

CLINICAL REVIEW

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Reviewer Name Tong Li, M.D.
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Established Name Gadofosveset Tridodium
(Proposed) Trade Name Vasovist (MS-325)
Therapeutic Class Gadolinium based MRA contrast agent
Applicant Epix Medical, Inc

Priority Designation S

Formulation 20 ml vials, 0.25 mmol/ml
Dosing Regimen 0.03 mmol/kg
Indication Contrast MRA agent for \square

Intended Population Adults with suspected or known vascular disease ³

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Table of Contents

1	EXECUTIVE SUMMARY.....	5
1.1	RECOMMENDATION ON REGULATORY ACTION	5
1.2	RECOMMENDATION ON POSTMARKETING ACTIONS	6
1.2.1	Risk Management Activity	6
1.2.2	Required Phase 4 Commitments.....	6
1.2.3	Other Phase 4 Requests.....	6
1.3	SUMMARY OF CLINICAL FINDINGS	6
1.3.1	Brief Overview of Clinical Program.....	6
1.3.2	Safety	8
1.3.3	Dosing Regimen and Administration.....	9
1.3.4	Drug-Drug Interactions.....	10
1.3.5	Special Populations.....	10
2	INTRODUCTION AND BACKGROUND.....	11
2.1	PRODUCT INFORMATION	11
2.2	CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS.....	11
2.3	AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES	13
2.4	IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS	13
2.5	PRESUBMISSION REGULATORY ACTIVITY	13
2.6	OTHER RELEVANT BACKGROUND INFORMATION.....	14
3	SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES	14
3.1	CMC (AND PRODUCT MICROBIOLOGY, IF APPLICABLE)	14
3.2	ANIMAL PHARMACOLOGY/TOXICOLOGY	15
4	DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY.....	15
4.1	SOURCES OF CLINICAL DATA	15
4.2	TABLES OF CLINICAL STUDIES	16
4.3	REVIEW STRATEGY	17
4.4	DATA QUALITY AND INTEGRITY	18
4.5	COMPLIANCE WITH GOOD CLINICAL PRACTICES.....	18
4.6	FINANCIAL DISCLOSURES.....	18
5	CLINICAL PHARMACOLOGY.....	18
5.1	PHARMACOKINETICS	18
5.2	PHARMACODYNAMICS.....	19
5.3	EXPOSURE-RESPONSE RELATIONSHIPS	19
6	INTEGRATED REVIEW OF EFFICACY	20
6.1	INDICATION.....	20
6.1.1	Methods	20
6.1.2	General Discussion of Endpoints.....	20
6.1.3	Study Design.....	21
6.1.4	Efficacy Findings.....	21
	Reviewer's comments for primary efficacy assessment.....	24
6.1.5	Clinical Microbiology.....	28
6.1.6	Efficacy Conclusions.....	28
7	INTEGRATED REVIEW OF SAFETY	29
7.1	METHODS AND FINDINGS	29
7.1.1	Deaths	29

7.1.2	Other Serious Adverse Events	32
7.1.3	Dropouts and Other Significant Adverse Events	34
7.1.4	Other Search Strategies.....	34
7.1.5	Common Adverse Events	34
7.1.6	Less Common Adverse Events	40
7.1.7	Laboratory Findings.....	40
7.1.8	Vital Signs	44
7.1.9	Electrocardiograms (ECGs).....	48
7.1.10	Immunogenicity	51
7.1.11	Human Carcinogenicity	51
7.1.12	Special Safety Studies.....	51
7.1.13	Withdrawal Phenomena and/or Abuse Potential.....	51
7.1.14	Human Reproduction and Pregnancy Data	52
7.1.15	Assessment of Effect on Growth.....	52
7.1.16	Overdose Experience	52
7.1.17	Postmarketing Experience.....	53
7.2	ADEQUACY OF PATIENT EXPOSURE AND SAFETY ASSESSMENTS	53
7.2.1	Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety	53
7.2.2	Description of Secondary Clinical Data Sources Used to Evaluate Safety.....	54
7.2.3	Adequacy of Overall Clinical Experience	55
7.2.4	Adequacy of Special Animal and/or In Vitro Testing	55
7.2.5	Adequacy of Routine Clinical Testing.....	55
7.2.6	Adequacy of Metabolic, Clearance, and Interaction Workup.....	55
7.2.7	Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study.....	55
7.2.8	Assessment of Quality and Completeness of Data	56
7.2.9	Additional Submissions, Including Safety Update	56
7.3	SUMMARY OF SELECTED DRUG-RELATED ADVERSE EVENTS, IMPORTANT LIMITATIONS OF DATA, AND CONCLUSIONS	57
7.4	GENERAL METHODOLOGY	57
7.4.1	Pooling Data Across Studies to Estimate and Compare Incidence.....	57
7.4.2	Explorations for Predictive Factors	58
7.4.3	Causality Determination	60
8	ADDITIONAL CLINICAL ISSUES	60
8.1	DOSING REGIMEN AND ADMINISTRATION	60
8.2	DRUG-DRUG INTERACTIONS	64
8.3	SPECIAL POPULATIONS.....	64
8.4	PEDIATRICS	69
8.5	ADVISORY COMMITTEE MEETING.....	69
8.6	LITERATURE REVIEW	69
8.7	POSTMARKETING RISK MANAGEMENT PLAN	70
8.8	OTHER RELEVANT MATERIALS	70
9	OVERALL ASSESSMENT.....	70
9.1	CONCLUSIONS	70
9.2	RECOMMENDATION ON REGULATORY ACTION	70
9.3	RECOMMENDATION ON POSTMARKETING ACTIONS	70
9.3.1	Risk Management Activity	71
9.3.2	Required Phase 4 Commitments.....	71
9.3.3	Other Phase 4 Requests.....	71
9.4	LABELING REVIEW	71
9.5	COMMENTS TO APPLICANT.....	71

Clinical Review
{Tong Li, M.D.}
{NDA 21711}
{Vasovist(MS-325)}

10	APPENDICES	72
10.1	REVIEW OF INDIVIDUAL STUDY REPORTS	72
10.2	LINE-BY-LINE LABELING	72
10.3	REFERENCES	72

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

From a clinical standpoint, the evidence presented in this NDA submission is not substantial and not adequate in support of the effectiveness and safety of MS-325 for a MRA application. All four Phase 3 studies have failed to demonstrate the improvement in sensitivity and specificity of MS-325 enhanced MRA, compared to that of non-contrast MRA. In addition, MS-325 enhanced MRA's performance appears to be sub-optimal and the studies were not designed to demonstrate efficacy (value) of steady state images. Such a deficiency is important given the prolonged half-life of MS-325 in human body.

