to have seizures as an adverse event by the Sponsor (see table below). This number is probably slightly larger when one cannot exclude seizures in a few of the cases that had a serious adverse event or dropped out due to an adverse event (these were not considered to be an ictal phenomenon by the Sponsor). Gadolinium compounds are known to increase or trigger pre-existing seizures. Magnevist®, the comparator in this study has this in its labeling. Similar warnings or precautions are recommended.
d) Symptomatic bradycardia lasting between 2hrs post to 8 hours post associated with EKG changes and hypocalcemia during the same period has been noted in the Japanese Study (all normal subjects). Renal patient in study 543 (543A003) experienced symptomatic arrhythmia ~ 48 hours post-dosing. Appropriate cautioning is recommended in labeling.
e) The severity and intensity of adverse events were reported more when there was a corresponding increase in the dose; when special populations such as patients with kidney disease were studied.

f) The phase 1 studies had the largest number of reported adverse events.

- **VITAL SIGNS:**

a) The Sponsor has presented vital sign changes as a mean and standard deviation without giving the actual values (baseline). Analyses and interpretations of changes are also presented as a mean change from the baseline. Interpretation of this information without a given baseline value is clinically meaningless.
b) Additionally, whether a change was significant or not was left to the site investigators' discretion. This may be very subjective. The guidelines or the rationale to make such decisions is not explained. Therefore, the data so presented as "statistically significant or insignificant" has very little clinical meaning based on how it was derived. Interpretation of this information is therefore restricted without a formal statistical analysis.
c) The chosen parameters are acceptable (the reviewer has noted that these were narrowed from a previously proposed values of SBP of >35m Hg, DBP of >25 mm Hg, Radial pulse of >20 beats in several trials).
d) Temperature recording, a critical vital sign parameter was not recorded in any of the trials. This deficiency is too late to be corrected at this time, nonetheless, retrospectively; a big part of the vital signs was not recorded.
e) There was no monitoring when the drug was being administered or during imaging (when performed). This was a critical period that called for monitoring. This deficiency, again, may be too late to be corrected, but should have been performed during the trials.

- **TOLERANCE:**

a) There were no significant differences between OptiMARK™ and Magnevist® on this subjective assessment.

- **SPECIAL POPULATIONS:**

a) Patients with CNS disease, kidney disease, liver disease, on hemodialysis were studied. Appropriate warnings in the labeling to caution this sub group of increased risk of adverse events/reactions is recommended; e.g., seizures, renal excretion, etc.

FINAL SAFETY REMARKS:

1. Non approval based on EKG safety concerns or
2. Conditional approval provided the Sponsor is able to demonstrate adequacy, completeness, and reader appropriateness using acceptable parameters for the existing records (retrospective). This would obviously overlook the concern of the lack of adequate frequency. The outcome of these may call for additional recommendations.
3. Conditional approval (pending 2 above) with labeling (in addition to the proposed labeling) to indicate:

a) caution/warnings in patients with known or pre-existing seizure disorder (or other CNS condition predisposing patients to seizures) and renal disorder
b) caution/warning to indicate possibility of bradycardia and potential EKG changes
c) caution/warning to indicate possibility of increased risk of developing adverse event if one has history of an allergic reaction to iodine or other contrast agents
d) caution/warning to indicate possibility of transient lab errors- calcium, iron, ferritin
e) caution/warning to reflect that drug-drug interaction has not been studied
f) caution/warning on fertility, carcinogenicity, pregnancy, lactation/breast feeding
g) caution/warning that pediatric patients have not been studied
h) caution/warning that repeat dosing has not been tested
i) caution/warning to indicate that the incidence or severity of the adverse events could potentially be greater than what is projected (referring to the trials during which time a significant number of patients were on steroids and or antihistamines)
j) caution to indicate that greater frequency and severity of adverse events was noted with higher doses
k) caution/warning to indicate that monitoring (vital signs and or EKG) during dosing or immediately thereafter may be necessary as indicated (since no data is available on this aspect from this clinical program)
l) caution/warning in renal patients that there may be delayed adverse reactions due to the delay in elimination (reference to the patient in study 543A003)
m) caution/warning to indicate that the effects of this drug either when it precedes or follows another contrast agent (at least 48 hours in patients with normal renal functions and longer for patients with renal disease) is unknown as it has not been studied

