

DIVISION DIRECTOR'S MEMORANDUM

NDA: 21-711
DRUG: Gadofosveset Trisodium (MS-325)
TRADENAME: Vasovist™
ROUTE: Intravenous
DOSE: 0.03 mmol/kg
FORUMULATION: 0.25 millimoles/mL (244 mg/mL)
MODALITY: Magnetic Resonance Angiography (MRA)
SPONSOR: EPIX Medical, Inc.
SUBMITTED: December 12, 2003
RECEIVED: December 15, 2003
CATEGORY: 1S

PDUFA ORIGINAL DUE DATE: October 15, 2004

PDUFA MAJOR AMENDMENT: August 30, 2004
DUE DATE-3-MONTH EXTENSION: January 15, 2005

DD MEMO COMPLETED: December 15, 2004

SPONSOR'S PROPOSED INDICATION:

VASOVIST™ injection is indicated for use with magnetic resonance angiography [

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RELATED DRUGS:

1. Magnevist (approved - 1989)
2. ProHance (approved - 1992)
3. Omniscan (approved - 1993)
4. Optimark (approved - 1999)
5. **MultiHance (approved - 2004)**

RELATED REVIEWS: Clinical: Tong Li, MD, Zili Li, MD
Statistics: Anthony Mucci, Ph.D., Mike Welch, Ph.D.

Chemistry: David Place, Ph.D. (8/26/04)
Pharmacology-toxicology: Siham Biade, Ph.D. (12/03/04)
Adebayo Laniyonu, Ph.D. (12/03/04)

Clinical Pharmacology: Christy John, Ph.D. (12/01/04)
Microbiology: Bryan S. Riley, Ph.D. (6/03/04)

PROJECT MANAGER: James Moore

RECOMMENDED REGULATORY ACTIONS:

1. **Approvable** for the 0.03 mmol/kg dose of Vasovist™ for use with magnetic resonance angiography [] b(4)
2. The sponsor must conduct new clinical trial(s) to demonstrate the efficacy and safety of Vasovist. The efficacy design and the number of clinical trials are to be consistent with the sponsor's **drug development plan** seeking a limited or global MRA efficacy indication.
 - A) The following efficacy issues must be addressed and incorporated in the efficacy design, as well as the **statistical analysis design of the sponsor's new clinical trial(s)**:
 - i. The baseline, unenhanced MRA comparator study must be prospectively designed, specifically described in the clinical trial protocol, and consistent with current standards of clinical imaging practice for unenhanced MRA. The protocol must require prospective assessment of the initial baseline, unenhanced MRA for adequacy of performance, and require repeat performance of inadequate/non-interpretable baseline, unenhanced MRA.
 - ii. The sponsor must establish a clinical site monitoring and quality assurance program to maintain compliance with the performance of all protocol defined imaging studies.
 - iii. Training of the independent reviewers must be documented and must incorporate training for the interpretation of the protocol defined baseline, unenhanced MRA as well as the Vasovist, enhanced MRA.
 - iv. If an imputation scheme is to be incorporated in the statistical analytical plan, the imputation scheme must be prospectively designed, and neutral in its imputation, such that the imputation scheme will not establish a bias in favor of the investigational imaging product, Vasovist.
 - B) In the safety design of the new clinical trial(s), the sponsor must incorporate a safety schema to adequately investigate and to demonstrate the stability of MS-325 in vivo. In this regard, the following elements must **be incorporated in the safety design of the sponsor's new clinical trial(s)**:
 - i. A direct comparison between MS-325 and one of the approved Gadolinium contrast agents in the appropriate and comparable patient population. (Literature data from different studies and/or different patient population is unlikely to meet this requirement.)
 - ii. The study population must include a sufficient number of renal insufficient subjects.
 - iii. The study must collect data on all clinical parameters or measurements that are relevant to the determination of the stability of MS-325 in vivo. In this regard, the sponsor must conduct a comprehensive literature review and propose a list of clinical parameters and measurements. In this regard, the following monitoring parameters must be considered:
 - a) Urine: Zinc, zinc-fosveset and calcium-fosveset
 - b) Blood: hemoglobin, albumin, calcium and free calcium ion, and magnesium
 - iv. Safety monitoring data must be collected at baseline and then daily for at least 7 days post dosing. The sponsor must propose a detailed data collection schedule, which further addresses the need for prolonged monitoring for renal insufficient subjects.
3. **Denial of the Sponsor's requested pediatric waiver.** Pending the approval of Vasovist in the adult population, Phase 4 commitments for pediatric efficacy and safety clinical trials with Vasovist must be established. However, at this time, further consideration of pediatric efficacy and safety studies should be deferred, given the unresolved efficacy and safety issues for the adult population.
4. Deferral, at this time, of the labeling issues, as recommended by the various review disciplines.
5. Deferral, at this time, of the final decision for the proposed Trade Name: Vasovist.

Background

Gadofosveset trisodium (Vasovist™) injection is an investigational trisodium salt of a gadolinium (III) complex of a substituted diethylenetriaminepentaacetate (DTPA) ligand that is proposed for Magnetic Resonance Angiography (MRA) imaging.

In Gadofosveset trisodium, the DTPA ligand is substituted by a phosphodiester moiety, which confers the albumin binding property of the drug, and prolongs the plasma half life for Vasovist. Vasovist is renally excreted with minimal clearance through the liver. The proposed dose of Vasovist™ is 0.03 mmol/kg in adults.

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X-ray angiograms, while providing high resolution radiographic imaging, requires an arterial puncture, the use of x-ray contrast agents, and exposes the patients to ionizing radiation. The procedure has been associated with a relatively high rate of serious adverse events, including nephrotoxicity. A clinical need exists for an alternative to catheter-base, contrast X-ray angiogram. In current clinical practice, many Gadolinium-based MRI contrast agents have been used for detecting a clinically significant stenosis.

Magnetic Resonance Angiography (MRA) is a more recent development in Magnetic Resonance Imaging (MRI). Enhancement of MR images with exogenous contrast agents such as chelates of gadolinium (Gd) has become common in clinical practice. Existing MR contrast agents are reported to increase the sensitivity of MRA by enhancing the signal from the blood. However, existing MR contrast agents provide only transient enhancement of vessels with relatively **higher doses (0.2 – 0.3 mmol/kg) as compared to the proposed dose** for Vasovist™ of 0.03 mmol/kg in adults.

Vasovist's proposed imaging efficacy advantage is due to reversible binding to serum albumin, which prolongs plasma half-life and retains the Vasovist in the blood pool. This reversible serum albumin binding is expected to result in increased relaxation rate of the water protons in plasma, and enables MRA imaging for up to one hour after administration in human subjects. Vasovist is being studied for intravenous use in MRA to visualize

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Regulatory History

The sponsor opened the initial IND (#51172) with the Division in July 1996. For the end of Phase 2 discussion on August 28, 2001, there was a general discussion of clinical development program. During that teleconference, the Division made the following recommendation, that "for a drug approval, the Sponsor will need to compare how much more effective MS-325 is to non-contrast imaging and how close it is to X-ray angiography as a gold standard". However, no specific guidance was provided to the Sponsor with regard to the following:

- (1) what constitutes a clinically significant level of performance improvement
- (2) what is the minimal performance level for MS-325 enhanced MRA in terms of sensitivity and specificity.

The NDA submission was received on December 15, 2003. On February 27, 2004 the Agency sent a Filing Communication letter. Two potential review issues were noted in the Filing Communication letter,

1. **Validity of data imputation method used in the primary efficacy analysis:** It appears that all uninterpretable MRA images in four pivotal trials were treated as either false negative in sensitivity calculation, or false positive in specificity calculation. It is not clear how uninterpretable have been defined. If uninterpretable includes those images with technical

problems then this method of data imputation may create a false impression of an improvement of post-contrast images in both sensitivity and specificity by differentially underestimating the sensitivity and specificity of pre-contrast images.

2. Generalizability of the study results: [

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The sponsor submitted a major amendment on August 30, 2004, which was within 3 months of the user fee goal date and therefore resulted in a 3 month extension of the review cycle timeline.

Clinical Review

The clinical review has been performed by Tong Li, M.D., medical officer, and Zili Li, M.D, Clinical Team Leader. I have reviewed Dr. Zili Li's and Dr. Tong Li's clinical review reports and I concur with their findings, comments and recommendations. Based on Dr. Zili Li's review, I have provided the following clinical review summary through quotation, summary with editing, as well as supportive additional comments.

Dr. Zili Li's summary recommendation is for an Approvable regulatory action for the Vasovist NDA.

Dr. Li's summary comments on efficacy in support of the recommended Approvable action are as follows,

"In summary, this NDA lacks substantial evidence to support the efficacy of MS-325 because all four clinical trials have failed to demonstrate, with the required statistical certainty, that MS-325 enhanced MRA outperforms baseline non-contrast MRA in terms of sensitivity and specificity as originally planned. In those arterial regions where the improved sensitivity or specificity was observed, either clinical significance of the improvement was questionable or MS-325 enhanced MRA failed to reach the minimal performance level. In addition, there is no adequate assurance that non-contrast MRA protocols at baseline were designed to achieve an adequate and optimal performance level."

Dr. Li provided significant additional reviewer comments related to the evaluation of efficacy as follows,

"Reviewer's Comments: Apparently the sponsor needs to conduct new trial(s) to demonstrate the efficacy of this product. Based on the findings of this review, there are key clinical comments regarding the design and conduct of new trials:

- It is particularly important to have a standardized baseline non-contrast imaging protocol to ensure the optimal performance of baseline imaging in those new trial(s). All non-interpretable baseline images should be repeated. The sponsor also needs to enhance the monitoring of compliance with the protocol, because of the findings from the DSI inspection. I am afraid that the non-compliance observations from the current trials may have contributed to suboptimal performance of MS-325 enhanced MRA procedure;
- I have no objection to a reread of the current studies #12 and 13 into one new study, if the reread is restricted to only those subjects whose non-contrast MRA imaging protocol (key parameters) at baseline are judged to be optimal, and the reread is designed to achieve both clinically significant improvement over baseline and a minimal performance level.

I would suggest that the dynamic and steady state images be read separately. There was some preliminary evidence suggesting that steady state images may have a negative impact on the sensitivity and specificity (see Table 3.3.1 below). Based on the 22 October 2004 response from the Sponsor, the majority decision from the current blinded read (>75%) was based on the steady-state images when both dynamic and steady-state images were presented together for the evaluation. This finding may also partially explain the suboptimal performance of MS-325 enhanced MRA in current clinical trials. The Sponsor should be reminded that **failure to demonstrate an “added” clinical value** of the steady-state images alone may have some negative impact on the evaluation of risk/benefit ratio, since MS-325 has a much longer half-life than other approved **MRI contrast agents.**”

Table 3.3.1

The performance of dynamic or steady state images, compared to that of pre-contrast MRA (Institutional Reader)

		Dynamic	Steady State
Sensitivity	63.7	73.2	51.4
Change from pre-contrast	--	9.6	-12.3
p-value	--	0.009	0.007
(# of patients = 168 and number of vessels = 366)			
Specificity	62.6	81.1	68.5
Change from pre-contrast	--	18.5	5.9
p-value	--	<0.001	0.012
(# of patients = 266 and number of vessels = 1474)			

Dr. Li has further defined the NDA efficacy deficiencies and the proposed resolution as follows:

NDA Deficiency

(1) Lack of substantial evidence to demonstrate the efficacy of MS-325:

Because of the availability of non-contrast MRA techniques in clinical practice, the Division has determined that an MRA contrast agent needs to **demonstrate an “added” clinical value**. Such a requirement is considered being met, if the performance of a contrast enhanced MRA, in terms of sensitivity and specificity, is superior to that of non-contrast MRA, and that the degree of the performance improvement is clinically meaningful. It is also expected that a contrast enhanced MRA reaches a minimal level of performance, in terms of sensitivity and specificity, to ensure its clinical usefulness.

Issue #1: There is a lack of statistically significant evidences to support the improved sensitivity and specificity of MS-325 enhanced MRA, as compared to that of non-contrast baseline MRA

[] this NDA contains data collected from a total of 672 patients in four Phase 3 studies - two for pelvic region, one for renal region, and one for pedal (foot) region. Those studies were designed to demonstrate that MS-325 enhanced MRA can improve the detection of a $\geq 50\%$ stenotic lesion in terms of sensitivity and specificity, by using X-ray angiogram as the gold standard. While the studies were powered to detect 10%-15% MS-325 associated performance improvement, **no minimal performance level of MS-325 enhance MRA was specified in the sponsor’s statistical analysis plan.**

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Based on the blinded assessment of all images (X-ray, non-contrast MRA and contrast enhanced MRA) by three independent radiologists, the sponsor's original statistical analyses showed that MS-325 was associated with a statistically significant improvement in specificity in _____ arterial regions, and an improvement in sensitivity in the pelvic _____]. The increases in sensitivity and specificity were estimated at 20% and 12%, respectively, in the pelvic region, _____].

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However, these seemingly positive statistical results rely on a data imputation method, in which all non-interpretable MRA vessels have been treated as "inaccurate." On review of the submission, there are a remarkably higher percentage of the vessels in the baseline, unenhanced (non-contrast) MRA images found to be non-interpretable (up to 41% in some regions) as compared to non-interpretable MS-325 (Vasovist) enhanced MRA vessels (< 3%). Thus, the sponsor's data imputation method for non-interpretables imputes a "far greater" decrease in sensitivity, specificity or both for the baseline, unenhanced MRA as compared to the Vasovist enhanced MRA. As a result of these review observations, there is an unresolved efficacy review issue. Is the sponsor's observed statistical improvement for the Vasovist enhanced MRA due to a true effect of the MS-325 (Vasovist) enhanced MRA procedure, or is the observed statistical improvement due to the suboptimal performance of the undefined, uncontrolled, baseline, unenhanced MRA comparator procedure? If suboptimal performance of the undefined, uncontrolled, baseline, unenhanced MRA has occurred, it may have resulted in an inappropriate number of non-interpretable vessels. If so, then the per protocol imputation scheme for the non-interpretable MRA findings has imputed a bias in favor of the Vasovist enhanced MRA.

In reference to this unresolved efficacy review issue, new statistical analyses, conducted by the Sponsor and the Division's statistician, using two alternative data imputation methods, have consistently failed to demonstrate, with the required statistical certainty, that MS-325 enhanced MRA outperforms non-contrast baseline MRA in terms of sensitivity and specificity. The alternative data imputation methods that have been conducted are as follows:

- **The Interpretables Scenario**, in which the statistics were calculated only for vessels which were interpretable for both non-contrast images at baseline and MS-325 enhanced contrast images post dosing;
- **Pre = Post Scenario**, in which the non-interpretable non-contrast images at baseline are assigned the same diagnoses as their contrast-enhanced interpretable counterparts.

Since the observed improvement in sensitivity only in the pelvic region (Study #13), and the observed improvement in the specificity only in the _____] remain statistically significant, the Sponsor has argued that the statistically significant improvement in sensitivity or specificity alone (but not both as originally planned in the statistical analysis) could serve as sufficient evidence for the efficacy determination. This issue is addressed below.

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Issue #2: There is not adequate assurance that the observed improvement in sensitivity or specificity is clinically significant and/or the performance of MS-325 enhanced MRA is clinically useful.

A statistically significant improvement may not be a clinically significant improvement. All four clinical trials have been powered to detect 10-15% improvement in sensitivity or specificity, however only sensitivity at pelvic region (Study #13 only) _____] appeared to reach that performance level with a reasonable certainty. Even in those cases, the sensitivity (Study #13) and _____] of MS-325 enhanced MRA only reached 79% _____]. The lower boundaries of 95% CI for those two statistics have clearly failed to reach 80%, the minimal performance level that is currently used to determine the clinical usefulness of a contrast-enhanced MRA procedure.

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Issue #3: There was no adequate assurance on the validity of the observed improvement in sensitivity or specificity from two alternative analyses.

The lack of a prospectively designed, standardized, controlled baseline unenhanced (non-contrast) MRA imaging protocol comparator for the multiple clinical sites is a key deficiency in the study design. This deficiency diminishes the validity of any observed statistical improvement for the Vasovist enhanced MRA from the four clinical trials. The variation in the rate of non-interpretable baseline MRA images at different clinical sites was substantial. For example, in the study MS-325-13, two of the sites (#68 and #77) employed two different baseline MRA imaging protocols (see Table D-2 below). For one site, most of the images were interpretable but for the other site, none of the images were interpretable.

Table D-2: Performance of non-contrast MRA at baseline at two sites using two different imaging protocols

Name of Test Center	MS-325-13 Site 68	MS-325-13 Site 77
2D-TOF Protocol	Flip=70 TE=10 TR=608	Flip=10 TE=5.1 TR=19.6
2D-TOF image inspection	Blood flow visible	NO blood flow signal
# of Vessels (Subjects)	208 (30)	42 (6)
2D-TOF Sensitivity	Reader A: 59% Reader B: 83% Reader C: 72% Ave: 71%	Reader A: 0 Reader B: 0 Reader C: 0 Ave:0
2D-TOF Specificity	Reader A: 88% Reader B: 85% Reader C: 89% Ave: 87%	Reader A: 0 Reader B: 0 Reader C: 0 Ave: 0
MS-325 Sensitivity	Reader A: 69% Reader B: 90% Reader C: 69% Ave: 76%	Reader A: 83% Reader B: 100% Reader C: 83% Ave: 87%
MS-325 Specificity	Reader A: 90% Reader B: 87% Reader C : 93% Ave: 90%	Reader A: 71% Reader B: 100% Reader C : 97% Ave: 89%

Source Data: primary MO review

As such, until the ranges of all key MR sequence parameters used at all clinical sites in the clinical trials are fully examined, the possibility that the improved sensitivity or specificity of MS-325 enhanced MRA may be due to a sub-optimal performance of the undocumented, uncontrolled non-contrast MRA as the baseline comparator cannot be reasonably excluded. In the October 22, 2004 response to the Division, the sponsor attempted to address this issue by examining the performance of the baseline MRA by one of the key MR sequence parameters (TR). As stated earlier, the validity of this approach cannot be determined at this time until we have a full understanding on the ranges of all key MR sequence parameters that were used in the clinical trials.