The drug may affect blood hemoglobin and calcium level. 34 subjects had experienced an acute hemoglobin drop, and 5 had a hypocalcaemia episode being reported as an adverse event (not by the measurement of serum calcium level), within 72 hours of dosing. Those observations, combined with the observed increase in urine Zinc level post dosing, raised a question of MS-325's in-vivo stability. The answer to this question is important because the serious cardiac events, including cardiac death, were reported from clinical trials, and there were patients with significant QTc increases of > 60 ms from the clinical trials. Unacceptable levels of Gd+3, if dissociated from MS-325, may contribute to those events and outcomes though those patients were at a higher risk for those cardiac events themselves due to their underlying cardiac conditions. Because of a lack of the adequate control group, the sub-optimal safety monitoring and follow-up in some cases and the evidence of AE underreporting from some of the clinical sites, the demonstration of in vivo stability will provide the needed assurance on the product's safety. This assurance is particularly important for the patients with renal insufficiency.

From a clinical perspective, this reviewer recommends that MS-325 for the MRA application receive an Approvable for the current indication. This deficiency may be corrected by conducting new adequate, prospectively designed safety and efficacy studies. Prior to the new study design, the sponsor should consider the means of reducing background enhancement, and venous signal contamination. Demonstrating efficacy and safety in different vascular territories is also an option.

The following issues should be considered in the new clinical trials:

1. Adequate evaluation of MS-325 stability in patients with and without renal insufficiency.
2. Standardization of the non-contrast imaging protocol at baseline to achieve an optimal performance level.
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4. Ensuring the validity of data imputation method used in the primary efficacy analysis. In the current studies, all uninterpretable MRA images were treated as either false negative in sensitivity calculation, or false positive in specificity calculation. Since a much higher percentage of non-contrast MRA images (up to 41% for some arterial regions) at baseline were considered as the uninterpretable, compared to that (<3%) of MS-325 enhanced MRA images, this so-called “conservative treatment of uninterpretable MR images” is problematic because it greatly underestimated both sensitivity and specificity of non-contrast MRA at baseline. As a result, it may create a false impression of an improvement of post-contrast images in both sensitivity and specificity.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

N/A

1.2.2 Required Phase 4 Commitments

N/A

1.2.3 Other Phase 4 Requests

N/A

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

As of June 30, 2004, the sponsor had completed a total of 18 human clinical trials with a single dose of MS-325 administration. 117 healthy volunteers had been exposed to a single dose of MS-325 ranging from 0.01 to 0.15 mmol/Kg. 1,203 patients had been exposed to a single dose of MS-325 ranging from 0.005 to 0.07 mmol/Kg. 767 patients had been exposed to the proposed clinical dose of 0.03 mmol/Kg.

Table 1.3.1 shows the starting dates for key clinical trials in the early clinical development stage. To support this MRA indication, the sponsor also submitted the results from four pivotal clinical studies in which a total 672 patients with suspected aortoiliac, femoral, renal and pedal artery diseases received MS-325 injection at the dose of 0.03 mmol/kg. Of these 672 patients, 65%

Clinical Review
 {Tong Li, M.D.}
 {NDA 21711}
 {Vasovist(MS-325)}

were male and 20% non-Caucasian with a mean age of 65. 54% of patients from Phase 3 clinical trials were enrolled from US/Canada sites.

Table 1.3.1 Start dates for key clinical trials:

Study Number	Design	Start Date
MS-325-01A	Phase 1 PK/Dose Escalation	Sept 1996
MS-325-01 C	Phase 1 PK/Dose Escalation	May 1997
MS-325-04/4A	Phase 2 Coronary Disease Feasibility	Sept 1997
MS-325-02	Phase 2 Dose Escalation	June 1997
MS-325-09	Phase 2 Pivotal PVD Dose Escalation	June 1999
MS-325-12	First Phase 3 Pivotal PVD	June 1999

Data source: Reviewer summary from IND 51,172.

Reviewer's Comments: MS-325 is a small gadolinium chelate. The efficacy of T1 relaxivity depends on its reversible albumin binding ability. It was developed as a blood pool agent so that it can be used to perform a steady-state imaging.

Because of the rapid development of the clinical development program, many important technique issues do not appear to be well addressed. The sponsor initiated Phase 2 Coronary disease feasibility trial in 1997 prior to Phase 1 MS-325-1C trial. When this trial [] the sponsor initiated concurrently Phase 2 and pivotal Phase 3 trials for PVD indication in 1999, without adequately addressing PK profiles of MS-325. During the bolus phase, the majority of MS-325 is not bound to albumin, which represents a severe disadvantage for a blood pool agent because optimal dose was difficult to achieve for adequate dynamic imaging. The increased tissue background signal is not only due to extravasations of the free form of MS-325, but also because that the extravasated part of MS-325 is capable of binding to any interstitial protein. In addition, MS-325 is nonselective in venous and arterial enhancement. Without the adequate development of artery-vein separation techniques, the steady-state images may result in substantial enhancement of background tissue. All those could significantly affect the performance of MS-325 in main arterial branches.

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Efficacy

Four Phase 3 trials were designed to evaluate the diagnostic performance, measured by sensitivity and specificity, of a 0.03 mmol/kg dose of MS-325-enhanced MRA versus pre-contrast MRA, by using X-ray angiography (XRA) as the standard of reference (SOR), in the evaluation of arterial stenosis in the patients with known or suspected aortoiliac, []

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The key efficacy conclusions are as follows:

- The studies were not designed to demonstrate the value of steady-state images, and efficacy [] was not studied in phase 3 program. **b(4)**
- There is no statistically significant improvement in sensitivity and specificity of MS-325, compared to that of non-contrast MRA. The sensitivity and specificity of MS-325 appeared to be suboptimal in all pivotal trials. There are significant reader-to-reader variations in sensitivity and specificity of MS-325, which could go below 60%.
- There is a lack of adequate assurance on the optimal performance of baseline MRA due to the lack of standardized imaging protocol, and the data imputation method used by the sponsor was not appropriate.
- There is concern that 0.03 mmol/kg of MS-325 may not be adequate to perform optimal dynamic images. **b(4)**

1.3.2 Safety

The safety evaluation in some cases may appear to be suboptimal. In some cases, there were lack of adequate documentation to support that adequate safety monitoring or follow-up were performed when patients developed severe hypoxia. **There is no "thorough QT" study with a positive control group.** Some patients had developed QT prolongation of > 60 ms. At this time, the possibility of a clinically important QT prolongation, as a result of drug administration, could not be totally ruled out in the target patient population.