RECOMMENDATION

See Page 13 in Regulatory Section

END OF SAFETY REPORT

APPENDIX - A

Deaths

Patient 486A027

1. Time of death: within 3 days of study participation
2. Dose: 0.1mmol/kg of OptiMARK™
3. Adverse Events: None reported or noted
4. History and Diagnosis: 45 year old male with end-stage AIDS, severe neutropenia and intestinal obstruction. Autopsy consistent with small bowel obstruction of terminal ileum with hemorrhage and necrosis. Also noted to have pneumonia.

Patient 486B004

1. Time of death: 29 days after study participation
2. Dose: 0.1mmol/kg of OptiMARK™
3. Adverse Events: None reported or noted
4. History and Diagnosis: 52 year old male with terminal colon cancer and multiple liver mets. Cause of death thought to be secondary to terminal cancer

Patient 486E016

1. Time of death: Seven weeks later
2. Dose: 0.2mmol/kg of OptiMARK™
3. Adverse Events: None reported or noted
4. History and diagnosis: 64 year old male with hx of COPD, IDDM, Metastatic liver disease with jaundice. Autopsy findings consistent with heart failure, hepatic failure and terminal cancer.

Patient 487E020

1. Time of death: Six months after study participation
2. Dose: 0.1mmol/kg of OptiMARK™
3. Adverse Events: None reported or noted except for transient elevation of urine WBC at two hours post dosing.
4. History and diagnosis: 49 year old male with hx of malignant melanoma, adenopathy and liver mets. Death due to multiple abscesses and cardiovascular failure.

Patient 487E023

1. Time of death: Eight months post dosing
2. Dose: 0.1mmol/kg of OptiMARK™
3. Adverse Events: None reported or noted
4. History and diagnosis: 52 year old male with hx of HTN, liver mass (neuroendocrine carcinoma) and abdominal pain. Death due to mets (cerebral) and hepatic disease.

Patient 490C001

1. Time of Death: Died one week post study/exposure
2. Dose: 0.1mmol/kg of OptiMARK™

3. Adverse Events: None significant noted or reported except for mild heat at injection site
4. History and Diagnosis: 61 year old male with hx of colon cancer and mets to liver, lung and possibly bone. Autopsy not performed and no additional information is available.

Patient 525E015

See page 151 of the review for full comments

Patient 526A026

1. Time of death: died 19 days later
2. Dose: 0.1mmol/kg of OptiMARK™
3. Adverse Events: None noted or reported.
4. History and Diagnosis: 67 year old male with hx of hepatocellular carcinoma, chronic hepatitis C and cirrhosis. Death thought to be secondary to advanced hepatocellular carcinoma, liver failure and sepsis.

END OF APPENDIX A (DEATHS)

NDA# 20-937 OPTIMARK

LIVER STUDIES

TABLE OF CONTENTS

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

NDA# 20-937 OPTIMARK

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

LIVER STUDIES

STUDIES REVIEWED			
Study Number Phase and doses	Study Title	Number of Patients Receiving Agent	
		Optimark	Magnevist
#467 Phase 2 0.1, 0.2 or 0.3 mmol/kg	A Multicenter Double Blind Multidose Within Patient Study to Evaluate the Safety, Tolerance and Efficacy of MP-1177/10 (Optimark) Injection for MRI of the Liver	88 patients	0
#486 and #487* Phase 3 0.1 or4 0.2 mmol/kg	A Multicenter Open-Label Study to Evaluate the Safety and Efficacy of Optimark (Gadoversetamide Injection) in MRI of the liver (data from two identical studies evaluated together)	227 patients	0
#490 Phase 3 Pivotal 0,1mmol/kg	A Multicenter randomized Double Blind Study to Evaluate the Safety, Tolerability and Efficacy of Optimark (Gadoversetamide Injection) Compared to Magnevist (Gadopentate Dimeglutamine Injection) in Patients with Liver Pathology	100 patients	97 patients
#526 Phase 3 Pivotal 0,1mmol/kg	A Multicenter randomized Double Blind Study to Evaluate the Safety, Tolerability and Efficacy of Optimark (Gadoversetamide Injection) Compared to Magnevist (Gadopentate Dimeglutamine Injection) in Patients with Liver Pathology	102 patients	104 patients
ALL STUDIES	----------	517 patients	201 patients