In summary, this NDA lacks substantial evidence to support the efficacy of MS-325 because all four clinical trials have failed to demonstrate, with the required statistical certainty, that MS-325 enhanced MRA outperforms baseline non-contrast MRA in terms of sensitivity and specificity, as prospectively

cardiac arrhythmia, severe chest pain and MI. Though it is highly likely that the patient's underlying cardiac conditions played an important role in the development of those events, the demonstration of the relative stability of MS-325 in vivo may provide supportive assurance. Such an assurance is particularly important in view of MS-325's long half-life, the likely use of MS-325 in renal insufficient patients with the anticipated extend half-life due to slowed urinary clearance, and the lack of a demonstrated "added" clinical value for the unique steady-state images of MS-325.

Resolution

The safety issues should be resolved prior to approval. In this regard, the sponsor should propose a solution to adequately demonstrate the relative stability of MS-325 in vivo. As such, an adequate demonstration should include the following components:

- i. A direct comparison between MS-325 and one of the approved contrast agents in the appropriate and comparable patient population. (Literature data from different studies and/or different patient population is unlikely to meet this requirement.)
- ii. The study population should include a sufficient number of renal insufficient subjects.
- iii. The study should collect data on all clinical parameters or measurements that are relevant to the determination of relative stability of MS-325 in vivo. The sponsor should conduct a comprehensive literature review to propose a list of measurements to assess the stability of MS-325. The following parameters should be considered:
 - a) Zinc, zinc-fosveset and calcium-fosveset in the urine,
 - b) Hemoglobin, albumin, calcium and free calcium ion, and magnesium concentration in the plasma.
 - c) Data should be collected at baseline and then daily for at least 7 days post dosing. The sponsor should propose a detailed data collection schedule.

Clinical Safety Review

Drug exposure

A total of 1,438 subjects, including 1,321 patients and 117 healthy volunteers, have received at least one dose of MS-325. In comparison, 79 subjects, including 49 patients and 30 healthy volunteers, were treated with placebo.

Of 1,321 MS-325 treated patients, 1,203 (91%) were with vascular disease, and 767 (58%) received the proposed clinical dose of Vasovist (0.03 mmol/kg).

The highest two doses tested in the clinical programs were 0.15 mmol/kg (n=6) and 0.10 mmol/kg (n=71).

Demographic

Of 1,321 patients who received at least one dose of MS-325, 865 (66%) were male, 638 (48%) 65 years of age and older, and 1,055 (80%) Caucasian.

The majority (93%) of MS-325 treated patients (n=1,321) reported cardiovascular abnormalities, including coronary artery disease (53%), and hypertension (63%). 440 (33%) had diabetes, 321 (24%) had cholesterol abnormalities, and 294 (22%) were pr had been smokers. In addition, 1,259 (95%) received concomitant medications, including ASA, b-blockers, statin drugs, ACE inhibitors etc.

Common Adverse Events

Of 767 patients who received the proposed clinical dose of 0.03 mmol/kg, 276 (36%) reported a total of 511 adverse events (AEs). Table 4.4.2 showed the number and percent of the patients who have experienced AEs that occurred at a frequency of >1 % among all patients received MS-325. As the comparisons, the AE frequencies in the patients who received 0.03 mmol/kg dose only and in a subgroup of patients in Study MS-325-09 with a placebo group were also presented.

Table 4.4.2 List of common adverse events with a frequency > 1% from all MS-325 treated patients

Adverse Events (Preferred Term)	All patients received MS-325 (N=1,321)	All patients received MS-325 0.03 mmol/kg (N=767)
Pruritus NOS	99 (7.5%)	38 (5.0%)
Headache NOS	77 (5.8%)	33 (4.3%)
Nausea	70 (5.3%)	32 (4.2%)
Vasodilatation	68 (5.1%)	25 (3.3%)
Paresthesia	80 (6.1%)	21 (2.7%)
Injection site bruising	22 (1.7%)	19 (2.5%)
Burning sensation NOS	61 (4.6%)	15 (2.0%)
Venipuncture site bruising	21 (1.6%)	17 (2.2%)
Dysgeusia	44 (3.3%)	17 (2.2%)
Hypertension NOS	17 (1.3%)	11 (1.4%)
Dizziness (excl Vertigo)	24 (1.8%)	8 (1.0%)
Feeling cold	22 (1.7%)	6 (0.8%)
Rash NOS	16 (1.2%)	3 (0.4%)
Diarrhea NOS	15 (1.1%)	4 (0.5%)

Source Data: Modified from Table 7-7 of ISS (page 36)

Of 511 adverse events in 0.03 mmol/kg group, 249 (49%) occurred within 2 hours of MS-325 injection and 132 (25%) within >2 and <24 hours. One-third of all AEs resolved within 5 minutes of onset and 56% within 2 hours.

Death and other (non-fatal) serious adverse events:

During the clinical development program, 13 patients were reported to have experienced serious adverse events, including three fatal ones. Two death cases occurred in MS-325-09 (Phase 2 dose ranging study) and one in MS-325-18 (Phase 2 PK study in subject undergoing chronic hemodialysis). All deaths and other (non-fatal) serious adverse events occurred in MS-325 treated group.

Table 4.3.1 Characteristics of three patients who have experienced fatal SAEs in MS-325 clinical development program

ID	Protocol #	Age/Sex	Re Group (mmol/kg)	Cause of Death	Time of death	Study Site	Assessment by PI
09/14/04	09	66/F	0.005	Myocardial Infarction (one hour post dosing)	8 days	USA	Unlikely
09/01/14	09	80/M	0.07	Cardiac event	3 days	USA	Possible
18/01/02	18	53/F	0.05	Unknown	15 days	USA	Unlikely

Source Data: Modified from Appendix 20.1 of ISS and MO review.

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Table 4.3.2 Characteristics of 10 patients who have experienced non-fatal SAEs in MS-325 clinical development program

Patient ID	Protocol #	Age/ Sex	Rx Group (mmol/kg)	SAEs	Time of Onset	Study Site	Assessment from PI
09/01/29	09	77M	0.005	Syncope	30 hours	US/ Canada	Possible
09/22/18	09	69M	0.07	Syncope	3 days	US/ Canada	Unlikely
09/09/06	09	60F	0.05	Chest Pain/ER/ Prolonged QT	27 hours	US/ Canada	Possible
12/38/07	12	63M	0.03	Chest Pain/PTCA	1 day	US/ Canada	Unlikely
15/81/02	15	75M	0.05	Myocardial Infarction/CABG	3 days	Germany	Unlikely
09/01/17	09	64M	0.05	Hypersensitivity	30 minutes	US/ Canada	Possible
13/136/03	13	66F	0.03	Anaphylactoid reaction	1 minutes	Germany	Possible
07/02/05	07	64/M	0.05	Abdominal Aortic Aneurysm	13 days	US/ Canada	Unlikely
12/04/03	12	64M	0.03	Hyperglycemia Coronary artery disease aggravated	3 days 6 days	US/ Canada	Unlikely Unlikely
12/20/12	12	72M	0.03	Gangrene of Toes on left Foot	83 minutes	US/ Canada	Unlikely

Source Data: Modified from Appendix 20.1 of ISS and MO review

Dr. Li provided the following review comments,

“I have reviewed both the primary medical officer’s assessment and the summary description provided by the sponsor under ISS Appendix 20.1 of the NDA submission. My main conclusions are as follows:

- I see no compelling evidence at this time to support a direct causal relationship between MS-325 and death/serious adverse events except for hypersensitivity reactions. Two patients appeared to experience mild urticaria and itchiness and resolved quickly after IV antihistamine treatment without any negative consequence. It does not appear that the events met the definition of a serious adverse event though they were reported as SAEs. I believe that this issue can be successfully resolved through product labeling, such as requesting a warning statement under the appropriate section of the labeling.
- Whenever syncope was reported, a comprehensive review **of the drug’s potential to cause QT prolongation** is warranted. QT prolonging effect has been studied both pre-clinically and clinically, including two Phase I placebo-controlled studies. I have not seen any consistent safety signals at this time. While a QT prolonging effect can never be ruled out with an absolute certainty, the possibility of MS-325 at the proposed dose to cause a clinically significant QT prolongation, in my opinion, is quite low after taking the totality of evidence into consideration. It is worth noting, however, that one of the syncope patients (09/22/18) experienced an episode of non-sustained episode of ventricular tachycardia rhythm while being hospitalized for syncope. The primary MO expressed the concern that drug-induced ventricular tachycardia might be the reason for syncope. While it was possible that syncope was associated with ventricular tachycardia, it is far from certain whether MS-325 played any role in inducing the cardiac event. Given the lack of significant QT safety signal, the implication of this event is limited at this time **unless there is a clear biological pathway or mechanism.”**

Focused Safety Assessments

Hemoglobin

Due to the potential safety signal identified from mean analysis, an outlier analyses was conducted to assess the impact of MS-325 on hemoglobin by using the safety datasets provided by the sponsor,. In the analysis, the clinically significant change in hemoglobin was defined as a drop of 2 gm in hemoglobin from baseline at any time within 72 hours post dosing. Table 4.5.2 showed the results of this analysis.

Table 4.5.2 Number and percent of subjects with an at least 2.0 gm drop in hemoglobin from baseline within 72 hours post dosing of MS-325, by type of subjects.

Dose Group	Patients			Healthy Volunteer		
	N	N	%	N	n	%
<0.03 mmol/kg	93	2	2.1%	14	0	0
0.03 mmol/kg	720	18	2.5%	10	0	0
0.05 mmol/kg	334	10	3.0%	57	1	1.8%
> 0.05 mmol/kg	106	3	2.8%	36	0	0
Placebo	78	0	0	30	0	0
Total	1,301	33	2.5%	147	1	0.7%

Source Data: Independent analysis based on dataset submitted in NDA

The results showed that approximately 2.5% MS-325 treated subjects experienced acute hemoglobin drop within 72 hours of dosing. Among 34 subjects who have experienced at least 2 gm drop in hemoglobin, 4 (12%) occurred at 2 hours, 8 (24%) at 24 hours, and 22 (64%) at 72 hours post dosing.

Serum calcium level

In the product labeling of other Gd-based MRI agent, there was concern that Gd-based MRI agents may affect calcium measurement. To address the potential concern over the trend of decreased calcium level from baseline among MS-325 treated patients, the sponsor included a pooled analysis, comparing all MS-325 treated patients at different doses (n > 1,200) with that of placebo (n=49). The results showed that placebo group had a “larger” decrease from baseline in serum calcium level within 72 hours post dosing and there were lack of dose-response effects

Dr. Li provided the following review comments,

“Reviewer Comments: Again I am concerned that the heterogeneity among the pooled patient population may conceal the potential safety signal. I have restricted the analysis to study MS-225-09 – the only randomized, placebo-controlled and dose-ranging study in the target population. Table 4.5.4 showed the results of this analysis. Data appeared to suggest that MS-325 may have a negative affect on serum calcium level at 2 hours post dosing. 24-hour and 72-hour data were not consistent. In addition, 71 MS-325 treated subjects were found to have hypocalcaemia within 72 hours post dosing. Hypocalcaemia is a clinically significant event and cause of those events, relationship to potential MS-325 stability issue in particular, should be further studied.”

Table 4.5.4 Baseline and mean change from baseline in serum calcium level (mmol/L) by dose of MS-325, including placebo group (Study MS-325-09)

Serum Calcium Level (mmol/L)	Placebo n=38	MS-325 Treated Group (mmol/kg)				
		0.005 n=44	0.01 n=34	0.03 n=39	0.05 n=43	0.07 n=40
Baseline	2.346	2.363	2.359	2.324	2.340	2.358
2-hours change	-0.017	-0.020	-0.051	-0.061	-0.026	-0.021
24-hour change	-0.017	0.014	0.012	0.019	0.002	0.009
72-hour change	0.008	-0.033	0.004	0.011	0.001	-0.054

Source data: Modified from Table S4.1-4.6 of Study Report of MS-325-09

Urine zinc level

In one of the Phase 2 PK studies (MS-325-16), the sponsor collected 24-hour urine for the measurement of Zinc level at baseline, and the two periods post dosing (1-24 hours and 49-72 hours) in 10 healthy subjects received 0.03 mmol/kg, and 10 healthy subjects received 0.05 mmol/kg MS-325. Table 4.5.5 showed the results of urine zinc excretion by dose and time point.

Dr. Li provided the following,

“Reviewer Comments: Urine zinc excretion may be a potential indicator for the degree of Gd-transchelation in vivo. It may serve as a surrogate for measuring MS-325 in-vivo stability. Data clearly shows increase zinc excretion post dosing. The increase appeared to be dose-related and it can last for at least 72 hours. There were at least two limitations in the study design which greatly reduced the value of this study in demonstrating that relative stability of MS-325, compared to other MRI contrast agent: (1) lack of a comparator group; and (2) insufficient time points for urine collection. Such assurance is important because of the long-half time of MS-325, potential use in the renal **insufficient patients, and the lack of demonstration of “added” clinical value of steady-state image at this time.**

The sponsor should be required to provide data to demonstrate relative stability of MS-325 in vivo, compared to that of an approved MRI agent. The detailed requirements are **discussed in Executive Summary of this review.**”

Table 4.5.5 Urine zinc excretion in 24-hour pooled urine samples in healthy subjects received two different doses of MS-325.

Time Point	MS-325 0.03 mmol/kg			MS-325 0.05 mmol/kg		
	N	Mean	Change	N	Mean	Change
Baseline	10	556	--	10	554	0
24 hours post-dose	10	837	281	10	1856	1,302
72 hours post-dose	10	622	66	10	622	68

Source data: Table 12-6 of Study Report of MS-325-16

QT safety

The primary MO reviewer noted that of 693 MS-325 treated patients in Phase 3 programs, 81 (11.6%) patients had a total 99 episodes of QTc increase over 30 ms and 12 over 60 ms. In addition, there were two reported cases of non-sustained ventricular tachycardia, one of which was associated with syncope.

Dr. Li provided the following comment,

“Reviewer Comments: It is well known that the daily variation of QTc could be more than 60 ms and the ventricular tachycardia could be due to the underlying conditions of the patients. The key question here is whether there is sufficient evidence to rule out the possibility of a significant QT effect from the administration of clinical relevant dose of MS-325. The sponsor responded to our concern on March 30, 2004 with data from two phase 1 studies in healthy subjects. Though they were not prospectively defined **QT safety study as required in FDA’s draft guidance on QT** assessment, they contained many key design figures:

1. placebo controlled
2. blinded and manually read by a cardiologist
3. ECG were taken at baseline and multiple time post baseline

The smaller QTcF change from baseline observed in MS-325 groups compared to that in placebo group, the magnitude of QTcF change from baseline, and the consistency of data from the trials, in my opinion, provide a reasonable assurance that MS-325 at the proposed clinical dose is unlikely to produce a clinically significant QTc change in the healthy subjects.

I see no reason to require a prospectively designed “thorough QT” study at this time given the evidences that were presented and the single-use nature of this product. This conclusion, however, could be reevaluated if future clinical data showed increased concern over MS-325 stability in vivo, compared to that of other Gd-based MRI contrast agent because the current QT studies, by containing no positive control, cannot rule out possibility of significant drug-induced QT prolongation with the highest degree of certainty.”

Other items that require resolution:

Labeling still must be reviewed and agreed-upon. [

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Statistical Review

The statistical review of the Vasovist NDA has been performed by **Tony Mucci, Ph.D.** I have read **Dr. Mucci's draft** statistical review report, which has been reviewed by Dr. Mike Welch, and I concur **with Dr. Mucci's reported** statistical analyses, findings, comments, and conclusions.

Based upon Dr. Mucci's statistical review, I have provided the following review summary through quotation, summary with editing, and supportive additional comments.

The Sponsor submitted four, primary Phase III diagnostic imaging studies of Vasovist Enhanced Magnetic Resonance Angiography (MRA) for the evaluation of patients with known or suspected peripheral vascular disease:

1. **MS-325-12:** Evaluation of known or suspected peripheral (distal aorta-common iliac) vascular disease.
2. **MS-325-13:** Evaluation of known or suspected peripheral (distal aorta-common iliac) vascular disease [Second study in the same population as MS-325-12].
3. **MS-325-14:** Evaluation of known or suspected renal artery disease.
4. **MS-325-15:** Evaluation of known or suspected pedal artery disease.

Common Imaging Design

Four cross-over design studies, in which patients underwent baseline, unenhanced MRA as the comparator, MS-325 (Vasovist) enhanced MRA, and X-Ray Angiography (XRA) as the Standard of Reference (SOR).

The unenhanced baseline MRA and Vasovist enhanced MRA were performed open label, continuous, and in sequence on the same equipment during one imaging session.

The XRA imaging was performed within 30 days of the MRA imaging, but no closer than 3 days of the MRA imaging.

Common Study Objective

To evaluate the performance of a 0.03 mmol/kg dose of MS-325-Enhanced MRA, when compared to pre-contrast (baseline), unenhanced MRA, using X-ray Angiography (XRA) as the Standard of Reference (SOR). The studies are performed for the diagnosis of vascular disease in patients with known or suspected disease in a designated vascular bed (evaluated region typically consisting of four to eight vessels).

Primary Efficacy Objective

The determination of the presence or absence of stenosis in the vessels under examination in the specified region.

Independent Review Design

The Primary Efficacy Analysis protocol interpretations were performed as follows:

- Three sets of MS-325 enhanced images (dynamic, steady state and digital subtraction) were presented together in the evaluation while for the non-contrast MRA there was only one set of images.
- The MRA images were read independently by three blinded readers. The individual images examined by each blinded reader were images randomized with respect to patient, side (left or right), and sequence (baseline or enhanced).