Other important safety-related findings are as follows:

- Safety reports submitted listed 9 serious cardiac events including three death cases. Although all patients had a history of cardiac disease, the role of MS-325 cannot be totally excluded. There were 5 subjects with syncope episodes, 2 subjects with transit ventricular tachycardia, 19 subjects with oxygen saturation of < 90% post dosing. The safety assessment for some of those patients does not appear to be optimal. The lack of a placebo group has made the causal assessment more challenging. Continuing safety monitoring, cardiovascular system in particular, is needed in the new clinical trials. But the key assurance will come from data supporting in vivo stability of MS-325.
- At a clinical study with the higher doses (0.125 and 0.15 mmol/kg), renal tubular cells were seen in urinary sediments. A few renal cells **were also observed approximately "24 hours"** post-dose in one individual (Subject No. 608) in dose group 0.1 mmol/kg. The appearance of renal tubular cells and inclusion bodies in the urinary sediments could be of concern. However, there were no clinically significant changes in any other parameters of renal functions. No renal cells were found in subjects receiving lower dose (0.05 and 0.075 mmol/kg) of MS-325 and proposed clinical dose of 0.03 mmol/kg, and renal tubular cells

were also observed in urinary sediments in placebo group. This safety parameter should be monitored in the future clinical trials of the proposed clinical dose to provide further assurance on the renal safety.

- Most of the adverse events appear to be dose-dependent but the majority of adverse events were mild to moderate at onset. The common adverse events of MS-325 appear to be higher to that of other marketed gadolinium based drugs. This observation is preliminary in nature because of lack of direct comparison from the controlled clinical trials. The adverse event profile of MS-325 appears to generalize cholinergic stimulation in nature. Headache (112), nausea (110), vasodilatation (88), dizziness (39), GI symptoms (59), chest pain (25), and respiratory syndrome (40) were the most frequently reported AEs post dosing. The possible mechanisms include the interaction with calcium channels, neurotransmitters and possible in vivo instability.
- The urinary excretion of calcium and iron is increased over baseline following MS- 325 injection for the proposed clinical dose of 0.03 mmol/kg. There is also a small amount of increased zinc excretion in urine over 72 hours post dosing, which may suggest Gd-transchelation. Given the safety profile of this product, the demonstration of in vivo stability of MS-325 is important.
- The exposure increased almost two folds in patients with moderate and severe renal impairment. The half-life increases 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. A total of 15 subjects with mild renal insufficiency, defined by a serum of creatinine of between 1.5 and 2.0 were enrolled in three of four phase 3 trials. Acute effects on hemoglobin and serum calcium were noted. This reviewer shares the same concerns of clinical pharmacology reviewer and the demonstration of MS-325 in vivo stability in renal insufficient patients is important.
- In addition to safety concerns, inadequate diagnostic images due to venous contamination may mislead the diagnosis.

1.3.3 Dosing Regimen and Administration

In the phase 3 clinical trials, each patient received a single intravenous bolus injection, manually or by power injection, at a dose of 0.12 mL/kg (0.03 mmol/ kg) over a period of 30 seconds followed by a 25-30 mL normal saline flush. Dynamic imaging began immediately upon injection, and steady-state imaging began within 15 minutes after injection and was completed within approximately one hour following injection.

The selection of 0.03 mmol/kg dose for the phase 3 studies was based on MRA literature entitled "**A single bolus of 0.1 mmol/kg of gadolinium has been shown to well visualize all iliac, renal, femoral, and lower limb vessels with a 3D subtraction MRA technique.**" **Using a 4:1 dose correction for the enhanced relaxivity of MS-325 compared to conventional Gd MRA agents**

(MS-325 $16-22\text{S}^{-1}\text{mM}^{-1}$ VS. Gd-ECS agents about $4.5\text{ s}^{-1}\text{mM}^{-1}$), the results showed that the 0.1 mmol/kg dose of conventional contrast are consistent with a 0.03 mmol/kg dose of MS-325.

Reviewer's Comments:

1. *For dynamic imaging, 0.03 mmol/kg may be suboptimal because this reviewer has noted, from the selected dynamic image samples, the suboptimal contrast artifact, and background noise. In addition, venous signal contamination was noted by this reviewer.*
2. *For steady-state imaging, the major problems were venous and background enhancement. Currently, there are no artery-vein separation techniques available. The background enhancement due to MS-325's potential to bind to any of interstitial protein may further decrease the clinical usefulness of the product. Those issues should be adequately addressed.*

1.3.4 Drug-Drug Interactions

Because warfarin may be used in patients with vascular disease, and because both warfarin and MS-325 bind to human serum albumin (HAS), a study was performed in subjects with arterial vascular disease to assess potential PK/PD interactions of MS-325 and warfarin. The results showed that the PK profile of MS-325 was unaltered in subjects on concurrent warfarin therapy as compared to those who did not receive warfarin therapy.

At this time, there is no information available **about MS-325's effects** on anticholinesterases, erythropoietin, and anti-diabetic medications.

1.3.5 Special Populations

- **Renal Insufficiency:** In renal impaired patients, the renal clearance decreased substantially in patients with moderate and severe renal impairment. The exposure (AUC) increased almost two folds in patients with moderate and severe renal impairment. The half-life of MS-3325 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.
- **Pregnancy and Nursing Mothers:** The animal studies show that MS-325 was excreted in the breast milk at rates that are usually found with other gadolinium compounds. This should be stated in the appropriate section of the labeling.
- **Pediatrics:** The sponsor has not conducted any clinical studies of MS-325 in the pediatric population. A pediatric waiver was requested. This reviewer believes that no pediatric studies should be conducted at this time until the pending efficacy and safety issues are resolved in adult population.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

VASOVIST™ (also referred to as MS-325) is a gadolinium-based MRA contrast agent that is comprised of an aqueous solution of 244 mg/mL of the drug substance, gadofosveset trisodium, and 0.27 mg/mL of ligand excipient, fosveset. The drug substance consists of the stable gadolinium diethylenetriaminepentaacetic acid (GdDTPA) complex substituted with a diphenylcyclohexylphosphate group. MS-325 binds reversibly to serum albumin, thus providing both an enhanced paramagnetic relaxivity and duration of action relative to existing Gadolinium contrast agents.

Reviewer's Comments: *Compared to other gadolinium-based MRI contrast agent, MS-325 binds to albumin which changes its PK profile considerably.*

2.2 Currently Available Treatment for Indications

The proposed indication is as follow: "VASOVIST™ Injection is indicated for use with magnetic resonance angiography ☐

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Atherosclerosis could occur in any vessel in the body, and it contributes to cardiac death, stroke, limb loss, and a range of other illnesses. There is an increased prevalence of arterial disease in individuals with diabetes mellitus, hypercholesterolemia, hypertension, and in cigarette smokers. Disease in the major arteries, including peripheral arteries, remains to be a major cause of morbidity and mortality in the US. The prevalence ranges from <3% in patients under 60 years of age to up to 20% in patients of 75 years and older, comprising of an estimated 8 to 10 million people in the US. As the average age of the population increases, the burden of vascular disease increases too. Overall, vascular disease represents one of the leading challenges with an increasing impact on society.