*The data from these studies were analyzed by the sponsor for safety only

The safety of Optimark was evaluated in one Phase 2 study (#467) and in four phase 3 studies (#486, #487, #490, #526) with a total of 517 patients who received any dose of Optimark. Efficacy was evaluated in one Phase 2 Study (#467) of Optimark alone and in two pivotal Phase 3 equivalence trials of Optimark vs. Magnevist (#490, #526). There were a total of 202 patients who received Optimark and 201 patients who received Magnevist in the two pivotal equivalence trials.

This reviewer is not familiar with the entire regulatory history of this drug, but the sponsor states that the efficacy data for studies #486 and #487 were not analyzed as a consequence of discussions with FDA concerning the need for a comparitor. Subsequently the equivalence trials #490 and #526 were opened

NDA#20-937
ptiMARK™
gadoversetamide Injection
Malinckrodt Medical St. Louis Mo.

M.O. Robert J. Yaes, Sc.D., M.D.
Document Date;
Date Assigned: 8/10/98
Date Completed:

Phase 2 Study # 467

TITLE A Multicenter, Double Blind Multidose within Patient Study to Evaluate the Safety, Tolerance and Efficacy of MP-1177/10 (Optimark) Injection on MRI for the Liver

1.1 STUDY DESIGN

This is a Phase 2 multicenter double blind dose ranging study of the safety and efficacy of intravenously administered Optimark in patients with known or highly suspected liver pathology

The objective of this study is to determine the dose-related safety and efficacy of intravenously administered P-1177/10 (Optimark) in patients with known or highly suspected liver pathology

88 patients were entered in this study at 5 study centers.86 were evaluable for efficacy and for safety

Inclusion Criteria:

Age > 18
Suspected or known liver pathology
Referred for contrast enhanced MRI of the liver
Had contrast enhanced CT or ultrasound prior to or following study
Signed informed consent

Exclusion Criteria:

Currently participating in another clinical trial
Pregnant or lactating female
Hypersensitivity to gadolinium
Any contraindication to MRI imaging
Hgb < 8, creatinine > 2.0

Dosage and Formulation

Patients were randomized to one of 3 dose groups. Each dose group received one of 3 pairs of intravenously administered doses of Optimark, 0.1 and 0.2 mmol/kg, 0.1 and 0.5 mmol/kg and 0.2 and 0.5 mmol/kg. Doses were given at least 24 hours apart at two separate imaging sessions and both pre contrast and post contrast scans were obtained at each session. There would therefore be 2 sets of scans for each patient for the entire group of 88 patients, there would be 176 pairs of scans for the study.

Reviewer's comment: With this study design, no single patient would receive all three doses, so that the efficacy of all three doses could not all be compared for any one patient

canning

Scans were obtained on a commercial MRI scanner with a field strength of at least 1.5 Tesla. Pre dose scans and post dose scans were obtained sequentially in the same position with the same imaging plane and scanning parameters. Pre dose, T1 and T2 series were obtained. Post dose, T1 series were obtained at 10 seconds, 60 seconds and 5 minutes after bolus injection The number of cuts obtained for each scan and the planes of these cuts was not specified.