- The XRA images were read independently by two blinded readers with a third independent and blinded adjudicator brought in, whenever the diagnoses from the original two readers were contradictory with respect to binary decisions based on the primary endpoints.
- The imaged vessels were evaluated for levels of stenosis. The stenosis level for any given vessel was the largest stenosis value found in the vessel.
- The Primary Efficacy Endpoint was vessel level stenosis, which was defined to be the presence of a stenosis level of at least 50% in the vessel. For each read (Baseline MRA, Vasovist Enhanced MRA, XRA) each vessel was assigned one of three values:
 1. Stenosis
 2. No Stenosis
 3. Uninterpretable

Common Primary Efficacy Endpoints

The primary efficacy endpoints were “vessel weighted” sensitivity and specificity.

- **Vessel level sensitivity** is the proportion of vessels (across all patients) identified as stenosed by XRA (SOR) which were correctly identified as stenosed by MRA.
- **Vessel level specificity** is the proportion of vessels (across all patients) identified as non-stenosed by XRA (SOR) which were correctly identified as non-stenosed by MRA.

Common Primary Efficacy Objectives

- (A): The rejection of the Null Hypothesis of Equality of baseline MRA sensitivity to Vasovist Enhanced MRA sensitivity.
- (B): The rejection of the Null Hypothesis of Equality of baseline MRA specificity to Vasovist Enhanced MRA specificity.

The Sponsor’s goal

Demonstrate improved sensitivity and specificity for Vasovist enhanced MRA over baseline unenhanced MRA.

The Sponsor’s statistical analysis criteria for improvement in diagnostic performance required that the lower value for the two-sided 95% confidence interval for the **difference – Vasovist enhanced MRA statistic minus baseline unenhanced MRA statistic - exceed zero (for both sensitivity and specificity)**

Criteria for Efficacy Evaluations in the Statistical Review

The Sponsor’s Efficacy Objectives translate into the following general **criterion for a statistical “Win:”**

The two-sided 95% confidence intervals for both

- (A) Vasovist enhanced MRA sensitivity minus baseline unenhanced MRA sensitivity
and
(B) Vasovist enhanced MRA specificity minus baseline unenhanced specificity

must have lower limits greater than zero. **That is, (A) and (B) below must both be obtained:**

- (A) Lower Limit of the 95% CI for Enhanced Sensitivity - Baseline Sensitivity > 0
and
(B) Lower Limit of the 95% CI for Enhanced Specificity - Baseline Specificity > 0

These criteria, in turn, require strengthening as follows:

Win Criterion: At an absolute minimum, (A) and (B) must jointly hold for at least two of the three independent readers.

Sample Size

Sample sizes were set to achieve at least 80% power for 10% to 20% increases in Vasovist Enhanced MRA sensitivity and specificity over baseline unenhanced MRA sensitivity and specificity, under study-specific assumptions on percentages of vessels that would be inaccessible for XRA, and study-specific assumptions on vessel level disease prevalence. **No assumptions were made concerning the expected percentages of uninterpretable vessels for unenhanced MRA or Vasovist enhanced MRA.**

No hypotheses were provided by the Sponsor regarding minimal performance levels for Vasovist MRA performance. The explicit Efficacy Objectives captured by rejection of the null hypotheses, along with the particulars on sample size determinations, can be conservatively interpreted as indications that the Sponsor expected Vasovist enhanced MRA to increase both Sensitivity and Specificity by at least 10% over baseline MRA, but no specific hypotheses were provided by the Sponsor for testing such improvements.

As such, the Sponsor's criteria for a "Win" are explicitly reducible to rejection of the null hypotheses of equality of baseline unenhanced MRA performance with Vasovist Enhanced MRA performance. It is to be understood that the differences, Vasovist enhanced MRA over baseline unenhanced MRA statistics, necessary for rejection of equality must be positive differences, so that a "Win" requires that the lower limit of the two-sided 95% CI for differences for Enhanced over baseline performance for both Sensitivity and Specificity exceed zero.

Uninterpretable Vessels – Imputation Scheme

By imputation, uninterpretable vessels were assigned by the Sponsor's statistical analysis, per protocol, "Worst Outcome" values; that is, the binary assignment values for uninterpretable vessels were opposite to the XRA (SOR) assignment.

However, a significant finding in all four studies is the percentage of uninterpretable vessels for baseline unenhanced MRA image reads (ranging from 10% to 40% across studies), as contrasted with (less than 3% uninterpretables) Vasovist Enhanced MRA image reads.

Such a remarkable diminished level of performance for the baseline, unenhanced MRA to produce interpretable images, as compared to the Vasovist enhanced MRA to produce interpretable images, could be consistent with any or all of the following:

- (A) Inherent limitations of the baseline unenhanced MRA imaging procedure
- (B) Suboptimal performance and control of the baseline unenhanced MRA imaging procedure
- (C) Inadequate training of the independent reviewers for the interpretation of the baseline, unenhanced MRA

If the inherent limitations of the baseline unenhanced MRA are the only etiologies for lack of performance to produce **interpretable images, then the Sponsor's "Worst Outcome" imputation is appropriate. However, if the latter two etiologies are present, the Sponsor's "Worst Outcome" imputation scheme for uninterpretables (the outcome assignment opposite to the XRA truth) would introduce a bias in favor of Vasovist. Since suboptimal performance and control of the baseline, unenhanced MRA as well as inadequate training of the independent reviewers to interpret the baseline, unenhanced MRA cannot be discounted (see following review section Potential Sources of Uninterpretable Assessments), a statistical analysis restricted to the Sponsor's "Worst Outcome" imputation would not constitute an exhaustive and objective examination of the submitted results. As such, this review has expanded the statistical analyses to include examination of the sensitivity and specificity statistics for three distinct Imputation schemes:**

- (A) **The Sponsor's per protocol "Worst Outcome,"** in which all uninterpretables – baseline unenhanced MRA or Vasovist enhanced MRA – were classified as incorrectly diagnosed. As noted, the rationale for this imputation is appropriate when based on the assumption that the uninterpretable MRA imagings are intrinsic failures in the baseline, unenhanced MRA imaging technique and the Vasovist enhanced MRA. If suboptimal performance and control of the baseline, unenhanced MRA and/or inadequate training of the independent readers can not be excluded, this imputation introduces a potential bias in favor of the Vasovist enhanced MRA.
- (B) **The Interpretables only,** in which the statistics were calculated only for vessels which were interpretable both at baseline and post-contrast. This scenario avoids the issue of imputation. As such, this imputation scheme corrects for the possibility that the performance of the baseline unenhanced imaging was suboptimal and that reader training may be inadequate.
- (C) **Pre = Post Scenario,** in which the non-interpretable images are assigned the same diagnoses as their post-injection interpretable counterparts. This scenario is **consistent with the statistical analytical plan's null hypotheses of equality of pre-Vasovist MRA and post-Vasovist MRA imaging results.** Thus, this imputation scheme is appropriate and consistent with **the Sponsor's statistical study design.**

The results of the analyses under these three imputation schemes were the following:

- (A) **The Sponsor's per protocol "Worst Outcome:"** The Sponsor's results in three of the four studies (two peripheral vascular disease studies [distal aorta/common iliac], [] achieved a "Win" for at least two of the three readers. b(4)

- (B) **The Interpretables only:** Under this alternative imputation scheme, the statistics no longer support the claim that Vasovist enhanced MRA outperforms Baseline unenhanced MRA.

In Study#12 and [] b(4)
Interpretables or Pre = Post, only one reader provides improvement in both Sensitivity and Specificity.

In Study#13 and [] b(4)
No reader in either study provides improvement in both Sensitivity and Specificity for either the Interpretables scheme or the Pre = Post scheme.

- (C) **Pre = Post Scenario:** Under this alternative imputation scheme, the statistics no longer support the claim that Vasovist enhanced MRA outperforms Baseline unenhanced MRA.

In Study#12 and [] b(4)
Interpretables or Pre = Post, only one reader provides improvement in both Sensitivity and Specificity.

In Study#13 and [] b(4)
No reader in either study provides improvement in both Sensitivity and Specificity for either the Interpretables scheme or the Pre = Post scheme.

Reader-by-Reader Performance

Table 1.3.1 from Dr. Mucci's review is presented below. The table presents the Reader-by-Reader performances for Sensitivity and Specificity in the four Phase III Trials for each of the three Imputation schemes for uninterpretables. These reader performances are evaluated here strictly with **respect to the Sponsor's proposed criteria for a "Win,"** namely the rejection of the stipulated Null Hypotheses of Equality of performance. The reader performance assessments are understood here as the determination of a lower limit for the two-sided 95% CI for Enhanced minus Baseline performance that exceeds zero.

Table 1.3.1 Legend

A "Win" for a Reader occurs if both Hypotheses are rejected (at 2-sided .05 Level)

Y means a “Win” obtains for the Reader; N means a Win has not been obtained by the Reader

A “Win” for an Imputation Scheme requires, at a minimum, that at least two of the three Readers provide “Wins” simultaneously for both Sensitivity and Specificity.

N: (S) means NO “Win” for Sensitivity;

N: (Sp) means NO “Win” for Specificity

N: (S, Sp) means NO “Win” for both Sensitivity and Specificity

Win Profile by Study by Imputation Scheme and by Reader Table(1.3.1)

	Reader (A)	Reader (B)	Reader (C)
STUDY#12			
Worst Outcome	Y	Y	Y
Interpretables	N: (Sp)	N: (S)	Y
Pre=Post	N: (Sp)	N: (S)	Y
STUDY#13			
Worst Outcome	Y	Y	Y
Interpretables	N: (Sp)	N: (Sp)	N: (Sp)
Pre=Post	N: (Sp)	N: (Sp)	N: (Sp)

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Potential Sources of Uninterpretable Assessments

Seeking trends for potential etiologies/relationships of the uninterpretable findings for the baseline, unenhanced MRA procedure, the uninterpretable findings are assessed against the following five study design features:

1. Protocol Design
2. Study site
3. Independent readers
4. Hardware equipment and software
5. Patient characteristics

The average numbers and percentages of Baseline Interpretable vessels are displayed in the Table 1.3.3, below, stratified by disease status, Gender, and Age Group.

(Note: Vasovist enhanced MRA interpretables consistently exceeded 98% and are not displayed.)

It is noted that there are two columns for Study #14. Column (A) displays a “derived” percentage for Interpretables; column (B) displays the real percentage for Interpretables.

Table (1.3.3) Average levels of Interpretable Vessels by Study and Category

Category	Study #12	Study #13
Overall	89%	84%
Stenosis	90%	87%
No Stenosis	87%	84%
Male	90%	84%
Female	88%	85%
Age<65	93%	83%
Age>=65	87%	85%

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Relationship to Protocol design

For Vasovist enhanced MRA, the sponsor established specific MRA imaging procedures based upon each specific MRA equipment manufacturer. However, the sponsor did not establish a specific MRA imaging procedure for the baseline comparator, unenhanced MRA imaging. Instead, the protocol allowed the clinical sites to perform the standard sequence of each institution or a sequence recommended by the MR vendor. Specific information from the **Sponsor’s protocol Section 9.3 is reproduced below, documenting the protocols’ lack of a pre-specified baseline MRA protocol as well as referencing the section of the protocol with the pre-specified, manufacturers’ specific, Vasovist enhanced MRA protocols.**

9.3 Efficacy Assessments

9.3.1 MR Image Acquisition

9.3.2

The MR system to be used will have a 1.0 to 1.5 Tesla field strength magnet with Food and Drug Administration (FDA)-cleared hardware and software.

Prior to MS-325 administration, pre-contrast (baseline) MRA images will be obtained of the vascular region according to the standard sequence of each institution or sequence recommended by the MR vendor. Prior to MS-325 dosing, a subtraction mask will be obtained utilizing the same imaging parameters as specified for the dynamic images.

Post-contrast MRA imaging of dynamic and steady-state time points will then be performed according to the image sequences provided in Appendix 15.4, with start time for dynamic scanning described in Section 8.1. Steady-state images must begin within 15 minutes of MS-325 administration and may immediately follow the dynamic phase images.

In addition, there is an absence of documented evidence of the assessment for adequacy of the baseline MRA study at the clinical sites, prior to the Vasovist enhanced MRA. Furthermore, the sponsor did not provide a protocol for repeat of the baseline MRA when the baseline was found to be inadequate and/or non-interpretable.

Hence, while the sponsor established detailed imaging protocols by equipment manufacturers for the Vasovist enhanced MRA, the sponsor failed to establish a standardized protocol for the baseline, unenhanced MRA and failed to implement a quality assessment plan for the baseline, unenhanced MRA. As noted, clinical sites were allowed to implement baseline, unenhanced MRA imaging according to unknown institutional sequences or unknown sequences

recommended by an MR vendor. Thus, the introduction of a potential bias in favor of the Vasovist enhanced MRA through the variable, uncontrolled protocol design features for the baseline unenhanced MRA, as well as the lack of quality control for the baseline unenhanced MRA, can not be excluded.

Relationship to study site

The table below provides evidence that the percentages of non-interpretables varies remarkably from clinical site to clinical site. The variability suggests the undefined, uncontrolled, baseline, unenhanced MRA at the individual clinical sites may be related to the non-interpretables. Thus, a bias in favor of Vasovist enhanced MRA can not be excluded. The potential bias in favor of Vasovist, is the result of the uncontrolled, clinical site variable, MRA protocols for the baseline unenhanced MRA and possible variability in quality assurance of the baseline, unenhanced MRA at the individual clinical sites.

Table (3.1.5.1)
Uninterpretable Percentages by Center
 (Percentages refer to % of Vessels)
 (For Studies 12, 13, 14, centers with 10 or more patients are presented)
 (For Study 15, centers with 7 or more are presented)

Study #12							
38	10	4%	0	0	0	0%	1
13	16	11%	4%	0	4%	3%	2
27	41	12%	1%	0	7%	3%	3
40	33	13%	29%	3%	31%	21%	7
20	40	15%	9%	3%	10%	7%	4
34	13	17%	32%	3%	38%	24%	8
21	13	18%	14%	8%	9%	10%	5
19	36	24%	16%	5%	12%	11%	6
All others	99		13%	5%	20%		
Study #13							
66	18	3%	38%	21%	20%	26%	6
83	30	10%	16%	12%	12%	13%	4
68	30	14%	4%	14%	3%	7%	2
114	16	15%	15%	13%	32%	20%	5
108	13	16%	16%	2%	11%	10%	3
67	29	17%	6%	3%	5%	5%	1
All others	42		35%	24%	29%		

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Relationship to independent reader

The percentages of uninterpretables vary considerably amongst readers (see Table C-1 below, Readers A, B, and C). Reader A and C have remarkably higher rates of uninterpretable vessels as compared to Reader B. These reader related uninterpretable rates suggest variability in reader training for the undefined, uncontrolled, baseline, unenhanced MRA. Thus, the potential introduction of a bias in favor of Vasovist enhanced MRA can not be excluded.

Table C-1 Summary of non-interpretable vessels by reader and study protocol

Protocol # (MS-325)	Number of Vessels	Post-contrast images			Pre-contrast images		
		Reader A	Reader B	Reader C	Reader A	Reader B	Reader C
12	1754	1.4%	0.6%	1.0%	15.2%	4.0%	19.2%
13	1206	2.5%	1.7%	2.6%	19.5%	12.4%	16.3%

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Source Data: Modified from Table 8-7 (page 47) of ISE.

* Each reader may have a different number of total renal arteries because the assessment on accessory renal arteries

Hardware equipment and associated software

It is noted that the baseline, unenhanced MRA (non-interpretables as high as 41.3% for reader A) is performed in sequence and continuously on the same hardware equipment and associated software with the Vasovist enhanced MRA (non-interpretables as high as 3.8% for reader A). Thus, the utilized hardware and software is unchanged between the compared MRA studies and is utilized in a continuous sequential MRA imaging for the individual subjects. Thus, differential hardware equipment and associated software have not been associated with the increased uninterpretable rate for the baseline, unenhanced MRA as compared to the Vasovist enhanced MRA.

Relationship to patient characteristics

If high levels of uninterpretables were intrinsic to baseline, unenhanced MRA alone, it would be reasonable to assume possible correlations may be present between uninterpretable **MRA images for any particular patient and the patient's profile – gender, age, health status (stenosis, no stenosis)**. If such a relationship could be demonstrated for a patient characteristic, as a source of uninterpretable baseline, unenhanced MRA, then a potential advantage for Vasovist enhanced MRA over the baseline, unenhanced MRA may be suggested. In the following tables for each of the four clinical trials, there is some statistical evidence suggestive of randomness in the occurrence of uninterpretable images for various subgroups. No statistically significant relationship between patient characteristics and uninterpretable baseline, unenhanced MRA is found.

**Table (Study: MS-325-12)
Percentages of Interpretable Images for Health, Gender, and Age Strata**

Overall	89%
Stenosis	90%
No Stenosis	87%
Male	90%
Female	88%
Age <65	93%
Age ≥ 65	87%

Appears This Way
On Original

Table (Study MS-325-13)
Percentages of Interpretable Images for Health, Gender, and Age Strata

Overall	84%
Stenosis	87%
No Stenosis	84%
Male	84%
Female	85%
Age < 65	83%
Age ≥ 65	85%

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Clinical Pharmacology and Biopharmaceuticals (OCPB) Review

Dr. Christy John completed the Clinical Pharmacology and Biopharmaceuticals Review, Dr. Young Moon Choi, Team Leader, concurs with Dr. John's review. Dr. John's review states, "OCPB finds this application acceptable from a clinical pharmacology and biopharmaceutics perspective, provided that the sponsor demonstrates the in-vivo stability of Vasovist in the patients with renal insufficiency by comparing the amount of zinc-fosveset and calcium-fosveset in the urine collected as compared to health volunteers."

Dr. John notes, "...the potential of in-vivo dissociation of gadolinium cannot be ruled out completely as evidenced by increased zinc-fosveset excretion in urine after injection of Vasovist." "Also, the total recovery of gadolinium-fosveset after injection of Vasovist was incomplete (average 83.7% in urine and 4.7% in feces)."