X-ray angiogram (XRA) is widely used in vascular disease diagnosis and is considered as the gold standard because of its accuracy relative to other less invasive alternatives. In 2002, over ☐ diagnostic XRA studies were done in the US for peripheral vascular disease, renal artery disease, and pedal arterial disease. The procedure, however, is associated with a certain level of morbidity and even mortality, including vascular injury, conservatively estimated at 0.4%, and nephrotoxicity, conservatively estimated at 1.6%. In addition, the procedure also was associated with the substantial discomfort, which often requires the use of medications for sedation and pain management, and the complications that may arise from the use of these medications. The infection or bleeding at the puncture site is also quite common.

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EPIX requests that the FDA grant VASOVIST™ a priority review status because that:

- The incidence and medical impact of vascular disease in the US is significant;

- Catheter X-ray angiography is invasive and risky;
- **The diagnostic performance of VASOVIST™ -enhanced MRA compares well to catheter angiography;**
- MRA provides a patient safety benefit by avoiding the need for arterial catheterization; and,
- **The clinical trial results included in this NDA show that VASOVIST™ -enhanced MRA is a clinically valuable alternative to XRA for the** []

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Off-label use of five gadolinium-based MRI agents (approved for CNS indication) for a MRA application is common. Literature data appear to suggest that:

- Carotid MRA, alone or in combination with Ultrasound examination, has been widely used for preoperative evaluation;
- MRA has gained widespread acceptance for imaging the aorta. The use of XRA is only limited to a few special situations.
- For the renal arteries, MRA has been used as a screening tool. Additional advances will be required to replace CA for evaluation of intrarenal vessels and nuclear medicine for renal functional evaluation.
- MRA use for the peripheral vascular disease is limited and it is mainly used for those patients who are at an increased risk for catheter introduction or iodinated contrast.

The potential clinical use of gadolinium-base MRA agents is summarized as follows:

- Aorto-Iliac (Inflow)vessels:
To determine the length of the stenotic or occluded segment, therefore to determine whether the patient will need percutaneous angioplasty or surgical intervention.
- Distal (runoff) Vessels:
The diagnostic accuracy and reproducibility of 3D contrast MRA in the distal runoff vessels has not yet been demonstrated. It is particularly challenging to perform on distal lower extremity vessels due to the substantial variations in contrast travel time.
- Renal Artery stenosis:
To visual renal artery pathology that affect both the proximal as well as distal renal arteries.

Reviewer's Comments: *Many noninvasive tests, including segmental pressure measurements or plethysmographic determinants of flow, are available for the diagnosis of PVD. When a significant lesion is suspected, an arteriogram is performed to define the location and extent of the arterial pathology. Due to the risks associated with the procedure, the non-contrast MRA has been used in the clinical practice for such a purpose. The original concept of MRA was to use the contrast intrinsic to the interaction between flowing blood and stationary tissues to produce angiographic images. Despite considerable efforts, flow artifacts in conjunction with lengthy acquisition times have limited the use of no contrast MRA to the carotid arteries and the intracerebral vasculature.*

The first pass contrast-enhanced MRA was designed to overcome those limitations. Under current practice, the first-pass contrast-enhanced MRA has been used for the majority of clinical-performed MRA exams. Between January 1991 and June 2002, approximately [] CE-MRA procedures have been performed in the United States.

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Based on a total of 33 controlled studies of 979 subjects, covering the peripheral arteries, the weighted sensitivity is 94%, and weighted specificity is 97%.

A blood pool contrast agent is being appreciated for its potential to perform a steady-state image. This would allow either submillimetric spatial resolution or a prolongation of the arterial examination, which is particularly important for coronary MR angiography. However, venous overlap and potential safety issues related to product's long half life are two major challenges for any blood pool contrast agents.

For a PVD indication, clinical practice and literature data appear to suggest that 3D contrast MRA can be performed well without steady-state imaging (provided by blood pool agents). First pass agents provide not only reasonable image quality, but also potentially favorable safety profile because of its short half life in the body.

2.3 Availability of Proposed Active Ingredient in the United States

MS-325 has not been approved or marketed in any countries at this time.

2.4 Important Issues with Pharmacologically Related Products

Based on the product labeling of other gadolinium-based MRI agents, literature data and post-marketing experience, a transient increase in the iron levels was observed. There was a concern that the products may affect serum calcium measurement. It appears that the subjects were well tolerated for a dose up to 0.3 mmol/kg.

***Reviewer's comment:** This review does not involve the reevaluation of the safety data of other gadolinium-based MRI contrast agents, and there are no major safety concerns at this time for those five approved MRI contrast agents. MS-325 should be treated differently because of 4-fold increase in AUC, compared to an equivalent dose of Gd-DTPA.*

2.5 Presubmission Regulatory Activity

The important timeline for the regulatory activities related to MS-325 are as follows:

- July 19, 1996 - Initial IND 51-172 was opened to study MS-325 as an intravenous agent for use with MRI to provide contrast enhancement of arteries in adult patients.
- August 1998 - A dose-ranging phase 1 trial (MS-325-1C) in health subjects has to stop at a dose level of 0.125 mmol/kg because the urinalyses revealed renal cells in 8 of 9 patients received a dose of 0.15 mmol/kg (both treated and placebo groups).
- **March 1999 – the following comments** were provided to the sponsor:
 - If the dose ranging study shows that a dose other than 0.03 mmol/kg, is optimal, then the results of a Phase 3 study, using this dose, would not very useful.

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- August 28, 2001 - End of Phase 2 Meeting with the following comments:
 - 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.
 - The Sponsor should prospectively specify the values of sensitivity, specificity, and accuracy that will be demonstrated in the Phase 3 study. Need study hypothesis with study effect size based on goal of equivalence to X-ray and superiority (clinical relevant) to baseline MRA.
- March, 2003 - Pre-NDA Meeting for MS-325
 - December 2003 - Submission of NDA 21711

Reviewer's comment: This reviewer is not sure whether dose for phase 3 is adequate, and also noted there was no placebo group in phase 3 trials.