Evaluation

Safety Monitoring

Patient monitoring schedule for each imaging session is shown in table 1

Table 1.1 Monitoring

	baseline	predose	postdose		
Test			1hr	2hr	24 hr
history & physical	x				
vital signs	x	x	x	x	x
serum chemistry	x				x
hematology (CBC, dif, Plt, PT, PTT,	x				x
inalysis	x				x
HCG (females only)	x				x
Monitoring adverse events			x	x	x

Efficacy Evaluation

Pairs of images (pre and post dose) were evaluated by the principal investigator and two expert radiologist blinded readers, for each dose and image time. For each patient the entire set of images from each imaging session were evaluated together.

Reviewer's comment: For each imaging session there would be 4 sets of images, the pre dose scan, and the post dose scans obtained at 10sec. 60sec and 5 minutes . All 4 sets of scans were evaluated together rather than being evaluated by the reader in sequence. The reader would have had the post dose scans available when evaluating the pre dose scan

The principal investigators answered the following questions about each pair of images

, Pre contrast diagnosis
2) Was the pre contrast study technically adequate?
3) Was the post contrast study technically adequate?
4) Number of lesions seen pre contrast and number seen postcontrast
5) Was additional information provided by the post contrast images
6) If the answer to question 5 was yes then for each image set (10 sec, 60 sec ,5 min) did the post dose image provide
   a) improved lesion visualization
   b) improved lesion border visualization
   c) new lesions detected (describe new lesions
   d) identification of edematous tissue
   e) identification of recurrent tumor
   f) would alter patient management
   g) improved confidence in diagnosis
   h) Post contrast diagnosis

7) Did post dose images provide ***less*** information than the pre dose images (describe and explain)

Reviewer's comment; A copy of a separate CRF for the blinded readers was not included. Presumably the blinded readers were asked the same questions as the investigators using a similar or identical case report form, although this is not explicitly discussed by the sponsor

Based on the medical record, the investigator was also asked to specify
1) The final clinical diagnosis
2) The basis for that diagnosis (histology, radiology studies, laboratory studies, physical exam, other)
3) The patient's clinical course

Reviewer's comment: There is no single standard of truth for the final diagnosis, but this diagnosis would be based on whatever workup that was ordered for the patient, Since all patients in this study were referred for a diagnostic MRI scan that was needed by the attending physician, presumably a diagnostic MRI scan was performed using an approved contrast agent, in addition to the scans required for this study. If the final clinical diagnosis was based on radiology, the MRI scan would be the most definitive diagnostic case. In comparing diagnoses, one would be comparing one MRI diagnosis to another. The absence of a single consistent definitive "standard of truth" is a serious error in study design.

For both the pre dose and post dose images the investigators and the blinded readers assessed the agreement between their own reading and the final diagnosis as "absolute", "basic" " partial" or " none" Specificities were obtained from these results.

Reviewer's comment. It is not clear how these comparisons were made. Presumably the investigators did this at a later date when the final diagnosis was known, and the blinded readers were told the final diagnosis **after** *they had completed their reading of the images. It is not clear how the terms "absolute", "basic" " partial" or "none" were defined or, given that there are 4 possible answers rather than 2, how specificity is defined.*

The contrast to noise ratio was determined for the largest lesion for 10 patients selected at random for each dose

1.2**RESULTS**

Patient Disposition

8 patients were enrolled in the study. 2 patients refused to continue in the study before receiving any drug. 86 patients were included in the efficacy analysis by the investigators and 75 in the analysis by the blinded readers. Because the protocol called for 75 patients, 11 patients were excluded from the blinded reader assessment. It is not specified how these 11 were chosen. 75 patients were included in the efficacy analysis. The demographics of the 75 included patients were not compared to the demographics of the 11 excluded patients.

Reviewer's comment: *The sponsor states that the protocol called for 75 patients, so only 75 of the 88 patients enrolled were included in the Blinded Reader analysis. There is no discussion of how the 11 patients to be excluded from the analysis were selected. It is not stated whether the scans from these excluded patients were*

read by the blinded readers, but the implication is that they were not. If this were a pivotal study, this would be a serious flaw in the study implementation, but since this is only a phase 2 study this error should entail no regulatory consequences.