Dr. John further notes, "In vivo dissociation of Gd-fosveset may lead to the complexation of free ligand with calcium, magnesium, zinc and iron etc." Lastly, Dr. John states, "It should be noted that during the review

process, the sponsor was asked on 8/30/2004 to provide zinc data. The sponsor reported that they do not **have such data.**"

Dr. John also noted the following, "The mean QTc values did not show an appreciable increase as compared to the placebo group. The placebo and the test group did show mean QTc increase of greater than 10 msec in some patients. A label warning about Vasovist effect on QTc is warranted."

I have reviewed the Clinical Pharmacology and Biopharmaceuticals review completed by Dr. John and I concur with his review and his recommendations.

Microbiology

Dr. Bryan Riley completed the product quality microbiology review. Dr. Peter Cooney, Microbiology Supervisor, concurs with Dr. Riley's review. **Dr. Riley states in his summary, "This submission is recommended for approval on the basis of product quality microbiology."**

I have reviewed the product quality microbiology review completed by Dr. Riley and I concur with his review and his recommendation.

Chemistry

Dr. David Place completed the chemistry review. Dr. Eldon Leutzinger, Chemistry Team Leader, concurs with Dr. Place's review. **Dr. Place states in his summary, "The chemistry recommendation is 'Approval.'"**

Dr. Place's summary further states, "Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable, The sponsor should commit to those items identified in the Action letter to Applicant. These fall under three broad categories.

1. Continued full characterization of the Drug Substance isomers (A & B)
2. Minimize GdEDTA in the drug substance and drug product
3. Provide confidence bands for the **stability data plots for drug product"**

I have reviewed the chemistry review completed by Dr. Place and I concur with his review and his recommendations.

Pharmacology/Toxicology Review

Dr. Siham Biade completed the pharmacology/toxicology review. Dr. Adebayo Laniyonu, Supervisory Pharmacologist concurs with Dr. Biade's review. **Dr. Biade states in her summary, "The preclinical studies conducted support safety and efficacy (measured by relaxation rates). No additional studies are required. This reviewer recommends VASOVIST™ be approved."**

Dr. Biade summary further states **recommendations on the sponsor's proposed labeling** to more appropriately reflect findings from preclinical studies. These proposed labeling recommendations relate to the following label sections: precautions, drug interactions, fertility, pregnancy category, and nursing mothers.

I have reviewed the pharmacology/toxicology review completed by Dr. Biade and I concur with her review and her recommendations for label changes.

Pediatric Safety and Efficacy – Waiver Request

The sponsor submitted a request for waiver of pediatric studies for Vasovist to IND 51,172, in July 2001. The request for waiver was supported by the following stated limitations for the use of Vasovist in the pediatric population:

1. No meaningful therapeutic benefit over existing treatments and it is unlikely to be used in a substantial number of pediatric patients;
2. Studies are impossible or highly impractical because the number of patients is so small or geographically dispersed;
3. Disease-specific waiver indicated **for the treatment of the condition in adults – Arteriosclerosis.**

Dr. Zili Li, in his review noted the following:

“The sponsor provided X-ray angiography use data from both pediatric and adult population in 1998 and 1999 to support the request. The use data, even if it is true, is clearly out-dated now.”

In addition, Dr. Li cited [redacted] an MRI expert [redacted] has provided a written consult to the Division. In her consult, [redacted]

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[redacted] believes that **“MRA can provide a wealth of morphologic and functional information in an accurate and noninvasive fashion.”** As a result, **“use of MRA in the pediatric patients is likely to continue to increase.”**

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Dr. Li recommends the sponsor’s request for waiver not be granted. Dr. Li states that consideration of pediatric efficacy and safety studies should be deferred at this time, given the unresolved efficacy and safety issues in adults at this time.

I concur with Dr. Li’s review and recommendations to reject the sponsor’s request for waiver of pediatric efficacy and safety studies and I support deferral at this time of consideration of pediatric safety and efficacy study development until the efficacy and safety of Vasovist are to be approved in adults.

Proposed Labeling

Proposed labeling changes by the various review divisions are deferred for comment to the next review cycle.

Trade Name Review

The Division of Drug Marketing, Advertising, and Communications (DDMAC) finds the proprietary name Vasovist acceptable from a promotional perspective.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

George Mills
1/11/05 04:09:54 PM
MEDICAL OFFICER

NDA 21711

Medical Team Leader's Memorandum: New NDA

Date submitted: December 15, 2003
Original due date: October 15, 2004
Due date after 3-month extension: January 15, 2005
Memo completed: January 10, 2005

Drug: Gadofosveset Trisodium (MS-325)
Tradename: Vasovist™
Dosage Strength: 0.25 mmol/mL
Proposed Dose: 0.03 mmol/kg
Route of Administration: IV Injection
Proposed Indications: VASOVIST™ injection is indicated for use with magnetic resonance angiography

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1. Executive Summary:

The purpose of this memo is to provide the Division Director with my recommendation regarding regulatory action on this NDA. I recommend that this NDA receive an Approvable action. My rationale for this recommendation is as follows: the NDA does not contain substantial evidence, as required by the federal regulation, to support that Gadofosveset Trisodium (MS-325),

In particular, the four Phase 3 studies submitted in the NDA have failed to demonstrate the improved sensitivity and specificity in all three arterial regions under the investigation. In many cases, the sensitivity and specificity of MS-325 enhanced MRA are too low to be considered clinically useful.

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The size of the safety database, in general, is consistent with what is typically required for a single-use contrast agent. There are, however, some unresolved safety issues related to the role of MS-325 in the patients who had experienced an acute hemoglobin drop or hypocalcaemia within 72 hours post dosing, which raises issue of the stability of MS-325 in vivo. The NDA deficiencies and resolution items are described herein:

NDA Deficiency:

(1) There is a lack of substantial evidence to demonstrate the efficacy of MS-325

Because of the availability of non-contrast MRA techniques in the clinical practice, the Division has determined that a MRA contrast agent needs to demonstrate an "added" clinical value by showing the improved sensitivity and specificity, compared to that of non-contrast MRA. The degree of the performance improvement should be clinically meaningful and a contrast enhanced MRA should reach a minimal performance level in terms of sensitivity and specificity to ensure its clinical usefulness.

Issue #1: There is a lack of statistically significant evidence to support the improved sensitivity and specificity of MS-325 enhanced MRA, compared to that of non-contrast baseline MRA

[] this NDA contains data from a total of 672 patients in four Phase 3 studies - two for pelvic region, one for renal region, and one for pedal (foot) region. Those studies were designed to demonstrate that MS-325 enhanced MRA can improve the detection of a $\geq 50\%$ stenotic lesion in terms of sensitivity and specificity, by using X-ray angiogram as the gold standard. While the studies were powered to detect 10%-15% MS-325 associated performance improvement, no minimal performance level of MS-325 enhanced MRA were specified.

b(4)

Based on the blinded assessment of all (X-ray, non-contrast MRA and contrast enhanced MRA) images by each of three independent radiologists, **the sponsor's original analyses** showed that MS-325 was associated with statistically significant improvement in specificity for _____ arterial regions, and the improvement in sensitivity for pelvic [] The increases in the sensitivity and specificity were estimated at 20% and 12%, respectively, for pelvic region, []

b(4)

Those seemingly positive results, however, were based on a data imputation method, in which all non-interpretable MRA images were **treated as "inaccurate"**. **Since a higher** percentage of non-contrast MRA images (up to 41% in some regions) at baseline were considered as non-interpretable, compared to that (<3%) of MS-325 enhanced MRA images, **this data imputation method allows the "greater"** decreases in sensitivity, specificity or both at baseline. As a result, it may have created an artificial impression of improved sensitivity and specificity of MS-325 enhanced MRA.

The new analyses, conducted by the Sponsor and **the Division's statistician using two** alternative data imputation methods, have consistently failed to demonstrate, with the required statistical certainty, that MS-325 enhanced MRA outperforms non-contrast baseline MRA in terms of sensitivity and specificity. The alternative data imputation methods are as follows:

- The Interpretables Scenario, in which the statistics were calculated only for vessels which were interpretable for both non-contrast images at baseline and MS-325 enhanced contrast images post dosing;
- Pre=Post Scenario, in which the non-interpretable non-contrast images at baseline are assigned the same diagnoses as their contrast-enhanced interpretable counterparts.

Since the improvement in sensitivity for pelvic region, []

[] the Sponsor has argued that the statistically significant improvement in sensitivity or specificity alone (not both as originally planned) could serve as sufficient evidence for the efficacy determination. This issue is addressed below.

b(4)

Issue #2: There is a lack of adequate assurance that (1) the observed improvement in sensitivity or specificity is clinically significant and/or (2) that the performance of MS-325 enhanced MRA is clinically useful.

It is well known that statistically significant improvement may not be a clinically significant one. All studies have been powered to detect 10-15% improvement in sensitivity or specificity, however, only sensitivity for pelvic region (Study #13) [] appeared to reach that level with a reasonable certainty. . Even with that level of improvement, the sensitivity (Study #13) and [] of MS-325 enhanced MRA, on average, only reached 79% [] There was a significant reader-to-reader variability and the lower boundaries of 95% CI for those two statistics have clearly failed to reach the minimal performance level of 80%, which is currently used to determine the clinical usefulness of a contrast-enhanced MRA procedure.

b(4)

Issue #3: There is a lack of adequate assurance on whether non-contrast MRA imaging protocol at baseline was designed to achieve an optimal level of performance.

The variation in the rate of non-interpretable MRA images at baseline from different clinical sites was substantial. For example, in the study MS-325-13, two of the sites (68# and #77) employed two different baseline MRA imaging protocols. For one site, the most of the images were interpretable but for the other site, none of the images were interpretable. Lack of a standardized non-contrast MRA imaging protocol at baseline across different clinical sites appears to be one of the key deficiencies in the study design, which raises an issue of whether the non-contrast MRA at baseline was designed to achieve an optimal level of performance.

In the 22 October 2004 response to the Division, the sponsor presented a subgroup analysis showing a relatively stable sensitivity and specificity of non-contrast MRA when the non-contrast MRA images obtained from different clinical sites with different repetition times (TR) were divided into two groups: i.e. those with < 30 ms vs. those with \geq 30 ms. The validity of this approach cannot be determined at this time until we have full understanding on the ranges of all key MR sequence parameters that were used in the clinical trials. Until such an examination is done, the possibility of the improved sensitivity or specificity of MS-325 enhanced MRA due to a sub-optimal performance of non-contrast MRA at baseline cannot be reasonably excluded.

In summary, this NDA lacks substantial evidence to support the efficacy of MS-325 because all four clinical trials have failed to demonstrate, with the required statistical certainty, that MS-325 enhanced MRA outperforms baseline non-contrast MRA in terms of sensitivity and specificity as originally planned. For those arterial regions where the improved sensitivity or specificity (not both) was observed, either clinical significance of the improvement was questionable or MS-325 enhanced MRA failed to reach the minimal performance level. In addition, there is no adequate assurance that non-contrast MRA protocols at baseline were designed to achieve an adequate and optimal performance level.

Resolution:

The sponsor should conduct new adequate and well-controlled studies to demonstrate the efficacy of MS-325. The number of clinical trials required depends on the indication that is

sought. [

] The sponsor, however, should have an option to seek a **“limited” indication** to a particular arterial region. In this case, two new clinical trials are required to demonstrate the efficacy for that region.

b(4)

In the new clinical trials, non-contrast MRA imaging protocol should be predefined and standardized across all clinical sites to ensure an optimal performance. Non-interpretable images at baseline should be repeated and data imputation method should not favor the drug effort. The sensitivity and specificity improvement is expected to be at 10% with a minimal performance level of 80% (the lower boundary of 95% CI) for MS-325 enhanced MRA in terms of sensitivity and specificity.

If the sponsor is interested in **pursuing this “limited” indication** at pelvic region, a blinded re-read from the current Study MS-325-12 and MS-325-13 into one new study could be considered. In this case, the sponsor would need only to conduct one new clinical trial. If the sponsor choose this approach, the Sponsor should agree to:

- collect and analyze the key non-contrast MRA imaging parameters used for each subject in Study 12 and 13, and restrict the re-read only to those subjects whose non-contrast MRA imaging protocol at baseline are judged to be optimal;
- predefine the independent review charter and statistical plan, including data imputation method, and blinded read method, allowing for a separate assessment of dynamic and steady-state MRA images;
- Utilize the same minimal improvement and performance criteria as stated earlier in declaring the efficacy.

(2) There are some unsolved safety issues related to clinical significance of an acute hemoglobin drop, hypocalcaemia, and an increased urine zinc excretion within 72 hours post dosing

In clinical trials, 34 and 71 subjects, respectively, had experienced an acute hemoglobin drop (> 2 gm/dL decrease from baseline) or a hypocalcaemia episode (< 8.5 mg/dL), within 72 hours of dosing. Also there were some preliminary evidences suggesting that the drug was associated with the mean decreases in hemoglobin and serum calcium levels. At this time, the possibility of the drug effect cannot reasonably be excluded. Given this uncertainty, there is a concern over the increased urine zinc excretion observed within 72 hours of dosing, which raises the issue of stability of MS-325 in vivo. Since there are no established thresholds in determining how stable a contrast agent is in vivo, we are particularly interested in a demonstration of a relative stability of MS-325 in vivo, compared to that of other approved MRI contrast agents.

There were two cases of non-sustained ventricular tachycardia, one of which was associated with syncope. There were also some other cardiac events being reported from clinical trials, including various cardiac arrhythmia, sever chest pain and MI. Though it is highly likely that **the patient’s underlying cardiac conditions have** played an important role in the development of those events, the demonstration of the relative stability of MS-325 in vivo provides the **needed assurance. Such an assurance is particularly important because of MS-325’s**

prolonged half-life in human body, the likely use in renal insufficient patients, and a lack of **demonstration of an "added" clinical** value of steady-state images.

Resolution:

Those safety concerns should be resolved prior to approval. The sponsor should propose a solution to adequately demonstrate the relative stability of MS-325 in vivo. Such a demonstration should include the following components:

1. There is a need for a direct comparison between MS-325 and one of the approved contrast agents in an appropriate and comparable patient population. Literature data from different studies and/or different patient population is unlikely to meet this requirement.
2. The study population should include a sufficient number of renal insufficient subjects.
3. The study should collect data on all clinical parameters or measurements that are relevant to the determination of relative stability of MS-325 in vivo. The sponsor should conduct a comprehensive literature review to propose a list of measurements. The following parameters should be particularly considered:
 - Zinc, zinc-fosveset and calcium-fosveset in the urine,
 - Hemoglobin, calcium and free calcium ion, and magnesium concentration in the plasma.
 - All other measurements that may affect interpretations of the parameters mentioned above.
4. Data should be collected at baseline and then daily for at least 7 days post dosing. The sponsor should propose a detailed data collection schedule. Data should be collected at multiple time points during the first 24 hours.

Other items that require resolution:

Labeling still must be reviewed and agreed-upon. ☐

b(4)

2. Scientific and Regulatory Background:

Peripheral vascular disease (PVD) is a common medical condition with a significant public health importance. Techniques used to diagnose PVD include medical history, physical exam, ultrasound, non-contrast MRA and x-ray angiogram which is considered as the gold standard.

X-ray angiogram, while providing high resolution, requires an arterial puncture, uses x-ray contrast agents, and exposes the patients to ionizing radiation. The procedure has been associated with a relatively high rate of serious adverse events, including nephrotoxicity. A clinical need exists for an alternative to catheter-base, contrast X-ray angiogram. In today's clinical practice, many Gadolinium-based MRI contrast agents have been used for detecting a clinically significant stenosis, or even for preparing for a surgery while such a use or indication has not been approved by the Agency.

Unlike other approved MRI contrast agents, MS-325 can non-covalently bind to albumin in the blood. The sponsor believes that serum albumin binding gives MS-325 three properties that are potentially valuable for vascular imaging with MRI:

- Increased plasma concentration of the contrast agent;
- Prolonged plasma lifetime of the contrast agent, and
- Increase signal enhancement per mole of agent

As the result, MS-325 may be used at a lower dose to achieve a longer-lived vascular enhanced vascular enhancement (up to 60 minutes) for MRA compared with other MR agents. These advantages, in my opinion, however, may be tempered by problems associated with venous overlap and some safety concerns due to a much longer half-life of MS-325.

The sponsor opened the initial IND (#51172) with the Division in July 1996. While I have not located the meeting minutes for the EOPII discussion, there was a general discussion of clinical development program on August 28, 2001. During that t-con, the Division had made the following recommendation, which stated that "for a drug approval, the Sponsor will need to compare how much more effective MS-325 is to non-contrast imaging and how close it is to X-ray angiography as a gold standard". However, no specific guidance was provided to the Sponsor with regard to (1) what constitutes a clinically significant level of performance improvement, and (2) what is the minimal performance level for MS-325 enhanced MRA in terms of sensitivity and specificity.

Five Gadolinium-based MRI agents are currently approved for CNS indications. The off-label use for MRA indication is common in the US. Table 2.1 summarizes the major differences between MS-325 and other MRI contrast agents.