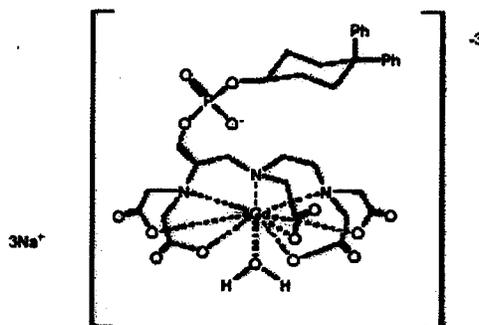
2.6 Other Relevant Background Information

None

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

MS-325 Injection contains the active pharmaceutical ingredient, gadofosveset, which is designated chemically as trisodium-{(2-(R)-[(4,4-diphenylcyclohexyl) phosphonoxy]methyl)-diethylenetriaminepentaacetato}(aquo) gadolinium(III)} with a molecular weight of 975.88 g/mol and empirical formula of $C_{33}H_{40}GdN_3Na_3O_{15}P$. The structural formula of gadofosveset trisodium in aqueous solution is:



Drug product is 0.25 mmol/mL in WFI, along with a small amount of free ligand to scavenge any free gadolinium. [

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Reviewer's Comments: *There is only [] free gadolinium ion in vitro. It fulfills current chemical standard.*

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3.2 Animal Pharmacology/Toxicology

The key findings from Pharmacology review are as follows:

- Cardiovascular safety-related findings: Arrhythmia in anesthetized dogs (unifocal and multifocal PVC) at 1.8X the clinical dose. One or more PVCs observed in monkey (n=2) at 0.27X and 2.7X the clinical dose. Findings are likely related to the drug.
- CNS-related effects: Transient hyperexcitability was the most remarkable effect. It is noted that administration of the high doses of MS-325 to monkeys induced salivation and vomiting during or immediately following administration, which are suggestive of a cholinergic stimulation.
- Effects on renal system: The toxicity studies identified the kidney as the main target organ for MS-325, with a dose-dependent proximal convoluted tubules vacuolation. Two week repeat-dose studies showed that dose-dependent kidney vacuolation was observed in all treated animals. It was accompanied in males by a BUN increase and creatine increase. The vacuolation was not reversible at 0.3X and higher doses, biochemical changes were reversible at 28 day. Overall, the renal system was inadequately investigated.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sponsor requests that the Agency consider the information presented in four Phase 3 studies (MS-325-12, MS-325-13, MS-325-14 & MS-325-15) as the primary evidence for determining the efficacy and safety of MS-325 for a general MRA indication. In addition, two Phase 2 dose ranging study (MS-325-02 & MS-325-09) was submitted as the supporting evidence. For the safety evaluation, data from all MS-325 exposure population (N=1,350) were submitted, including subjects from a total of 18 clinical trials.

**Appears This Way
On Original**

4.2 Tables of Clinical Studies

Table 4.2.1 List of Phase III clinical studies

Study No.	Study Title	Design	Dose (mmol/kg)	# of Vessel Segments	Control Treatment
MS-325-12	A Multicenter, Comparative, Phase III Study to Determine the Safety and Efficacy of MS-325-Enhanced MRA for Evaluation of Aortoiliac Occlusive Disease in Patients with Known or Suspected Peripheral Vascular Disease	Pivotal PVD (AIOD)	0.03	1. Infrarenal abdominal aorta (IRAA) 2. Left common iliac artery (CIA) 3. Right common iliac artery (CIA) 4. Left external iliac artery (EIA) 5. Right external iliac artery (EIA) 6. Left common femoral artery (CFA). 7. Right common femoral artery (CFA).	None
MS-325-13	A Multicenter, Phase III Study to Determine the Safety and Efficacy of MS-325-enhanced MRA in Patients with Suspected Peripheral Vascular Disease	Pivotal PVD (AIOD)	0.03	1. Infrarenal abdominal aorta (IRAA) 2. Left common iliac artery (CIA) 3. Right common iliac artery (CIA) 4. Left external iliac artery (EIA) 5. Right external iliac artery (EIA) 6. Left common femoral artery (CFA). 7. Right common femoral artery (CFA).	None
MS-325-14	A Phase 3, Multicenter Study to Determine the Safety and Efficacy of MS-325-enhanced MRA in Patients with Known or Suspected Renal Arterial Disease	Pivotal PVD (Renal)	0.03	1. Right renal artery (proximal and distal segments) 2. Left renal artery (proximal and distal segments) 3. Right accessory renal arteries (where present). 4. Left accessory renal arteries (where present).	None
MS-325-15	A Multicenter, Randomized, Open-Label, Two Dose, Comparative, Phase III Study to Determine the Safety and Efficacy of MS-325-Enhanced MRA in Patients with Known or Suspected Pedal Arterial Disease	Pivotal PVD (Pedal)	0.03, 0.05	1. Left posterior tibial 2. Right posterior tibial 3. Left dorsalis pedis 4. Right dorsalis pedis 5. Left medial plantar 6. Right medial plantar 7. Left lateral plantar 8. Right lateral plantar artery	None

Source Data: NDA 21711 Clinical Summary 3.8.3 p261

Table 4.2.2 List of Phase II Clinical studies

Study No.	Study Title	Design	Dose (mmol/kg)	Control Treatment
MS-325-02	A Phase II study of the Safety and Preliminary Efficacy of MS-325 Enhanced Magnetic Resonance Angiography in Carotid and Peripheral Arteries	Dose Escalation	0.01, 0.03, 0.05	None
MS-325-09	A Phase II, Randomized, Multicenter, Comparative, Dose-Ranging, Placebo-Controlled Study to Determine the Safety and Efficacy of MS-325-enhanced MRA for Evaluation of Aortoiliac Occlusive Disease in Patients with Known or Suspected Peripheral Vascular Disease	PVD Dose Escalation	0.005, 0.01,0.03,0.05,0.07	Placebo

Source Data: NDA 21711 Clinical Summary 3.8.3 p261

4.3 Review Strategy

The efficacy and safety reviews were conducted separately. Only data from pivotal phase 3 trials **were considered in determining MS-325's efficacy**. No pooled analysis was allowed for the efficacy determination.

The safety review was not limited to the four pivotal phase 3 trials. Death and serious adverse event cases from all clinical trials regardless of treatment indications were evaluated. A pooled analysis was employed to calculate the frequency of the safety outcomes of interest.