Demographics (88 patients)
Age 56.5 ± 14,5 years
42 male,46 female
74 White 9 Black, 2 Asian, 3, Other

Safety

Adverse Events, (86 patients)

Deaths 0

Withdrawals due to adverse events 0

Serious adverse events 0

Severe adverse events 3

36 patients experienced 79 adverse events

Table 1.2 Adverse Events By Dose

	patients	adverse events	mild	moderate	severe
0.1 mmol/kg	13/57 (22.8%)	17	11	6	0
0.2 mmol/kg	14/56 (25%)	27	17	7	3
0.5 mmol/kg	23/58 (39.7%)	35	29	6	0

The most common adverse events were taste perversion, 21 pts and vasodilatation, 19 patients

Reviewer's Comment: *There appears to be a trend of increasing number of mild adverse events with increasing dose. No such trend is evidence for moderate or severe adverse events*

The 3 severe adverse events occurred in a single patient (E-003-69-M) who experienced severe vomiting sweating and abdominal pain, and moderate dizziness, ***of 4 hour duration***. (pgs 16.1443 & 16.1446) These events are not attributable to the drug since they occurred ***56 minutes before Optimark dosing..***

Reviewer's comment: No narrative description of these events is supplied. How a patient could have been scanned while experiencing severe nausea and abdominal pain is not clear

Clinical and Laboratory Monitoring

Laboratory

Statistically significant increases in serum creatinine, alkaline phosphatase and WBC, and statistically significant decreases in PT and serum phosphorus were seen , but these changes were not clinically significant in the opinion of the investigators

Vital signs

Changes in vital signs that were considered notable by the sponsor were

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

Table 1.3 Clinically Significant Changes

Parameter	Number of events		
	0.1 mmol/kg	0.2 mmol/kg	0.5 mmol/kg
Increased Heart Rate	12	4	13
Decreased Heart Rate	10	10	16
Increased respiration	1	0	3
Decreased respiration	1	0	1
Increased Blood Pressure	11	6	11
Decreased Blood Pressure	17	21	13

These changes were attributed to the drug for only 2 patients, The changes would be regarded as mild to moderate in severity

Reviewer's Comment These "clinically significant" changes are not really of clinical concern. For example patient G-025-67-M experienced a drop in blood pressure from 182/105 pre dose to 125/75 120 minutes post dose. This is called a clinically significant change since there is a fall of systolic BP of 57 mm and of diastolic BP of 30 mm hg. However the fall is from a abnormally high BP into the normal range.

Efficacy

Efficacy variables included the following comparisons between post dose images and pre dose images by the vestigators and by the blinded readers:

1) Improved visualization of lesion borders
2) Improved identification of edematous tissue
3) Improved confidence in the diagnosis
4) Difference in number of lesions detected
5) Sensitivity (sensitivity was assessed by comparing scan reading to "final diagnosis". Since all patients had liver pathology, specificity was not assessed
6) Signal intensity in region of interest (ROI)

Results for border delineation, edematous tissue identification, confidence in diagnosis and sensitivity are given in the sponsor's tables 11.4.1.1-1 to 11.4.1.4.3-1 in appendix 1

Reviewer's Comment *For some reason some results are reported for each of the 3 post dose images (10sec., 60 sec. and 5 minutes) individually, where others are reported for "post dose images" (presumably all 3 sets of images together)*

The difference in the number of lesions seen pre dose to the number seen post dose ranged from +20 to -7 (ie.7 more lesions seen on the pre dose scans than on the post dose scans). For the majority of patients, the number of lesions seen pre dose and the number seen post dose were the same

ROI measurements showed a 2 fold enhancement with contrast, which was the same for all 3 doses of contrast given.

Sponsor's Conclusion

Safety

There were no deaths or serious adverse events in this study. More patients in the 0.5 mmol/kg group experienced adverse events than in either of the other 2 groups.. Although there were statistically significant changes in some laboratory parameters and vital signs, none of these changes were clinically significant

Efficacy

Higher doses were usually determined to be more optimal in terms of border delineation, diagnostic confidence and identification of edematous tissue, but none of these differences were statistically significant. .For the blinded readers, no change in sensitivity was seen between pre dose and post dose scans. Sensitivity was much higher for the investigators, and increased from pre to post dose, but this increase was not statistically significant.