Table 2.1 Comparison between MS-325 and other gadolinium-based contrast agents

Items	MS-325	Other Gadolinium-Based Agents
Trade Name	Vasovist	Prohance, OptiMARK, Omniscan and Magnevist
Drug class	Blood Pool Agent	Extracellular Agent
Proposed clinical does for MRA	0.03 mmol/kg	0.1-0.3 mmol/kg
Plasma protein binding (Albumin)	Yes 80% and 87% at 3 min and 1 hour	No
Elimination half-life (hours)	16	1.3-1.7
T1/2 increase under renal insufficiency (fold)	Mild/Mod/Severe = 1.2/2.6/3.7	Renal impairment = 5 (Optimark)
AUC increased under renal insufficiency (fold)	Mild/Mod/Severe = 1.1/1.8/2.3	---
Elimination	Urine 84% and feces 5% (14 days)	Urine 91-94% (24 hours)

3. Clinical Efficacy:

3.1 Design of Phase 3 Clinical Development Program

The sponsor has submitted four Phase 3 pivotal trials (MS-325-12, -13, -14 and -15) to support [] which covers the following three arterial regions: pelvis, renal and pedal. Table 3.1.1 listed the arteries that were studied. For each trial, a standard dose of 0.03 mmol/kg was tested. In MS-325-15 (pedal region), one additional dose of 0.05 mmol/kg was also tested.

b(4)

Those were open-label and non-contrast (baseline) controlled studies. No placebo groups were used in the trials. The primary efficacy endpoint was the presence of clinically significant stenosis ($\geq 50\%$), which was expressed in terms of sensitivity and specificity at a vessel level, by using X-ray angiogram as the gold standard. Non-contrast MRA imaging protocol at baseline was not standardized across the study sites while MS-325 enhanced MRA imaging protocol was. All MRA images were independently assessed by three qualified radiologists in a blinded fashion. All patients with evaluable X-ray images were included in the primary analysis. If MRA images were missing or uninterpretable, then the **MRA results were considered "inaccurate"** compared with the X-ray angiogram results. Three sets of MS-325 enhanced images (dynamic, steady state and digital subtraction) were presented together in the evaluation while for non-contrast MRA there was only one. Appendix A summarized the key design features of MS-325 Phase 3 clinical development program and a time table for different image procedures.

In addition to three Phase 3 studies, the NDA also included data from two Phase 2 studies. Table 3.1.2 showed the patient's distribution by dose and arterial region.

Table 3.1.1. List of arteries that were evaluated under each Phase 3 study

MS-325-12 (06/1999-09/2001)	MS-325-13 (12/2001-10/2002)	MS-325-14 (03/2002-02/2003)	MS-325-15 (02/2002-02/2003)
Intra-renal abdominal aorta	Intra-renal abdominal aorta	Proximal renal artery (left and right)	Posterior tibial (below the ankle)
Common iliac artery (left and right)	Common iliac artery (left and right)	Distal renal artery (left and right)	Dorsalis pedis
External iliac artery (left and right)	External iliac artery (left and right)		Medial plantar artery
Common femoral artery (left and right)	Common femoral artery (left and right)		Lateral plantar artery

Source Data: CRF in the NDA submission

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Table 3.1.2 Number of subjects in Phase 2 and 3 clinical development program by dose and arterial regions under the investigation

Protocol # (MS-325-	Arterial Region	Placebo	0.005	0.01	0.03	0.05	0.07
Phase 3 Pivotal Trials							
12	Aortoiliac Arteries	--	--	--	268	--	--
13	Aortoiliac Arteries	--	--	--	175	--	--
14	Renal Arteries	--	--	--	136	--	--
15	Pedal Arteries	--	--	--	93	87	--
Phase 2 Dose Range Trials							
02	Carotid and Peripheral Arteries	--	--	14	28	31	--
09	Aortoiliac Arteries	37	44	34	39	40	39

Source Data: Table 5-1 of ISE (page 10)

Reviewer's Comments: *Though MS-325 imaging protocol was standardized, there is a concern over the level of the compliance with the standardized procedure. DSI inspection has revealed that at least two of six sites that were inspected have failed to demonstrate the compliance to a 30-second requirement for the IV dose administration (Please refer to Section 5 of this review for a detailed discussion).*

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3.2 Demographic Information:

Of 672 subjects included in the primary analysis, approximately 60% was 65 year of age or older. The percentages of subjects who were female or white were 34% or 78%, respectively. While 42% of subjects came from the US sites, there was a significant study-to-study variation. For renal and pedal studies, less than ten percent came from the US sites (Table 3.2.1).

Table 3.2.1 Demographic characteristics of individual Phase 3 studies

Variables	MS-325-12	MS-325-13	MS-325-14	MS-325-15	Total
	(N=268)	(N=175)	(N=136)	(N=93)	(N=672)
Mean Age (range)	65 (33-87)	65 (29-83)	60 (21-80)	68 (43-91)	65 (21-91)
% with > 65	56	59	46	61	56
% male	70	65	57	69	66
% Caucasian	75	97	71	66	78
% US subjects	89	36	6	7	42
Number and percentage of patients having at least 1 interpretable image by XRA	251 (94%)	173 (99%)	127 (94%)	80 (86%)	631 (94%)

Source Data: Modified from Table 8-1 and 8-2 ISE (page 837) and sponsor's response dated 15 September 2004

3.3 Primary Efficacy Results:

Based on the blinded assessment of all (X-ray, non-contrast MRA and contrast enhanced MRA) images by three independent radiologists, **the sponsor's original analyses showed that MS-325 was associated with the statistically significant improvement in specificity in — arterial regions, and the sensitivity in pelvic r** —. The increases in sensitivity and specificity were estimated at 20% and 12%, respectively, in pelvic region,

b(4)

Reviewer's Comments: *Those seemingly positive results, however, were based on a data imputation method, in which all non-interpretable MRA images were treated as "inaccurate". Since much higher percentage of the vessels in non-contrast MRA images (up to 41% in some regions) at baseline were non-interpretable, compared to that (<3%) in MS-325 enhanced MRA images (Appendix C: Table C-1), the Sponsor's data imputation method allowed a "greater" decrease in both sensitivity and specificity at baseline, which may result in artificial improvement of MS-325 enhanced MRA images. Though this data imputation method was pre-defined, it cannot be accepted as a valid method.*

The new analyses, conducted by the Sponsor and our statistical reviewer using two alternative data imputation methods, have consistently failed to demonstrate, with the required statistical certainty, that MS-325 enhanced MRA outperforms non-contrast baseline MRA in terms of sensitivity and specificity (Appendix C: Table C-2). The alternative data

imputation methods are as follows (Please refer to Table 1.2.0.1 of statistical review for a detailed description of the new analyses and the results):

- The Interpretables Scenario, in which the statistics were calculated only for vessels which were interpretable for both non-contrast images at baseline and MS-325 enhanced contrast images post dosing;
- Pre=Post Scenario, in which the non-interpretable non-contrast images at baseline are assigned the same diagnoses as their contrast-enhanced interpretable counterparts.

Reviewer's Comments: *In a response to the Division on 22 October 2004, the Sponsor argued that the statistically significant improvement in sensitivity or specificity alone (not both as originally planned) could serve as sufficient evidence for efficacy determination. In the new analyses, statistically significant improvement was observed in pelvic region for the sensitivity, [] (Appendix C: Table C-2).*

b(4)

Statistically significant improvement may not be a clinically significant one. All studies have been powered to detect 10-15% improvement in both sensitivity and specificity, however only sensitivity at pelvic region (Study #13) []

[] appeared to reach that level with a reasonable certainty. Even in those cases, the lower boundary of 95% CI for the sensitivity or the specificity of MS-325 enhanced MRA failed to reach 80%, the minimal performance level used to determine the clinical usefulness of the contrast-enhanced MRA procedure.

b(4)

One of the reasons to set up this minimal performance level is to address the concern that it is already possible to artificially maximize the sensitivity or specificity of a diagnostic procedure at the expense of the other component. This 80% minimal performance level reflects our experience with other drug products for the similar indication, and level of risk that we are willing to take in determining whether a contrast enhanced MRA is clinically useful at this time.

Even if there were no requirements for the demonstrating clinical significance of the observed improvement or for meeting the minimal performance level, we still do NOT have a sufficient assurance on the validity of the observed improvement from those two alternative analyses. The key deficiency is the lack of a standardized non-contrast MRA imaging protocol at baseline across different clinical sites, designed to achieve an optimal performance at baseline. The possibility that the improvement in sensitivity or specificity may be due to a sub-optimal performance of non-contrast MRA at baseline cannot be reasonably excluded.

The variation in the rate of non-interpretable baseline MRA images at different clinical sites was substantial (Appendix D: Table D-1). For example, in the study MS-325-13, two of the sites (68# and #77) employed two different baseline MRA imaging protocols. For one site, the most of the images were interpretable but for the other site, none of the images were interpretable (Appendix D: Table D-2).

In 22 October 2004 response to the Division, the sponsor attempted to address this issue by examining the performance of baseline MRA by one of the key MR sequence parameters (TR). The validity of this approach cannot be determined at this time until we have full understanding on the ranges of all key MR sequence parameters that were used in the clinical trials.

In summary, this NDA lacks substantial evidence to support the efficacy of MS-325 because all four clinical trials have failed to demonstrate, with the required statistical certainty, that MS-325 enhanced MRA outperforms baseline non-contrast MRA in terms of sensitivity and specificity as originally planned. In those arterial regions where the improved sensitivity or specificity was observed, either clinical significance of the improvement was questionable or MS-325 enhanced MRA failed to reach the minimal performance level. In addition, there is no adequate assurance that non-contrast MRA protocols at baseline were designed to achieve an adequate and optimal performance level.

Reviewer's Comments: *Apparently the sponsor needs to conduct new trial(s) to demonstrate the efficacy of this product. Based on the findings of this review, here are key clinical comments regarding the design and conduct of new trials:*

- It is particularly important to have a standardized baseline non-contrast imaging protocol to ensure the optimal performance of baseline imaging in those new trial(s). All non-interpretable baseline images should be repeated. The sponsor also needs to enhance the monitoring of compliance with the protocol because of the findings from DSI inspection. I am afraid that those non-compliance observed from the current trials may have contributed to suboptimal performance of MS-325 enhanced MRA procedure;*
- I have no objection to a reread of the current studies #12 and 13 into one new study if the re-read is restricted to only those subjects whose non-contrast MRA imaging protocol (key parameters) at baseline are judged to be optimal, and reread is designed to achieve both clinically significant improvement over baseline and a minimal performance level.*
- I would suggest that the dynamic and steady state images be read separately. There was some preliminary evidence suggesting that steady state images may have a negative impact on the sensitivity and specificity (Table 3.3.1). Based on the 22 October 2004 response from the Sponsor, the majority decision from the current blinded read (>75%) was based on the steady-state images when both dynamic and steady-state images were presented together for the evaluation. This finding may also partially explain the suboptimal performance of MS-325 enhanced MRA in current clinical trials.*

*The Sponsor should be reminded that failure to **demonstrate an "added"** clinical value of steady-state images alone may have some negative impact on the evaluation of risk/benefit ratio since MS-325 has a much longer half-life than other approved MRI contrast agents.*

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Table 3.3.1 The performance of dynamic or steady state images, compared to that of pre-contrast MRA (Institutional Reader)

Measurements	Pre-Contrast	Post-Contrast	
		Dynamic	Steady State
Sensitivity	63.7	73.2	51.4
Change from pre-contrast	--	9.6	-12.3
p-value (# of patients = 168 and number of vessels = 366)	--	0.009	0.007
Specificity	62.6	81.1	68.5
Change from pre-contrast	--	18.5	5.9
p-value (# of patients = 266 and number of vessels = 1474)	--	<0.001	0.012

Source Data: Modified from Table E-9.1a and E9.1b of the Study Report of MS-325-12 (page 3054-3055)

4. Clinical Safety:

4.1 Drug exposure

A total of 1,438 subjects, including 1,321 patients and 117 healthy volunteers, have received at least one dose of Ms-325. In comparison, 79 subjects, including 49 patients and 30 healthy volunteers, were treated with placebo. Of 1,321 MS-325 treated patients, 1,203 (91%) were with vascular disease, and 767 (58%) received the proposed clinical dose of Vasovist (0.03 mmol/kg). The highest two doses tested in the clinical programs were 0.15 mmol/kg (n=6) and 0.10 mmol/kg (n=71).

Reviewer's Comments: Size of safety database appears to be adequate.

4.2 Demographic

Of 1,321 patients who received at least one dose of MS-325, 865 (66%) were male, 638 (48%) 65 years of age and older, and 1,055 (80%) Caucasian. Table 4.2.1 summarizes the demographic characteristics by dosing group (including placebo patients).

Table 4.2.1 Demographic characteristics by dosing groups, including placebo group

Variables	Placebo (n=49)	MS-325 (mmol/kg)				Total (n=1,321)
		<0.03 (n=95)	0.03 (n=767)	0.05 (n=348)	>0.05 (n=111)	
Mean Age	63	64	64	60	62	63
% with ≥ 65	39	46	54	36	45	48
% male	74	75	66	60	72	66
% caucasian	90	91	79	78	86	80

Source Data: Modified from Table 6-1 ISS (page 8-45470).

The majority (93%) of MS-325 treated patients (n=1,321) reported cardiovascular abnormalities, including coronary artery disease (53%), and hypertension (63%). 440 (33%) had diabetes, 321 (24%) had cholesterol abnormalities, and 294 (22%) were smokers. In addition, 1,259 (95%) received concomitant medications, including ASA, b-blockers, statin drugs, ACE inhibitors etc.

4.3 Death and other (non-fatal) serious adverse events:

During the clinical development program, 13 patients were reported to have experienced serious adverse events, including three fatal ones. Two death cases occurred in MS-325-09 (Phase 2 dose ranging study) and one in MS-325-18 (Phase 2 PK study in subject undergoing chronic hemodialysis). All deaths and other (non-fatal) serious adverse events occurred in MS-325 treated group. Table 4.3.1 and 4.3.2 show the characteristics of the patients who have experienced fatal or non-fatal serious adverse events, respectively.

Table 4.3.1 Characteristics of three patients who have experienced fatal SAEs in MS-325 clinical development program

ID	Protocol #	Age/Sex	Rx Group (mmol/kg)	Cause of Death	Time of death	Study Site	Assessment by PI
09/14/04	09	66/F	0.005	Myocardial Infarction (one hour post dosing)	8 days	USA	Unlikely
09/01/14	09	80/M	0.07	Cardiac event	3 days	USA	Possible
18/01/02	18	53/F	0.05	Unknown	15 days	USA	Unlikely

Source Data: Modified from Appendix 20.1 of ISS and MO review.

Table 4.3.2 Characteristics of 10 patients who have experienced non-fatal SAEs in MS-325 clinical development program

Patient ID	Protocol #	Age/Sex	Rx Group (mmol/kg)	SAEs	Time of Onset	Study Site	Assessment from PI
09/01/29	09	77M	0.005	Syncope	30 hours	US/Canada	Possible
09/22/18	09	69M	0.07	Syncope	3 days	US/Canada	Unlikely
09/09/06	09	60F	0.05	Chest Pain/ER/Prolonged QT	27 hours	US/Canada	Possible
12/38/07	12	63M	0.03	Chest Pain/PTCA	1 day	US/Canada	Unlikely
15/81/02	15	75M	0.05	Myocardial Infarction/CABG	3 days	Germany	Unlikely
09/01/17	09	64M	0.05	Hypersensitivity	30 minutes	US/Canada	Possible
13/136/03	13	66F	0.03	Anaphylactoid reaction	1 minutes	Germany	Possible
07/02/05	07	64/M	0.05	Abdominal Aortic Aneurysm	13 days	US/Canada	Unlikely
12/04/03	12	64M	0.03	Hyperglycaemia Coronary artery disease aggravated	3 days 6 days	US/Canada	Unlikely Unlikely
12/20/12	12	72M	0.03	Gangrene of Toes on left Foot	83 minutes	US/Canada	Unlikely

Source Data: Modified from Appendix 20.1 of ISS and MO review

Three fatal cases are briefly summarized as follows:

Patient 09/14/04, a 66-year-old, morbidly obese white female with severe COPD, hypertension, and diabetes mellitus with lower extremity ulcers, received 0.005 mmol/kg study drug on –
] one day after surgical debridement bilaterally to both lower legs. One and half hours after the dosing, the patient developed bradycardia with ECG evidence of an inferior MI.

b(6)

Subsequently, she sustained a cardiac arrest and developed multiorgan system failure and died eight days later.

It was noted that the ischemic changes were noted on a March 2000 ECG. Prior to receiving study drug, the patient was found to have oxygen desaturation with room air values of as low as 72%. The sponsor believes that this was probably related to her underlying disease along with multiple doses of IV narcotic given for pain.