The following amendments (electronic version) were also reviewed:

- The original copy of NDA 21711 submitted on December 17, 2003
- The 120-day safety update of NDA 21711 submitted on 14 March 11, 2004
- The response to clinical request about QTc information submitted on April 14, 2004
- The response to clinical request for syncope information submitted on May 15, 2004
- The response to clinical request for hypoxia information submitted on June 11, 2004
- The response to clinical request for ST-T information submitted on July 16, 2004.
- The response to clinical request for clinical efficacy information submitted on September 2, 2004
- Annual report for IND 51722

4.4 Data Quality and Integrity

The following strategies were employed to evaluate data quality and integrity:

1. Conducted an independent analysis based on the original data sets provided by the sponsor;
2. **Cross checked patient's safety information (death and serious AE) with the Case Report Forms (CRF).**

4.5 Compliance with Good Clinical Practices

All pivotal trials were conducted in accordance with applicable laws and regulations and the ethical principles that have their origin in the Declaration of Helsinki. There were some **incidences of suboptimal patients' follow-up and record-keeping.**

- For one death patient, there were no vital sign on chart during first 24 hours.
- There was inconsistency regarding the cause of death between death certificate and NDA summary for one subject;
- The occurrence of non-sustained VT was not specifically mentioned for one patient who developed syncope.
- There was lack of documentation to support adequate safety evaluation and monitoring for two patients who developed severe hypoxia ($O_2Sat < 75\%$).
- The frequencies of AEs reported from some non-US sites appear to be significantly lower than that of US sites.

4.6 Financial Disclosures

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 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

- The plasma concentration-time profile of intravenously administered MS-325 conforms to a two-compartment open model. After bolus intravenous injection of 0.03 mmol/kg dosed at a rate of 1.5 mL/sec, the plasma gadofosveset concentrations declined more rapidly during the distribution phase compared to the elimination phase beyond 1 hour. The mean (\pm SD) concentration at 1 hour after the injection (0.24 ± 0.03 mmol/L) was 56% of the concentration (0.43 ± 0.04 mmol/L) recorded at 3 minutes after the injection. The mean half-life of the distribution phase ($t_{1/2\alpha}$) was 0.48 ± 0.11 hours and the mean half-life of the elimination phase ($t_{1/2\beta}$) was 16.3 ± 2.6 hours. The mean total clearance following the administration of 0.03 mmol/kg was 6.57 ± 0.97 mL/h/kg.
- **Distribution:** The volume of distribution at steady state for MS-325 was 148 ± 16 mL/kg, roughly equivalent to that of extracellular fluid. A significant portion of circulating

gadofosveset is bound to plasma proteins. At 0.05, 0.5, 1 and 4 hours after the injection of 0.03 mmol/ kg dose the plasma protein binding of gadofosveset was 79.8 (4% CV), 85.4 (2% CV), 86.7 (3% CV), and 87.4 (2% CV), respectively. Protein binding plays an important role in the pharmacokinetics and MR imaging properties of MS-325.

- Metabolism: The results from various evaluations of plasma and urine samples indicate that gadofosveset does not undergo measurable metabolism in humans and in laboratory animals.
- Elimination: In a study of 10 healthy volunteers at a dose of 0.03 mmol/ kg, gadofosveset was predominantly eliminated in the urine with **83.7% (range 79.0 – 94.0%) of the injected dose excreted in the urine in 14- days**. Ninety- four percent (94%) of the urinary excretion occurred in the first 72 hours. A small portion of gadofosveset dose was recovered in the **feces (4.7%, range 1.1 – 9.3%), indicating a minor role of biliary excretion in the elimination of gadofosveset.**

***Reviewer's comment:** During the bolus phase, a significant amount of MS-325 is in free form. Since MS-325 is administrated at a significantly lower dose, compared to that of other Gd-based contrast agents, the inability of taking the advantage of protein binding potential at the initial stage, along with the increased background tissue signal due to extravasations of the free form and subsequent binding to interstitial protein may affect the performance of MS-325.*

The other concern is that there are only 89% MS-325 were recovered from urine and feces, which appeared to be lower than that of other Gd-based agents. A detailed discussion of PK profile of MS-325 and the factors that may affect the PK profile can be found in clinical pharmacologist's review.

5.2 Pharmacodynamics

There is a concern regarding the potential pharmacodynamic effect of MS-325 because of its long half-life. This issue will be addressed in clinical safety review.

5.3 Exposure-Response Relationships

In one of the Phase 2 studies (MS-325-09), all patients evaluated for efficacy were scanned at 5 minute post-MS-325 administration. Clinical **pharmacologist's findings** are as follows:

- All regions Combined: Each MS-325 enhanced MRA image was analyzed in comparison to X-ray angiography image (the gold standard) for sensitivity, specificity, accuracy and kappa for the determination of disease state of the clinically significant stenosis in all three artery regions combined. The sponsor claims that MS-325 enhanced MRA performed well compared to conventional X-ray angiography. However, no clear dose response was seen.

- Results for Iliac Region: A positive dose response was noted at a dose range of 0.005 to 0.05 mmol/kg. A decreased response is reported at 0.07 mmol/kg.
- Results for Femoral Region: No dose response was noted since sensitivity and specificity were at 100% at all dose levels.
- Results for Carotid Region: A negative dose response was noted. Specificity and sensitivity decrease while the dose increases.
- Results for renal and foot Region: not performed.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

MS- 325 Injection is indicated for use with magnetic resonance angiography [

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Reviewer's Comments: This reviewer noted that [

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6.1.1 Methods

General approach to the efficacy review is as follows:

- Review the proposed indication;
- Identify all phase 3 pivotal studies used to support the indication;
- Image quality inspection;
- Conduct a detailed review of each of the pivotal studies.

6.1.2 General Discussion of Endpoints

Primary Endpoint: Ability to detect a clinically significant stenosis (50% as a cut-off point) measured by sensitivity and specificity.

Secondary Endpoint: Patient management decisions and percentage of uninterpretable images.

6.1.3 Study Design

The Phase 3 studies were open-label, multicenter studies performed to evaluate safety and efficacy of MS-325 at the 0.03 mmol/kg dose at pelvic, renal and foot regions (as well as the **0.05 mmol/kg dose in study MS-325-15 – foot region**).

These trials were prospectively designed to determine the sensitivity, specificity, and overall accuracy of MS-325 -enhanced MRA compared to pre-contrast MRA at baseline using catheter X-ray angiography (XRA) as the standard of reference for the detection of vascular disease.

Key inclusion & exclusion criteria:

- Known or suspected peripheral vascular disease diagnosed by physical examination and/or medical history. An X- ray angiogram including aortoiliac evaluation should be scheduled within 30 days prior or post- study enrollment.
- Not have undergone surgery or PTA of the target vessels within 30 days prior to study enrollment.
- No major cardiovascular events (e.g., myocardial infarct or stroke) within 30 days prior to enrollment.
- Have a serum creatinine level within the normal range for the site laboratory immediately prior to MS-325 administration for Study MS-325-12.