Reviewer's Comment: *The sensitivity for the blinded readers ranged from 0.48 to 0.62 which is not much different than what would be expected from chance alone. Sensitivity ranged from 0.83 to 0.93 for the investigators, and this is probably due to the fact that the investigators knew all the clinical information on the patients. while the blinded readers did not*

1.3 REVIEWER'S ANALYSIS

Safety

5 patients were evaluable for safety. There were no deaths or serious adverse events. The only 3 severe adverse events occurred in the same patients and were not drug related since they occurred 56 minutes before the drug was administered. Changes in vital signs or laboratory values do not raise any significant safety concerns. Optimark appears to be safe at all 3 dose levels, and there appears to be a trend towards increased incidence in the total number of adverse events with increasing dose.

Efficacy

This was a Phase 2 dose ranging study. Efficacy variables for 3 different doses of Optimark were compared. No comparisons were made with placebo or with any other MRI contrast agent The sponsor has concluded that, .while there was a trend of increasing efficacy with increasing dose , there were no statistically significant differences between doses for any of the efficacy variables. This reviewer agrees with the sponsor's conclusion.

Conclusion

Optimark is safe at all doses tested. There is a trend of increasing efficacy with increasing dose but the differences between different doses are not statistically significant There appears to be a trend of increasing number of mild adverse events with increasing dose. No such trend is evident for moderate or severe adverse events

NDA#20-937
ɔtiMARK™
ˌadoversetamide Injection
Malinckrodt Medical St. Louis Mo.

M.O. Robert J. Yaes, Sc.D., M.D.
Document Date;
Date Assigned: 8/10/98
Date Completed: 9/21/98

Phase 3 Studies # 486 and #487

Reviewer's Comment: The design of study 486 and 487 are identical, and are reported together by the sponsor as a single study. This study had been terminated after discussions with the FDA regarding further studies using Magnevist as a comparator and efficacy data from these studies were not analyzed by the sponsor

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

Study Title: A Multicenter Open-Label Study to Evaluate the Safety, Tolerability, and Efficacy of Optimark (Gadoversetamide Injection) in MRI of the Liver

Abstract: A total of 227 patients with highly suspected liver pathology previously detected with contrast ⁻nhanced computed tomography were enrolled in this study at 10 study centers in the US and 2 study centers in ːrmany (2 of the 10 US sites did not enroll any patients). Patients received a single intravenous dose of either ʊ.1 mmol/kg Optimark or 0.2 mmol/kg Optimark, at the discretion of the investigator (the study was not randomized) by IV bolus injection. Patients had a pre dose MRI with both T1 and T2 weighted images covering the entire liver, immediately before dosing. Pre dose + post dose images were obtained at 15-25 sec (arterial phase), 55-65 sec (venous phase) and 5 min (equilibrium phase). post dosing. Images were to be evaluated by the principal investigator at each study site and by 2 blinded readers, . Safety was assessed by monitoring physical examination, vital signs, CBC, serum chemistries, urinalysis, EKG, and adverse events. Efficacy data was not analyzed in this study because the study was terminated in order to start two different studies which would incorporate Magnevist as a comparator.

Reviewer's Comment The requirement that patients have liver pathology previously detected with computed tomography, would tend to bias the patient selection process. CT is generally believed to be a less sensitive test than MRI. The patients normally referred for MRI would usually be those patients for whom a definitive diagnosis could not be made by CT, not those for whom pathology could be seen on CT. Since the CT results would be known to the principal investigator before the patient was enrolled, this could bias the enrollment process

STUDY OBJECTIVES:

To evaluate the safety, tolerability, and efficacy of intravenously administered Optimark (Gadoversetamide ˌjection), in patients with known or highly suspected liver pathology, previously detected by computer ˌomography.