Patient 09/01/14, an 80-year old, black male with a past medical history of peripheral vascular disease, COPD, longstanding diabetes mellitus (type 1), and a known abdominal aortic aneurysm (approximately 7 cm), received one dose study drug at 0.07 mmol/kg on [redacted] Safety monitoring, including vital signs and ECG, immediately and again 24 hours post dosing and revealed no significant concerns. Only notable change was the decrease of hemoglobin to 10.4 g/dl at 24 hours post dosing from the baseline value. Patient died three days later as noted by the Emergency Medical Services. The Medical Examiner office reports that there were no signs of trauma or distress on the deceased. The immediate cause of death was atherosclerotic cardiovascular disease and the manner of death was listed due to natural causes. No autopsy was performed. This SAE (arteriosclerosis) was deemed as severe and possibly related to study drug by the investigator. b(6)

Patient 18/01/02, a 53-year old, black female with a medical history of long standing diabetes, end-stage renal disease (on dialysis), and hypertension, received 0.05 mmol/kg study drug on [redacted] Ten days later she was hospitalized and treated with Vancomycin for osteomyelitis and retropharyngeal infection and later died at home for unknown reason. The Medical Examiner planned to do an autopsy but the family refused to grant permission. The investigator determined the AE unlikely related to MS-325. b(6)

Reviewer Comments: *The causality assessments for death and SAE are often difficult because of their low frequency. It is particularly challenging in the case of MS-325 because of the lack of an adequate control group (it is quite common in the studies of imaging products) and because almost all subjects were elderly with many underlying medical conditions, cardiovascular disorders in particular, and were taking multiple concomitant medications. These patients are prone to developing syncope, chest pain, MI, and/or other cardiovascular events.*

I have reviewed both primary medical officer's assessment and summary description provided by the sponsor under ISS Appendix 20.1 of the NDA submission. My main conclusions are as follows:

- I see no compelling evidence at this time to support a direct causal relationship between MS-325 and death/serious adverse events except for hypersensitivity reactions. Two patients appeared to experience mild urticaria and itchiness and resolved quickly after IV antihistamine treatment without any negative consequence. It does not appear that the events met the definition of a serious adverse event though they were reported as SAEs. I believe that this issue can be successfully resolved through product labeling, such as requesting a warning statement under the appropriate section of the labeling.*

- *Whenever syncope was reported, a comprehensive review of the drug's potential to cause QT prolongation is warranted. QT prolonging effect has been studied both pre-clinically and clinically, including two Phase 1 placebo-controlled studies. I have not seen any consistent safety signals at this time. While an QT prolonging effect can never be ruled out with an absolute certainty, the possibility of MS-325 at the proposed dose to cause a clinically significant QT prolongation, in my opinion, is quite low after taking the totality of evidence into consideration (please refer to the Section 4.7 of this review for a detailed discussion). It is worth noting, however, that one of the syncope patients (09/22/18) experienced an episode of non-sustained episode of ventricular tachycardia rhythm while being hospitalized for syncope. The primary MO expressed the concern that drug-induced ventricular tachycardia might be the reason for syncope. While it was possible that syncope was associated with ventricular tachycardia, it is far from certain on whether MS-325 played any role in inducing the cardiac event. Given the lack of significant QT safety signal, the implication of this event is limited at this time unless there is a clear biological pathway or mechanism.*
- *There were two cases of chest pain and two cases of MI (including one fatal case), requiring medical or surgical intervention within three days post dosing. While I do not see any compelling evidence suggesting a direct causal relationship, the finding of hemoglobin drops in at least two cases prior to the events were not reassuring. The relationship between MS-325 and acute hemoglobin drop should further explored and studied prior to the drug approval (Please refer to Section 4.5-A for a detailed discussion).*
- *The primary MO reviewer also expressed the concern over possibility of Gd-transchelation and its relationship with death and SAEs. While I see no compelling evidence for such a relationship, I agree that in-vivo stability of MS-325 has not been adequately demonstrated. Reevaluation of death and SAEs, cardiovascular events in particular, may be warranted when that information is available from any future resubmission.*

4.4 Common adverse events:

A total of 1,292 adverse events were reported in 1,321 MS-325-treated patients. Of those, 571 (43%) experienced at least one adverse event (AEs) and 170 (13%) experienced more than two AEs. There was a dose-related increase in the overall percentage of patients experiencing AEs, which ranged from 25% in <0.03 mmol/kg dose group, 36% in 0.03 mmol/kg dose group, 53% in 0.05 mmol/kg dose group to 78% in >0.05 mmol/kg dose group. Table 4.4.1 showed a dose-response in the frequency of AEs in MS-325 treated patients and healthy volunteers, respectively.

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Table 4.4.1 Percentage of subjects experiencing at least one AE by dose group in healthy volunteers and patients with cardiovascular disorders

Type of Subjects	Placebo	MS-325 Treated Groups (mmol/kg)				Total
		<0.03	0.03	0.05	>0.05	
Healthy Volunteers	60% (n=30)	36% (n=14)	70% (n=10)	74% (n=57)	83% (n=36)	72% (n=72)
Patients	47% (n=49)	26% (n=95)	36% (n=767)	53% (n=348)	78% (n=111)	43% (n=1321)

Source Data: Modified from Table 7-1 and 7-4 ISS (page 28 and 31).

Reviewer Comments: Based on the frequency shown in Table 4.4.1, the sponsor has concluded that "these results suggest that patients, including those with known or suspected vascular disease do not experience an increased frequency AEs upon MS-325 administration". I consider this conclusion premature. The seemingly higher AE frequencies observed in healthy volunteers may be due to the longer follow-up period in the studies involving healthy volunteers, which could last as long as 21 days. The typical follow-up period for the patients was 72 hours.

Of 767 patients who received the proposed clinical dose of 0.03 mmol/kg, 276 (36%) reported a total of 511 adverse events (AEs). Table 4.4.2 showed the number and percent of the patients who have experienced AEs that occurred at a frequency of >1 % among all patients received MS-325. As the comparisons, the AE frequencies in the patients who received 0.03 mmol/kg dose only, and in a subgroup of patients in Study MS-325-09 with a placebo group were also presented.

Table 4.4.2 List of common adverse events with a frequency > 1% from all MS-325 treated patients

Adverse Events (Preferred Term)	All patients received MS-325 (N=1,321)	All patients received MS-325 0.03 mmol/kg (N=767)
Pruritus NOS	99 (7.5%)	38 (5.0%)
Headache NOS	77 (5.8%)	33 (4.3%)
Nausea	70 (5.3%)	32 (4.2%)
Vasodilatation	68 (5.1%)	25 (3.3%)
Paresthesia	80 (6.1%)	21 (2.7%)
Injection site bruising	22 (1.7%)	19 (2.5%)
Burning sensation NOS	61 (4.6%)	15 (2.0%)
Venipuncture site bruising	21 (1.6%)	17 (2.2%)
Dysgeusia	44 (3.3%)	17 (2.2%)
Hypertension NOS	17 (1.3%)	11 (1.4%)
Dizziness (excl Vertigo)	24 (1.8%)	8 (1.0%)
Feeling cold	22 (1.7%)	6 (0.8%)
Rash NOS	16 (1.2%)	3 (0.4%)
Diarrhea NOS	15 (1.1%)	4 (0.5%)

Source Data: Modified from Table 7-7 of ISS (page 36)

Of 511 adverse events in 0.03 mmol/kg group, 249 (49%) occurred within 2 hours of MS-325 injection and 132 (25%) within >2 and <24 hours. One-third of all AEs resolved within 5 minutes of onset and 56% within 2 hours.

Reviewer's Comments: *The most common AEs in 0.03 mmol/kg groups were headache, nausea and vasodilatation. Based on the AE information contained in the product labeling of other Gd-based MRI agents, the AE profile of MS-325 appears to be comparable though MS-325 appeared to be associated with a higher frequency. It is not clear whether this seemingly higher frequency was a result of a longer elimination half-life of MS-325 or longer period of follow-up for AEs in MS-325 trials. The primary MO also noted in her review that pattern of common AEs may resemble that of generalized cholinergic stimulation. However, regardless of the reasons, the fact that approximately 50% of AEs occurred within 2 hours of administration, including vasodilatation, nausea/vomit and headache/dizziness in particular, provided a good window opportunity to monitor and manage those AEs at a supervised clinical setting. [*

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should be part of the labeling negotiation with the sponsor.] This

It is worth noting that the number of AE reported from US sites was significantly higher than that from the foreign sites (1.2 vs. 0.57 events per patients from US and foreign sites respectively).

4.5 Laboratory Findings:

In MS-325 clinical development program, the laboratory tests that were routinely performed included:

- Hematology and coagulation
- Blood chemistry, including ALT and AST
- Urinalysis
- Metals

While the tests have been performed at baseline and multiple time points post dosing, the following time points were selected for the analysis because they represented the most frequently used data collection points:

- Baseline
- 2 hours post dosing
- 24 hours post dosing
- 72 hours post dosing

There were little evidence to suggest that MS-325 could affect AST/ALT and creatinine. The monitoring of laboratory values, however, appeared to suggest a trend of decline for hemoglobin, hematocrit, RBC, platelets and calcium and an increase for serum glucose (Table 4.5.1).

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Table 4.5.1. Baseline and mean change from baseline in hemoglobin, hematocrit, RBC, platelets and serum glucose for all patients who received MS-325 regardless of dosage

Variables (Normal values)	Baseline	Change from Baseline		
		2 hours post dose	24 hours post dose	72 hours post dose
Serum Glucose (70-115 mg/dL)	121.1 (n=1,277)	9.9 (n=1,204)	6.2 (n=1,178)	-0.3 (n=1,168)
Calcium (8.4 – 10.3 mg/dL)	9.5 (n=1,293)	-0.1 (n=1,243)	0 (n=1,215)	-0.1 (1,203)
Hemoglobin (12.5-17 g/dL)	14.2 (n=1,253)	-0.1 (n=1,162)	-0.3 (n=1,137)	-0.4 (n=1,120)
Hematocrit (37.0-51.0%)	42.2 (n=1,232)	-0.4 (n=1,115)	-0.9 (n=1,088)	-1.4 (n=1,084)
RBC (4.0-5.8) X 10 ⁶ /uL	4.5 (n=1,253)	0.0 (n=1,162)	-0.1 (n=1,137)	-0.1 (n=1,120)
Platelets (140-400) X10 ³ /uL	261.9 (n=1,238)	-3.6 (n=1,133)	-2.9 (n=1,116)	-2.5 (n=1,090)

Source data: Modified from ISS Table 8-2 (page 59) and Table 8-7 (page 66)

Reviewer Comments: The pattern of the change of serum glucose appeared to suggest a potential but temporary interference of MS-325 to serum glucose level. □

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Since mean change is not a good indicator for assessing the clinical significance of the changes, a detailed safety analyses were conducted to assess the potential impact of MS-325 on hemoglobin or calcium.

A. Hemoglobin:

Due to the potential safety signal identified from mean analysis, an outlier analyses was conducted to assess the impact of MS-325 on hemoglobin by using the safety datasets provided by the sponsor. In the analysis, the clinically significant change in hemoglobin was defined as a drop of 2 gm in hemoglobin from baseline at any time within 72 hours post dosing. Table 4.5.2 showed the results of this analysis.

Table 4.5.2 Number and percent of subjects with an at least 2.0 gm drop in hemoglobin from baseline within 72 hours post dosing of MS-325, by type of subjects.

Dose Group	Patients			Healthy Volunteer		
	N	N	%	N	n	%
<0.03 mmol/kg	93	2	2.1%	14	0	0
0.03 mmol/kg	720	18	2.5%	10	0	0
0.05 mmol/kg	334	10	3.0%	57	1	1.8%
> 0.05 mmol/kg	106	3	2.8%	36	0	0
Placebo	78	0	0	30	0	0
Total	1,301	33	2.5%	147	1	0.7%

Source Data: Independent analysis based on dataset submitted in NDA

The results showed that approximately 2.5% MS-325 treated subjects experienced an acute hemoglobin drop within 72 hours of dosing. Among 34 subjects who have experienced at least 2 gm drop in hemoglobin, 4 (12%) occurred at 2 hours, 8 (24%) at 24 hours, and 22 (64%) at 72 hours post dosing. Appendix E showed the subject's demographic information and baseline/change from baseline at each time points post dosing.

Reviewer's Comments: The sponsor responded to our concern in 22 October 2004 submission. The sponsor has argued that:

- (1) Pooled analysis of all clinical trials of the target population showed that the mean decrease in MS-325 treated subjects (n=1,253) were similar to that of placebo group (n=48). The decreases were -0.1, -0.2 and -0.3 gm/dL at 2-hours, 24-hour and 72-hour post dosing in placebo group vs. -0.1, -0.3, and -0.4 gm/dL for MS-325-treated group, respectively.
- (2) There were two cases of acute hemoglobin drop in placebo group of the clinical trials involving healthy subjects (Subject #428 and 519 in Study MS-325-01C);
- (3) Since most patients had an acute hemoglobin drop at 72 hours posting dosing, which were likely due to hydration that patients received prior to XRA procedure (10 of 34 subjects had the procedure at Day 3 post MS-325 dosing).

Due to the concerns over heterogeneity of pooled population, I have restricted the mean analysis to study MS-225-09 – the only randomized, placebo-controlled and dose-ranging study in the target population. Table 4.5.3 showed the results of this analysis. Data appeared to suggest that MS-325 may have a negative affect on hemoglobin level which could last for at least 72 hours post dosing, and the effect appeared to be dose related. The underling cause for such a potential effect is not well understood at this time. I am concerned about any potential impact of this drop on cardiac patients with abnormal hemoglobin level at baseline. While this issue may be resolved

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additional data from hemoglobin measurement beyond 72 hours and requiring the demonstration of relative stability of MS-325 in vivo will enhance the safety use of this product.

Table 4.5.3 Baseline and mean change from baseline in hemoglobin level (gm/dL) by dose of MS-325, including placebo group (Study MS-325-09)

Hemoglobin Level (gm/dL)	Placebo n=38	MS-325-Treated Group (mmol/kg)				
		0.005 n=44	0.01 n=34	0.03 n=39	0.05 n=43	0.07 n=40
Baseline	14.4	14.3	14.2	14.2	14.5	14.6
2-hours change	-0.08	0.04	-0.04	-0.28	-0.15	-0.07
24-hour change	-0.23	0.05	-0.25	-0.28	-0.33	-0.24
72-hour change	-0.32	-0.25	-0.29	-0.45	-0.40	-0.76

Source data: Modified from Table S5.1-5.6 of Study Report of MS-325-09

B. Serum calcium level:

In the product labeling of other Gd-based MRI agent, there was concern that Gd-based MRI agents may affect calcium measurement. To address the potential concern over the trend of

decreased calcium level from baseline in MS-325 treated patients (Table 4.5.1 of this review), the sponsor included a pooled analysis, comparing all MS-325 treated patients at different doses (n > 1,200) with that of placebo (n=49). The results showed that placebo group had a “larger” decrease from baseline in serum calcium level within 72 hours post dosing and there were lack of dose-response effects. Those results were presented in Table 8-14 of ISS of the NDA submission and section of 7.1.7.5 of the primary MO review.

Reviewer Comments: Again I am concerned that the heterogeneity among the pooled patient population may conceal the potential safety signal. I have restricted the analysis to study MS-225-09 – the only randomized, placebo-controlled and dose-ranging study in the target population. Table 4.5.4 showed the results of this analysis. Data appeared to suggest that MS-325 may have a negative affect on serum calcium level at 2 hours post dosing. 24-hour and 72-hour data were inconsistent. In addition, 71 MS-325 treated subjects were found to have hypocalcaemia within 72 hours post dosing (Appendix F). Hypocalcaemia is a clinically significant event and cause of those events, relationship to potential MS-325 stability issue in particular, should be further studied.

Table 4.5.4 Baseline and mean change from baseline in serum calcium level (mmol/L) by dose of MS-325, including placebo group (Study MS-325-09)

Serum Calcium Level (mmol/L)	Placebo n=38	MS-325-Treated Group (mmol/kg)				
		0.005 n=44	0.01 n=34	0.03 n=39	0.05 n=43	0.07 n=40
Baseline	2.346	2.363	2.359	2.324	2.340	2.358
2-hours change	-0.017	-0.020	-0.051	-0.061	-0.026	-0.021
24-hour change	-0.017	0.014	0.012	0.019	0.002	0.009
72-hour change	0.008	-0.033	0.004	0.011	0.001	-0.054

Source data: Modified from Table S4.1-4.6 of Study Report of MS-325-09

C. Urine zinc level:

In one of the Phase 2 PK studies (MS-325-16), the sponsor collected 24-hour urine for the measurement of Zinc level at baseline, and the two periods post dosing (1-24 hours and 49-72 hours) in 10 healthy subjects received 0.03 mmol/kg, and 10 healthy subjects received 0.05 mmol/kg MS-325. Table 4.5.5 showed the results of urine zinc excretion by dose and time point.

Reviewer Comments: Urine zinc excretion may be a potential indicator for the degree of Gd-transchelation in vivo. It may serve as a surrogate for measuring MS-325 in-vivo stability. Data clearly shows increase zinc excretion post dosing. The increase appeared to be dose-related and it can last for at least 72 hours. There were at least two limitations in the study design which greatly reduced the value of this study in demonstrating that relative stability of MS-325, compared to other MRI contrast agent: (1) lack of a direct comparison group; and (2) insufficient time points for urine collection. Such assurance is important because of the long-half time of MS-325, potential use in the renal insufficient patients, and the lack of demonstration of “added” clinical value of steady-state image at this time.

The sponsor should be required to provide data to demonstrate relative stability of MS-325 in vivo, compared to that of an approved MRI agent. The detailed requirements are discussed in Executive Summary of this review.

Table 4.5.5 Urine zinc excretion in 24-hour pooled urine samples in healthy subjects received two different doses of MS-325.

Time Point	MS-325 0.03 mmol/kg			MS-325 0.05 mmol/kg		
	N	Mean	Change	N	Mean	Change
Baseline	10	556	--	10	554	0
24 hours post-dose	10	837	281	10	1856	1,302
72 hours post-dose	10	622	66	10	622	68

Source data: Table 12-6 of Study Report of MS-325-16

4.6 Vital Signs:

There was a general trend of suggesting the decrease in systolic and diastolic blood pressures and the increases in heart rates with 72 hours post dosing among 764 subjects received the proposed clinical dose of MS-325. The mean changes, appeared to be small (Table 4.6.1).

Table 4.6.1. Baseline and mean change from baseline in systolic/diastolic blood pressure and heart rates for all patients who received clinically proposed dose of MS-325 (0.03 mmol/kg and n= 764)

Variables	Baseline	Change from Baseline		
		2 hours post dose	24 hours post dose	72 hours post dose
Systolic blood pressure (mmHg)	143.0	-2.1	-3.9	-3.1
Diastolic blood pressure (mmHg)	77.3	-1.0	-2.0	-0.9
Heart rate (bpm)	71.5	1.0	1.4	1.0

Of all MS-325 treated subjects in phase 2 and phase 3 trials, 19 subjects experienced oxygen Sat. drop to below 90 within 15 minutes of MS-325 administration (Appendix G). In a response dated 11 June 2004, the sponsor argued that of 19 subjects, 13 had a baseline oxygen Sat. measurement of below 95%. The primary MO reviewer was particularly concerned about the fact that two subjects had a post-dosing reading of below 75% but the events were not reported as SAEs. The sponsor did provide the data to support that the **patients' vital signs were stable within 10 minutes** of dosing though it is not certain whether the measurements was taken at the time of oxygen Sat. measurement. Also two principal investigators have certified in writing that those two patients were stable during the procedure and the readings were likely due to measurement errors.

Reviewer Comments: It is likely that many patients indicated for MRA takes anti-hypertensive treatment. ☹

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While I shared the concerns over oxygen Sat. change, I felt that there is little need for a further investigation. [

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4.7 ECG:

A. QT safety:

The primary MO reviewer noted that of 693 MS-325 treated patients in Phase 3 programs, 81 (11.6%) patients had a total 99 episodes of QTc increase over 30 ms and 12 over 60 ms. In addition, there were two reported cases of non-sustained ventricular tachycardia, one of which was associated with syncope. It was suggested that QTc safety issue should be studied as Phase IV commitments.