Reviewer's comments: *A total of 15 subjects with mild renal insufficiency (creatinine >1.5<2.0) had been enrolled in three other three trials.*

Selection of the Standard of Truth: XRA which could have been either intra-operative XRA or digital subtraction X-ray angiography (DSA)

Comparator: 2D-TOF (non-contrast MRA) at baseline

Reviewer's comments: *The fundamental concern is that there is a lack of standardized non-contrast protocol to ensure the optimal performance of MRA at baseline.*

6.1.4 Efficacy Findings

759 patients were evaluated in four adequate and well-controlled Phase 3 clinical trials. Of these, 672 evaluable patients were included in efficacy analysis. The demographic distribution showed in Table 6.1.4.1.

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Table 6.1.4.1 Summary of Demographic Characteristics for All Patients for 0.03 mmol/kg Dose group

Age	
N	767
Mean	64.4
Median	66
(min, Max)	(21,91)
Age Category (n%)	
<65 yrs	347 (45)
>=65yrs	420 (55)
Race(n%)	
Caucasian	604 (79)
Black	46 (6)
Hispanic	113 (15)
Other	4 (0.5)
Sex (n%)	
Male	505 (66)
Female	262 (34)
Country(N)	
US	321
Non-US	438
Mild renal insufficiency	15

Source data: Original NDA clinical data 08-6.1 P27. The number of mild renal insufficiency patients came from original safety data base.

Primary efficacy analysis by sponsor:

Table 6.1.4.2 shows how non-interpretable images were used in the sensitivity and specificity analysis in sponsor's original analyses.

Table 6.1.4.2 Primary analysis of Sensitivity, Specificity, and Accuracy for MRA Readers versus XRA Readers

Reader Response for MRA (Test Result)	XRA	
	Abnormal (>. 50% stenosis)	Normal (<50% stenosis)
Abnormal (>. 50% stenosis)	True Positive (TP)	False Positive (FP)
Non-interpretable	False Positive (FN)	False Positive (FP)
Normal (<50% stenosis)	False Negative (FN)	True Negative (TN)

Source data: NDA 21711 SSE Appendix1.1 p283

Clinical Review
 {Tong Li, M.D.}
 {NDA 21711}
 {Vasovist(MS-325)}

Table 6.1.4.3 and 6.1.4.4 showed the results of primary analysis based on the data imputation method stated in Table 6.1.4.2.

Table 6.1.4.3 Sensitivity of MS-325-enhanced MRA: Summary of Phase III Blinded Read Results for the 0.03 mmol/kg Dose provided by the sponsor

Study	MS-325	2D-TOF	Difference (%)
MS-325-12 AIOD (140 Patients, 237 Vessels)			
MRA Reader A	80.2	62	18.1***
MRA Reader B	73	66.7	6.3
MRA Reader C	69.8	41.8	19.0***
MS-325-13 AIOD (85 Patients, 146 Vessels)			
MRA Reader D	82.9	52.1	30.8***
MRA Reader E	84.2	60.3	24***
MRA Reader F	70.5	48.6	21.9***

Source Data: NDA Labeling , page 9

Table 6.1.4.4 Specificity of MS-325-enhanced MRA: Summary of Phase III Blinded Read Results for the 0.03 mmol/kg Dose provided by the sponsor

Study	MS-325	2D-TOF	Difference (%)
MS-325-12 AIOD (250 Patients, 1409 Vessels)			
MRA Reader A	84.5	71.5	9.4***
MRA Reader B	93.2	84.8	8.4***
MRA Reader C	95.3	75.4	19.9***
MS-325-13 AIOD (172 Patients, 1018 Vessels)			
MRA Reader D	80	70.7	9.2***
MRA Reader E	83	74.5	8.5***
MRA Reader F	90.1	78.2	11.9***

Source data: NDA Labeling, page 9

*p<0.05, **p<0.01, ***p<0.001 for improvement between VASOVIST. Injection Enhanced MRA and Unenhanced MRA based on corrected McNemar's Test

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b(4)

Clinical Review
 {Tong Li, M.D.}
 {NDA 21711}
 {Vasovist(MS-325)}

Notes: Uninterpretable MRA values were considered inaccurate for this analysis. Patients may contribute vessels to both sensitivity and specificity. Clinically significant disease is defined as .50% stenosis.

[1] Sensitivity population is the number of patients or vessels determined to be abnormal by XRA. Specificity population is the number of patients or vessels determined to be normal by XRA. Accuracy population is the total number of patients or vessels interpretable by XRA.

[2] Difference= (post-contrast MRA - pre-contrast MRA).

[3] P-value is from the modified McNemar test

Reviewer's comments for primary efficacy assessment

Those seemingly positive results, however, were based on a data imputation method, in which all non-interpretable MRA images were treated as **"inaccurate"** (Table 6.1.4.2). **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 statistical reviewer conducted a few alternative analyses. Table 6.1.4.5 showed the results of **"total exclusion strategy" i.e. excluding all non-interpretable** from the analysis. The analysis shows no statistically significant improvement in sensitivity and specificity from two out of three readers for all studies. Also we noted the performance of MS-325 were suboptimal. No trials have reached a minimal performance level of 80% for sensitivity and specificity.

Table 6.1.4.5 Changes of sensitivity and specificity of MS-325 enhanced MRI from baseline by reader and study

	Reader A		Reader B		Reader C	
	Change	95% CI	Change	95% CI	Change	95% CI
Study#12						
Sensitivity	.12	(.06, .18)	.05	(-.01, .11)	.10	(.05, .15)
Specificity	-.04	(-.07, -.01)	.05	(.03, .07)#	.03	(.01, .03)#
Study#13						
Sensitivity	.24	(.16, .32)	.18	(.10, .26)#	.15	(.06, .24)#
Specificity	-.08	(-.11, -.05)	-.02	(-.05, .01)	-.01	(-.03, .01)



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Source Data: NDA statistical review

In addition, this reviewer conducted a few subgroup analyses. The results are as follows:

Table 6.1.4.6 Sensitivity by type of selected vessels

Trials	Vessel	# of patients	# of Vessels	Sensitivity of MS-325
MS-325-12	Infra-Renal Abdominal Aorta	140	10	40
MS-325-12	Common Iliac Artery	140	100	74
MS-325-12	External Iliac Artery	140	88	76
MS-325-12	Common Femoral Artery	140	39	60
MS-325-13	Infra-Renal Abdominal Aorta	85	4	50
MS-325-13	Common Iliac Artery	85	61	92
MS-325-13	External Iliac Artery	85	54	74
MS-325-13	Common Femoral Artery	85	27	64

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Source: Reviewer summary from sponsor submitted data base on 06/03/2004. The sensitivity results are based reader-averaged analysis.