Reviewer Comments: It is well known that the daily variation of QTc could be more than 60 ms and the ventricular tachycardia could be due to the underlying conditions of the patients. The key question here is whether there is sufficient evidence to rule out the possibility of a significant QT effect from the administration of clinical relevant dose of MS-325. The sponsor responded to our concern on March 30, 2004 with data from two phase 1 studies in healthy subjects. Though they were not prospectively defined QT safety study as required in FDA's draft guidance on QT assessment, they contained many key design figures:

- (1) placebo controlled
- (2) blinded and manually read by a cardiologist
- (3) ECG were taken at baseline and multiple time post baseline

Table 4.7.1 showed mean QTcF change from baseline at each time point post baseline from those two Phase 1 placebo-controlled studies. The smaller QTcF change from baseline observed in MS-325 groups compared to that in placebo group, the magnitude of QTcF change from baseline, and the consistency of data from the trials, in my opinion, provide a reasonable assurance that MS-325 at the proposed clinical dose is unlikely to produce a clinically significant QTc change in the healthy subjects.

*I see no reason to require a prospectively **designed "thorough QT" study at this time** given the evidences that were presented and the single-use nature of this product. This conclusion, however, could be reevaluated if future clinical data showed increased concern over MS-325 stability in vivo, compared to that of other Gd-based MRI contrast agent because the current QT studies, by containing no positive control, cannot rule out possibility of significant drug-induced QT prolongation with the highest degree of certainty.*

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Table 4.7.1 Mean QTcF (Fridericia's) change from baseline at each time point post baseline from two phase 1 placebo controlled studies

Time Post Dosing (Hours)	MS-325 (n=18)	Placebo (n=9)	MS-325 (n=42)	Placebo (n=21)
Baseline	375 ms	379 ms	381.3 ms	375.6 ms
0.25	1.5	1.5	5.1	2.0
1	-0.1	-2.1	0.2	0.6
3	1.2	4.0	1.9	-0.1
6	8.2	12.6	-2.6	3.2
24	2.5	-8.3	-2.4	2.8
36	7.1	3.8	-4.4	-3.7
72	7.2	10.4	4.2	2.6

Source data: Modified from Tables 1.1F -2.4F of 30 March 2004 submission

B. Ventricular Tachycardia:

Two cases of non-sustained episode of ventricular tachycardia are summarized as follows:

Case #1:

- Study MS-325-09 (Phase 2 Study)
- 69 year-old male with prior history of CVA (1993) and hypertension
- Received MS-325 0.07 mmol/kg on []
- Three days later, hospitalized for syncopal episode and experienced a non-sustained episode of ventricular tachycardia of 10-15 beats while in hospital. No MI.
- Ventricular tachycardia was not reported as AE

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Case #2:

- Study MS-325-07 (Renal Study)
- 47 year-old healthy male (#2042) taking no medications
- Received MS-325 0.05 mmol/kg on June 26, 2002 (7:40 AM)
- 24 hours later, Holter monitoring showed very rare PAVs, PVCs (including one triplet and one four-beat run of ventricular tachycardia)
- Patient had no symptoms and reported as mild AE

Reviewer's Comments: *Since there is reasonable assurance on QT safety, the possibility of those events being the drug-induced via a QT prolonging mechanism is reasonably low. While it is more likely that patient's underlying condition may have contributed to those events, additional assurance is needed given the fact that those events occurred within 72 hours posting dosing and MS-325 has a relatively long half life. In my opinion, the demonstrating relative stability of MS-325 in vivo will provide the needed assurance.*

5. Relevant Issues from other Disciplines, Consults, or Regulatory Matters

5.1 Clinical Pharmacology and Biopharmaceutics (OCPB)

In his draft review dated 3 December, 2004, Dr. John concludes the following:

- OCPB finds this application acceptable from a clinical pharmacology and biopharmaceutics perspective provided that the sponsor demonstrates the in-vivo stability of Vasovist in the patients with renal insufficiency by comparing the amount of zinc-fosveset and calcium-fosveset in the urine collected as compared to healthy volunteers.

In addition, we recommend that total calcium and free calcium ion concentration in the plasma be studied.

- The mean QTc values did not show an appreciable increase as compared to the placebo group. The placebo and the test group did show mean QTc increase of greater than 10 msec in some patients. A label warning about Vasovist effect on QTc is warranted.

Reviewer's Comments: *Clinical pharmacology team raised the same issue of MS-325 in-vivo stability but focused on the potential impact in renal insufficient patients. The issue is important because OCPB review indicated that "the half-life increased from 19 hrs in normal subjects to 49 hours in patients with moderate renal impairment and to 70 hours in patients with severe renal impairment".*

Unless new information supports a "thorough QT" study, I believe that any uncertainty on QT safety can be resolved through labeling. The final wordings cannot be determined at a later time.

5.2 Biometrics

In his Biometric draft review dated 30 November 2004, Dr. Mucci concludes the following:

- **The Sponsor's results in three of** the four studies (two peripheral, ——— achieved this goal for at least two of the three readers, but only under conditions which the Agency found arguable. The problem was the following: A significant feature in all four studies was the percentage of uninterpretable vessels for Baseline image reads (ranging from 10% to 40% across studies), as contrasted with less than 2% for Enhanced image reads.
- The protocols for the various studies do not include rigorous, across centers, specifications for Baseline imaging procedures; consequently the assumption that Worst Outcome is the appropriate imputation for uninterpretable reads is questionable.

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Dr. Mucci has conducted extensive analyses by using alternative imputation schemes. In the end, he concludes that **"under each of these alternative imputation schemes the statistics no longer support the claim that Vasovist MRA outperforms Baseline MRA."**

Reviewer's Comments: *The biometrics team identified the same deficiencies related to inappropriate data imputation scheme and lack of standardization for baseline imaging procedures.*

5.3 Pharmacology/toxicology

Base on the currently available draft review dated 2 December 2004, the pharmacology/toxicology reviewer concluded that **"the preclinical studies** conducted support safety and efficacy (measured by relaxation rates). No **additional studies are required"**. MS-325 is recommended to be approved.

The labeling changes to the following four sections were proposed:

1. Drug Interactions
2. Fertility
3. Pregnancy Category
4. Nursing Mothers

It is unclear whether the problem is isolated and whether it contributed to the lack of efficacy of MS-325 in the clinical trials, Study #12 in particular. The sponsor needs to enhance the monitoring of the compliance with the protocol in the future trials.

5.6 Office of Drug Safety/Division of Medication Errors and Technical Support (ODS/DMETS)

Based on the consult dated 10 October 2004, DMETS does not recommend the use of the proprietary name, Vasovist, because of concerns with potential confusion between Vasovist and Magnevist.

Reviewer's Comments: *I defer the final recommendation to a later time. Given the nature of this product's clinical use, I would be reluctant to reject this trade name unless there is a serious safety concern with a high dose of MS-325 from future studies and analyses.*

5.7 Financial Disclosure:

Dr. Tong Li, the primary medical reviewer, conducted a review of all financial disclosure information from required trials. In this regard, she concludes:

"Financial disclosure was made from all required studies. The disclosure appears to be adequate and no evidence suggests that financial relationship had any impact on the study findings".

5.8 Pediatric:

On 30 July 2001, the sponsor submitted a request for waiver of pediatric studies to IND 51,172. The following three reasons were cited to support the request:

- No meaningful therapeutic benefit over existing treatments and is unlikely to be used in a substantial number of pediatric patients;
- Studies are impossible or highly impractical because the number of patients is so small or geographically dispersed;
- **Disease-specific waiver indicated for the treatment of the condition in adults – Arteriosclerosis.**

Reviewer's Comments: *The sponsor provided X-ray angiography use data from both pediatric and adult population in 1998 and 1999 to support the request. The use data even if it is true is clearly out-dated now.*

_____ has provided a written consult to the Division.
In her consult, _____

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_____ believes that "MRA can provide a wealth of morphologic and functional information in an accurate and noninvasive fashion". As a result, "use of MRA in the pediatric patients is likely to continue to increase".

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I recommend this request not be granted. However, I believe that pediatric studies should be deferred to a later time when the efficacy and safety of this product is established in adults given those unresolved safety issues at this time.

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Appendix A
Summary of Phase 3 Clinical Trial Design and Conduct

A. Study Design:

- Open-label and pre-contrast MRA -controlled studies
- No placebo groups were used in the trial;

B. Patient Population

- Male or female patients of 18 years of age or older;
- Patients with known or suspected peripheral vascular disease who were scheduled for X-ray angiogram within 30 days prior or post-study enrollment;
- Patients with a normal creatinine level at baseline and with no history of abnormal renal function in MS-325-12. In other trials, maximum serum creatinine level increased to 2.0 mg/dL, allowing patients with mild renal impairment to participate in the study;
- Patients without any major cardiovascular events within 30 days prior to enrollment.

C. Primary Study Endpoints and the Endpoint Evaluation:

The primary efficacy endpoint was the presence of clinically significant stenosis ($\geq 50\%$), which was expressed as both sensitivity and specificity at a vessel level. The most severe diameter stenosis of each vessel segment was measured and recorded on the electronic CRF. The sponsor also includes accuracy as one of the primary endpoints.

- All images were presented to the readers in a randomized fashion at the core laboratory facility following a prospectively designed blinded read methodology protocol;
- Each study had a completely different set of blinded readers. The blinded readers for the X-ray angiogram (XRA) images were different than the blinded readers who read the interpreted the MRA images;
- The MRA and XRA blinded readers were provided no other clinical information about patients whose images were being evaluated;
- XRA was used as the standard of reference (SOR). XRA images were blindly read by two independent radiologists. If the 2 XRA readers' interpretations disagreed regarding presence or absence of clinically significant stenosis at a given vessel, a third radiologist acted as the adjudicator and made the final determination.

D. MR Image Acquisition

- MR system with a 1.0 to 1.5 Tesla field strength magnet with FDA-cleared hardware and software;
- Pre-contrast MRA images were obtained according to the standard sequence of each institution or sequence recommended by the MR vendor;
- Post-contrast MRA (dynamic and steady state) were performed according to a standard image sequences (pre-defined);
- Steady state images was performed within 15 minutes of MS-325 administration and could immediately follow the dynamic phase images, which was obtained shortly after the MS-325 injection.

E. Statistical Analysis:

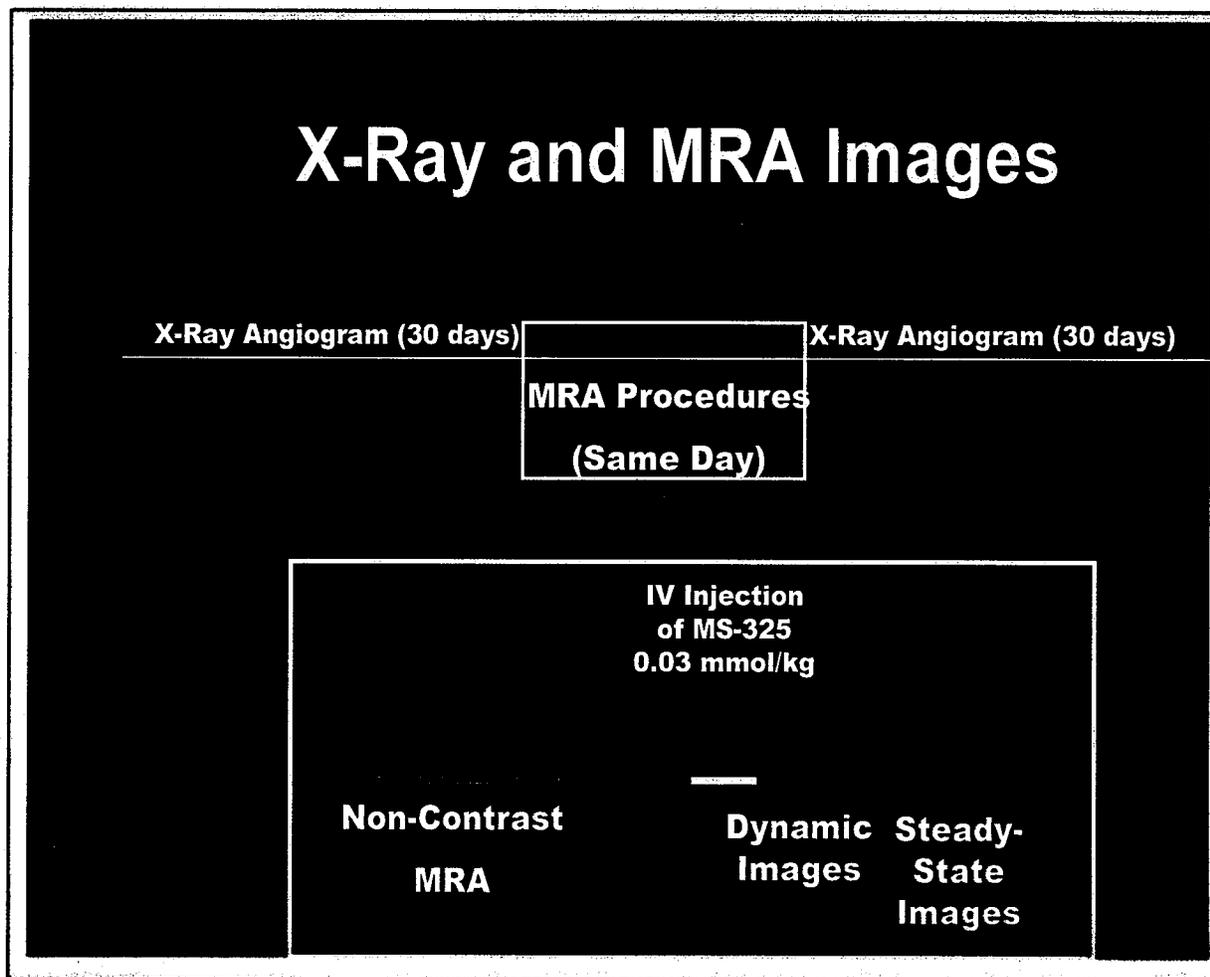
- Handling of missing data: If the XRA data were missing for a segment, then the corresponding segment was excluded from any analysis. If the MRA images were

missing or was not interpretable, then the **MRA results were considered “not accurate”** compared with the XRA results.

- Sample size was powered (80%-90%) to detect 10%-15% increase in sensitivity and specificity associated with contrast-enhanced MRA with a baseline sensitivity and specificity of 70%. However, those hypotheses were not formally incorporated into statistical testing protocol.

Despite of the similarity in the study design and blinded read procedures, there were some differences:

- In trial MS-325-12, the drug was diluted and administrated as either 30 mL for hand injection or 15 mL for power injection. In other three trials, the drug was not diluted. However the drug is injected over a short period of 25-30 seconds regardless of dilution.
- Presence of aneurysm not evaluated in trial 12.
- Institutional read in Study MS-325-12 evaluated dynamic and steady state images separately;
- In protocol MS-325-15 (pedal study), only one side (either right foot or left foot) was evaluated by MRA. For patients who presented with bilateral disease, the MRA study was conducted on the side referred for XRA evaluation.



Appendix B
Original Efficacy Results from four Phase 3 Clinical Trials

Protocol # (MS-325-	Measure- ments	Sensitivity			Specificity		
		Reader A	Reader B	Reader C	Reader A	Reader B	Reader C
12	Post-contrast	80.2	73.0	60.8	84.5	93.2	95.3
	Pre-contrast	62.0	66.7	41.8	75.1	84.8	75.4
	Difference (95% CI)	18.1	6.3	19.0	9.4	8.4	19.9
	P-value	<0.001	0.06	<0.01	<0.001	<0.01	<0.01
	(n - vessel)	237	237	237	1409	1409	1409
	(N - subject)	140	140	140	250	250	250
	13	Post-contrast	82.9	84.2	70.5	80.0	83.0
Pre-contrast	52.1	60.3	48.6	70.7	74.5	78.2	
Difference (95% CI)	30.8	24.0	21.9	9.2	8.5	11.9	
P-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	
(n - vessel)	146	146	146	1018	1018	1018	
(N- subject)	85	85	85	172	172	172	



b(4)

Source Data: Modified from Table 5-2 ISE (page 12) and 8-3 ISE.

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Appendix C

Table C-1 Summary of non-interpretable vessels by reader and study protocol

Protocol # (MS-325-	Number of Vessels	Post-contrast Images			Pre-contrast Images		
		Reader A	Reader B	Reader C	Reader A	Reader B	Reader C
12	1754	1.4%	0.6%	1.0%	15.2%	4.0%	19.2%
13	1206	2.5%	1.7%	2.6%	19.5%	12.4%	16.3%

b(4)

Source Data: Modified from Table 8-7 (page 47) of ISE.

* Each reader may have a different number of total renal arteries because the assessment on accessory renal arteries

Table C-2 Average Sensitivity and Specificity from Three Different Data Imputation Methods (From Statistical Review)

STUDY#12	N	Sensitivity				CI	N	Specificity				CI
		Pre	Post	Diff				Pre	Post	Diff		
Sponsor	237	.57	.72	.15		(.10, .20)	1409	.78	.91	.13		(.09, .16)
Interpretables	(210)	.63	.72	.09			(1223)	.90	.92	.02		
Pre=Post	237	.64	.72	.08		(.04, .12)	1409	.90	.91	.01		(-.01, .03)*
STUDY#13												
Sponsor	146	.53	.79	.26		(.21, .31)	1018	.74	.84	.10		(.05, .15)
Interpretables	(125)	.61	.80	.19			(835)	.89	.86	-.03*		
Pre=Post	146	.64	.79	.15		(.09, .22)	1018	.88	.84	-.04		(-.07, -.01)*

b(4)

Source Data: Table (1.2.0.2) of Statistical Review

Three different data imputation methods:

(A): **The Sponsor's chosen Worst Outcome Scenario**, in which all uninterpretables – baseline or enhanced image – were classified as incorrectly diagnosed. The rationale for this imputation rests on the assumption that large levels of uninterpretable imagings are evidence of intrinsic limitations in the Baseline diagnostic imaging technique.

(B): **The Interpretables Scenario**, in which the statistics were calculated only for vessels which were interpretable both at baseline and post-contrast. This scenario avoids the entire problem of imputation, but ignores the information in the relatively large subset of interpretable Vasovist images whose corresponding baselines were uninterpretable images. This imputation scheme corrects for the possibility that the Baseline imaging potential was underutilized.

(C): **Pre=Post Scenario**, in which the uninterpretable pre-images are assigned the same diagnoses as their post-injection interpretable counterparts. This scenario is consistent with the Null Hypothesis of equality of pre- and post-injection diagnostic statistics. In situations where the baselines have very high percentages of uninterpretables, this imputation scheme makes a good deal of sense. However, in cases where the percentages are significant, but not overwhelming, this scheme ignores the accumulated evidence gathered from the analyses of the joint pre- and post-injection performance on interpretables.

Appendix D

Table D-1: The rate of non-interpretable images by clinical sites and readers

Center	N	% Stenosis	Non-interpretable				
			Reader A	Reader B	Reader C	Total	Rank
Study # 12							
38	10	4%	0	0	0	0%	1
13	16	11%	4%	0	4%	3%	2
27	41	12%	1%	0	7%	3%	3
40	33	13%	29%	3%	31%	21%	7
20	40	15%	9%	3%	10%	7%	4
34	13	17%	32%	3%	38%	24%	8
21	13	18%	14%	8%	9%	10%	5
19	36	24%	16%	5%	12%	11%	6
All others	99		13%	5%	20%		
Study #13							
66	18	3%	38%	21%	20%	26%	6
83	30	10%	16%	12%	12%	13%	4
68	30	14%	4%	14%	3%	7%	2
114	16	15%	15%	13%	32%	20%	5
108	13	16%	16%	2%	11%	10%	3
67	29	17%	6%	3%	5%	5%	1
All others	42		35%	24%	29%		

Source Data: Statistical Review

b(4)

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Table D-2: Performance of non-contrast MRA at baseline at two sites using two different imaging protocols

Name of Test Center	MS-325-13 Site 68	MS-325-13 Site 77
2D-TOF Protocol	Flip=70 TE=10 TR=608	Flip=10 TE=5.1 TR=19.6
2D-TOF image inspection	Blood flow visible	NO blood flow signal
# of Vessels (Subjects)	208 (30)	42 (6)
2D-TOF Sensitivity	Reader A: 59% Reader B: 83% Reader C: 72% Ave: 71%	Reader A: 0 Reader B: 0 Reader C: 0 Ave:0
2D-TOF Specificity	Reader A: 88% Reader B: 85% Reader C: 89% Ave: 87%	Reader A: 0 Reader B: 0 Reader C: 0 Ave: 0
MS-325 Sensitivity	Reader A: 69% Reader B: 90% Reader C: 69% Ave: 76%	Reader A: 83% Reader B: 100% Reader C: 83% Ave: 87%
MS-325 Specificity	Reader A: 90% Reader B: 87% Reader C: 93% Ave: 90%	Reader A: 71% Reader B: 100% Reader C: 97% Ave: 89%

Source Data: primary MO review

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Appendix E
List of Subjects with hemoglobin decrease > 2.0 gram/dL within 72 hours post dosing

<u>patid</u>	<u>count</u> r	<u>age</u>	<u>gender</u>	<u>dosegr</u>	<u>hgb_b</u>	<u>hgb_c2h</u>	<u>hgb_c1d</u>	<u>hgb_c3d</u>
P09/004/008	US/CANADA	69	M	0.03 mmol/kg	16.7	-2.3	-.7	-1
P09/008/002	US/CANADA	65	M	0.03 mmol/kg	16.2	-1.4	-1.1	-2.3
P09/021/003	US/CANADA	60	F	0.03 mmol/kg	14.9	-1.8	-2.1	-.7
P12/004/006	US/CANADA	67	F	0.03 mmol/kg	15	-1.2	-1.8	-2.3
P12/020/012	US/CANADA	72	M	0.03 mmol/kg	13.3	.1	-1	-2.7
P12/020/032	US/CANADA	81	M	0.03 mmol/kg	13.1	.4	-.7	-2.1
P12/021/011	US/CANADA	84	F	0.03 mmol/kg	14.2	-.6	-2	-2.2
P12/021/012	US/CANADA	42	F	0.03 mmol/kg	13.2	-.5	0	-2.2
P12/027/044	US/CANADA	53	M	0.03 mmol/kg	16.4	-1.1	.	-2.1
P12/038/007	US/CANADA	63	M	0.03 mmol/kg	15.1	0	.	-2.3
P12/040/012	COLUMBIA	53	M	0.03 mmol/kg	18.6	.	-.2	-2
P12/041/001	US/CANADA	52	M	0.03 mmol/kg	18.4	-1.3	-.9	-2.1
P13/065/002	US/CANADA	82	M	0.03 mmol/kg	14.1	-1	-1.3	-2.3
P13/068/030	US/CANADA	83	F	0.03 mmol/kg	15.3	-.1	-.9	-2.2
P13/077/001	US/CANADA	61	M	0.03 mmol/kg	16.4	-1.4	-1	-2.3
P13/077/004	US/CANADA	69	F	0.03 mmol/kg	14.2	-.2	-.3	-2.9
P15/113/008	CHILE	63	M	0.03 mmol/kg	15.3	-1.8	-.6	-2
P15/146/007	CHILE	88	M	0.03 mmol/kg	12	.1	-2	-1.2
P01C/---/424	US/CANADA	32	M	0.05 mmol/kg	17	-1	-1.1	-2.1
P04/002/006	US/CANADA	52	F	0.05 mmol/kg	16.3	-2.2	-1.5	-1.2
P05/004/001	US/CANADA	38	F	0.05 mmol/kg	12.6	-2	-.3	-1.4
P05/004/002	US/CANADA	31	F	0.05 mmol/kg	14.1	.	-.1	-2.9
P06/001/021	US/CANADA	54	M	0.05 mmol/kg	16	-1.8	-2.2	-1.9
P07/002/005	US/CANADA	64	M	0.05 mmol/kg	14.1	-1.2	-2.1	-1.8
P07/002/048	US/CANADA	51	F	0.05 mmol/kg	13.7	-1.3	-1.7	-2.1
P09/003/005	US/CANADA	67	F	0.05 mmol/kg	16.3	-1.1	-1.7	-2.9
P15/113/015	CHILE	63	F	0.05 mmol/kg	15	-.5	-2.1	-1.8
P15/146/006	CHILE	47	M	0.05 mmol/kg	15.1	-1.4	-2.4	-1.6
P16/001/008	US/CANADA	68	M	0.05 mmol/kg	15.6	-1.2	-2.6	-3
P02/002/005	US/CANADA	64	M	<0.03 mmol/kg	14.8	-1.2	-1.7	-2.3
P09/011/032	US/CANADA	66	M	<0.03 mmol/kg	14	-2.2	-.3	0
P04/005/006	US/CANADA	70	M	>0.05 mmol/kg	12.5	.3	-.7	-2
P09/004/011	US/CANADA	83	M	>0.05 mmol/kg	17.2	.1	-1.2	-2
P09/022/010	US/CANADA	76	F	>0.05 mmol/kg	13.8	-.8	-.6	-2.4

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Appendix F
List of Subjects with Hypocalcaemia (Calcium < 8.5 mg/dl) within 72 hours post dosing

patid	count	age	gender	dosegr	cal_b	cal_2h	cal_1d	cal_3d
P12/011/004	US/CANADA	70	M	0.03 mmol/kg	8.6	8.3	9.2	8.8
P12/020/006	US/CANADA	75	F	0.03 mmol/kg	8.6	8.8	8.2	9.1
P12/040/015	COLUMBIA	43	M	0.03 mmol/kg	8.6	8.7	8.2	8.3
P12/001/001	US/CANADA	71	M	0.03 mmol/kg	8.7	8.2	8.4	8.5
P12/020/034	US/CANADA	85	M	0.03 mmol/kg	8.7	8.6	8.7	7.8
P12/027/010	US/CANADA	74	F	0.03 mmol/kg	8.7	9.4	7.8	8.2
P15/110/003	AUSTRALIA	67	F	0.03 mmol/kg	8.7	8.2	8.6	8.6
P12/009/003	US/CANADA	58	M	0.03 mmol/kg	8.8	8.3	7.7	.
P14/126/009	FRANCE	62	M	0.03 mmol/kg	8.8	9	8.9	8.4
P15/146/007	CHILE	88	M	0.03 mmol/kg	8.8	8.9	8.4	9
P12/004/001	US/CANADA	67	F	0.03 mmol/kg	8.9	9.5	5.2	9.2
P12/013/015	US/CANADA	54	F	0.03 mmol/kg	8.9	8.3	8.8	8.7
P12/027/008	US/CANADA	87	F	0.03 mmol/kg	8.9	9.2	8.3	.
P14/111/005	AUSTRALIA	70	F	0.03 mmol/kg	8.9	7.5	8.8	8.2
P09/004/008	US/CANADA	69	M	0.03 mmol/kg	9	5.8	9.1	9.1
P12/020/032	US/CANADA	81	M	0.03 mmol/kg	9	10	9.3	8.2
P15/104/002	GERMANY	50	M	0.03 mmol/kg	9	8.6	8.6	8.1
P12/019/021	US/CANADA	38	M	0.03 mmol/kg	9.1	9.2	6.9	.
P12/027/021	US/CANADA	83	M	0.03 mmol/kg	9.1	9	9	8.3
P12/027/044	US/CANADA	53	M	0.03 mmol/kg	9.1	8.7	.	8.2
P13/066/010	US/CANADA	75	M	0.03 mmol/kg	9.1	6.8	9.1	9.1
P13/083/012	GERMANY	80	M	0.03 mmol/kg	9.1	8.8	8.3	8.1
P15/058/011	GERMANY	68	M	0.03 mmol/kg	9.1	8.9	8.1	9.3
P15/058/006	GERMANY	55	M	0.03 mmol/kg	9.2	9.5	9.2	8.4
P14/129/006	CZECH REPUBLIC	50	M	0.03 mmol/kg	9.3	9.1	7.2	9.4
P09/004/001	US/CANADA	68	M	0.03 mmol/kg	9.4	7.9	9.1	8.9
P12/021/014	US/CANADA	57	F	0.03 mmol/kg	9.4	8	9.6	.
P15/058/002	GERMANY	65	M	0.03 mmol/kg	9.7	9.5	9.8	7.4
P12/021/013	US/CANADA	53	M	0.03 mmol/kg	9.9	9.9	9.2	7.3
P12/040/017	COLUMBIA	73	F	0.03 mmol/kg	10	9.4	8.3	.
P09/009/006	US/CANADA	60	F	0.05 mmol/kg	7	5.9	6.1	8.1
P15/058/008	GERMANY	69	F	0.05 mmol/kg	8	7.7	6.2	9.7
P07/002/010	US/CANADA	37	M	0.05 mmol/kg	8.2	8	8.2	8.2
P05/004/013	US/CANADA	49	F	0.05 mmol/kg	8.5	8.4	9.3	9.4
P06/001/015	US/CANADA	69	M	0.05 mmol/kg	8.6	8.4	8.4	9.2
P07/002/015	US/CANADA	45	M	0.05 mmol/kg	8.6	8.9	8.4	8.9
P07/002/028	US/CANADA	56	M	0.05 mmol/kg	8.6	8.1	8.4	8.4
P07/002/004	US/CANADA	45	F	0.05 mmol/kg	8.7	8.3	8.3	8.5
P07/002/005	US/CANADA	64	M	0.05 mmol/kg	8.7	7.8	8.5	8.2
P07/002/020	US/CANADA	57	F	0.05 mmol/kg	8.7	8.3	8.9	8.8
P15/146/006	CHILE	47	M	0.05 mmol/kg	8.7	8.6	8.4	9.2
P07/002/013	US/CANADA	22	F	0.05 mmol/kg	8.8	8.2	8.4	8.4
P09/004/009	US/CANADA	61	M	0.05 mmol/kg	8.8	6.4	8.9	8.9
P15/113/002	CHILE	67	M	0.05 mmol/kg	8.8	9	9.1	8.1
P06/001/001	US/CANADA	50	F	0.05 mmol/kg	8.9	8.2	8.5	8.7
P06/001/003	US/CANADA	68	M	0.05 mmol/kg	8.9	8.4	8.5	8.5
P07/002/012	US/CANADA	35	F	0.05 mmol/kg	8.9	9.1	8.4	10.2
P06/001/009	US/CANADA	52	M	0.05 mmol/kg	9	8.2	8.6	8.5
P07/002/046	US/CANADA	38	F	0.05 mmol/kg	9	8.4	8.7	8.7
P06/001/012	US/CANADA	62	M	0.05 mmol/kg	9.2	7.9	8.1	8.8
P06/001/042	US/CANADA	60	M	0.05 mmol/kg	9.2	8.3	8.8	8.7
P07/002/050	US/CANADA	53	F	0.05 mmol/kg	9.2	8.9	8.5	8.4
P15/058/009	GERMANY	51	M	0.05 mmol/kg	9.2	7.8	7.9	7.8
P06/001/008	US/CANADA	49	M	0.05 mmol/kg	9.3	8.2	8.9	9.1
P06/001/022	US/CANADA	47	M	0.05 mmol/kg	9.3	8.1	9.3	9.7
P08/001/005	US/CANADA	23	F	0.05 mmol/kg	9.3	8.4	8.8	8.8
P06/001/005	US/CANADA	64	M	0.05 mmol/kg	9.4	8	8.9	8.9
P09/004/020	US/CANADA	78	F	0.05 mmol/kg	9.5	7.1	9.3	9.4
P06/001/021	US/CANADA	54	M	0.05 mmol/kg	9.8	8.3	9.2	9.5
P09/011/009	US/CANADA	55	M	<0.03 mmol/kg	8.6	8.3	8.9	8.6
P09/011/003	US/CANADA	81	M	<0.03 mmol/kg	8.7	8.6	9	8.4

P09/004/012	US/CANADA	57	M	<0.03 mmol/kg	8.8	7.1	9.6	9.7
P08/001/002	US/CANADA	56	F	<0.03 mmol/kg	9	9.3	9.3	8.4
P02/001/001	US/CANADA	60	F	<0.03 mmol/kg	9.1	8.4	8.9	9.3
P09/004/005	US/CANADA	73	M	<0.03 mmol/kg	9.3	6.7	8.7	8.9
P09/022/009	US/CANADA	75	F	<0.03 mmol/kg	9.3	9.9	.	8.1
P09/010/006	US/CANADA	56	F	<0.03 mmol/kg	9.6	9	9	8.3
P09/004/006	US/CANADA	79	F	>0.05 mmol/kg	8.8	6.8	8.4	8.5
P04/002/028	US/CANADA	73	F	>0.05 mmol/kg	8.9	7	10.3	9.3
P09/008/009	US/CANADA	59	M	>0.05 mmol/kg	8.9	8.8	8.6	8.4
P09/011/017	US/CANADA	63	M	>0.05 mmol/kg	9	8.7	9.2	8.4
P09/025/001	US/CANADA	66	M	>0.05 mmol/kg	.	.	7.8	8.9
P09/010/014	US/CANADA	60	F	Placebo	8.6	8.5	8	8.5
P06/001/028	US/CANADA	67	M	Placebo	8.8	8.3	8.9	8.9
P06/001/030	US/CANADA	67	F	Placebo	8.9	8.3	8.7	8.6
P09/011/014	US/CANADA	60	F	Placebo	9.1	8.9	8.4	8.7
P09/011/008	US/CANADA	71	F	Placebo	9.4	8.4	9.2	9.2

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Appendix G
List of Subjects with Oxygen Sat. Changes

<u>patid</u>	<u>count</u>	<u>age</u>	<u>gender</u>	<u>dosegr</u>	<u>dosedt</u>	<u>oxsat</u> baseline	<u>oxsat</u> post (0-15)
P09/004/012	US/CANADA	57	M	<0.03 mmol/kg	02 May 00	93	90
P09/010/019	US/CANADA	56	F	0.05 mmol/kg	13 Nov 00	94	90
P09/025/003	US/CANADA	60	M	<0.03 mmol/kg	13 Nov 00	98	89
P12/019/016	US/CANADA	62	F	0.03 mmol/kg	01 May 00	95	90
P12/019/017	US/CANADA	67	M	0.03 mmol/kg	12 May 00	92	88
P12/020/002	US/CANADA	66	M	0.03 mmol/kg	28 Sep 99	91	90
P12/020/032	US/CANADA	81	M	0.03 mmol/kg	05 Jun 00	96	90
P12/034/012	US/CANADA	69	M	0.03 mmol/kg	05 Jun 01	94	75
P12/040/016	COLUMBIA	68	F	0.03 mmol/kg	02 Apr 01	92	88
P12/040/020	COLUMBIA	67	F	0.03 mmol/kg	04 Apr 01	96	90
P13/061/007	US/CANADA	82	F	0.03 mmol/kg	13 May 02	92	90
P13/066/008	US/CANADA	73	M	0.03 mmol/kg	11 Jul 02	98	90
P13/066/013	US/CANADA	66	M	0.03 mmol/kg	30 Jul 02	96	88
P13/066/014	US/CANADA	71	M	0.03 mmol/kg	06 Aug 02	92	90
P13/075/005	US/CANADA	43	M	0.03 mmol/kg	09 Jul 02	98	74
P13/117/003	US/CANADA	63	M	0.03 mmol/kg	05 Aug 02	94	90
P14/132/002	FRANCE	78	F	0.03 mmol/kg	09 Dec 02	92	85
P14/145/002	FRANCE	71	F	0.03 mmol/kg	06 Jan 03	91	87
P15/113/023	CHILE	63	F	0.03 mmol/kg	09 Dec 02	94	90

Source Data: Independent analysis from SAS transport file provided in NDA

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