Table 6.1.4.7 Sensitivity by of AIOD trials by Subgroup

Parameter	Sensitivity (%)
Age	
<65	72
>65	71
Race	
Causasian	72
Black	73
Hispanic	71
Gender	
Male	73
Female	67
Center	
Site19(n=31)	70
Site 20 (n=38)	73
Site27(n=29)	68
Site 40(n=30)	69
<i>Site with <5 subjects</i>	<i>91</i>

Source Data: Sponsor statistical Tables E-13-1, 13.2, 13.3 and 13.4

It appears that sensitivity may vary by the type of vessels. Since the vessels with the lowest sensitivity also had the smallest N, no definitive conclusion can be made at this time. It noted that sites with < 5 subjects appeared to have a higher sensitivity.

Other important findings of the efficacy review include:

- (1) A lack of demonstration of the value of steady state images:

Unlike the blinded readers' analyses, the institutional readers interpreted the dynamic and steady state data separately in study MS-325-12. The institutional read demonstrated clinically significant improvement in sensitivity (73% vs. 64%) and specificity (81% vs. 63%) using the dynamic MS-325-enhanced MRA images compared to non-contrast MRA. Steady state images alone provided no improvement compared to the device alone. The uninterpretable rate from the dynamic post-contrast data was 9.7%, from the steady-state post contrast data was 25.4%, and from the pre-contrast data was 25.4%. Compared to the blinded readers, who read dynamic and steady-state images together, the institutional readers' **sensitivity and specificity were generally lower**, and the uninterpretable rates were higher.

Table 6.1.4.8 and 6.1.4.9 showed the results of the analyses.

Table 6.1.4.8. Institutional Read of Pre-Contrast and MS-325 MRA Images in Determining the Disease State of the Most Severe Stenosis Using the Institutional Read X-Ray Angiographic Image as the Standard

Scan Type	Percentage of Stenosis of the Most Severe Stenosis Determined by MRA Images										
	0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
Sensitivity											
2D-TOF	100	84	82	78	73	64	58	54	47	41	30
Dynamic MRA	99	89	87	84	79	73	66	58	51	43	26
Steady State MRA	99	77	75	69	64	51	45	41	37	30	20
Specificity											
2D-TOF	0	51	53	58	61	63	67	68	72	76	82
Dynamic MRA	0	56	65	74	76	81	83	85	87	88	91
Steady State MRA	0	48	55	63	66	68	72	74	77	80	84

Data Source: MS-325-12 Section 11.4.1.2.10 Institutional read analysis Page 75.
 Uninterpretable MRA images had the percent stenosis imputed using the symmetrical rule. If the vessel was normal by X-Ray, then percent stenosis was imputed as 100-(minimum X-Ray stenosis value). If the vessel was abnormal by X-Ray, then percent stenosis was imputed as 100-(maximum X-Ray stenosis value).
 Physician readers recorded only the most severe stenosis within each vessel.

Table 6.1.4.9 Comparison of sensitivity and specificity of dynamic and steady state imaging

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	--	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)			

Data source: Reviewer independent analysis from SSE data base.

We noted again that sensitivity and specificity of MS-325 were sub-optimal. As stated earlier, rabbit model shows that immediately after the injection at the clinical dose, 74% of MS-325 was in free form. This may increase the tissue signal background, due to extravasation of the free form.

What is more interesting is that data show the steady imaging may decrease the sensitivity. In the published MS-325 phase 2 carotid trial, 10% carotid arteries were not depicted separately from the internal jugular vein on the 5-minute MS-enhanced images; an additional 24% of vessels were obscured.

(2) Potentials for medical errors:

During the clinical trials, surgeons were presented with MRA images and were asked to recommend the patients management decision. Table 6.1.4.10 showed the comparison of inappropriate decision rate between contrast enhanced MRA and non-contrast MRA.

Due to the lack of sensitivity and specificity improvement and suboptimal performance of MS-325 enhanced MS-325, it appeared that there was **lack of consistent improvement in patients' management decision-making**. This analysis was subjective and for exploratory purpose only. But it did demonstrate the importance of having the minimal performance standard for a contrast enhanced MRA.

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{Tong Li, M.D.}
{NDA 21711}
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Table 6.1.4.10 Inappropriate patient management decision by study

Study 12			
Reader A		Reader B	
2D-TOF	MS-325	2D-TOF	MS-325
59/233	55/233	60/233	62/233
Study 13			
Reader A		Reader B	
2D-TOF	MS-325	2D-TOF	MS-325
80/345	95/345	90/345	108/345

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6.1.5 Clinical Microbiology

The drug product is terminally sterilized using moist heat. This submission is recommended for approval on the basis of product quality microbiology.

6.1.6 Efficacy Conclusions

- There is no adequate evidence to demonstrate improved sensitivity and specificity from all studies
- No studies reached the minimal performance level of 80% for sensitivity and specificity;
- The studies were not designed to demonstrate the added value of steady-state images. The preliminary data appear to suggest a decreased performance of steady-state images, compared to that of dynamic images;
- There were no clear dose-response from phase 2 data
- Lack of standardized baseline MRA imaging protocol to ensure the optimal performance of MRA at baseline.

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7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

This review is guided by the FDA Draft Guidance – **conducting a clinical safety review of a new product application and preparing a report on the review**. The key considerations are summarized as follows:

- The safety review is carried out in the following order regarding the safety outcomes:
 1. Death
 2. Serious adverse events
 3. Adverse events that resulted in dropouts
 4. Common adverse events
 5. Less common adverse events
 6. Laboratory findings
 7. ECG findings and vital signs
 8. Safety outcomes of special interest
- The review focuses not only on four Phase 3 pivotal studies (MS-325-12, MS-325-13, MS-325-14 & MS-325-15), but also on one Phase 2 dose-ranging study (MS-325-09); three Phase I pharmacokinetic/safety study (MS 325-01A/B/C) and PK trials in special populations with renal impairment (MS-325-07), hepatic functional impairment (MS-325-16) and in ESRD undergoing dialysis treatment (MS-325-18).
- In addition to reviewing the safety results compiled by the sponsor, an independent safety analysis was conducted based on the original safety databases submitted in the NDA.

7.1.1 Deaths

As of April 14, 2004, the date of the 120-day safety update, three death reports had been received from all human clinical trials in MS-325 clinical development. All three deaths occurred in MS-325-treated groups during Phase 2 developing period, and no death reported in Phase 3 studies. Table 7.1.1 summarized characteristics of these three death cases.

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Table 7.1.1. Listing of subjects who died during MS-325 clinical development program

ID	Protocol #	Age/Sex	Rx Group	Cause of Death	Time	Relation with MS-325		Test center
						Sponsor	Reviewer	
09/14/14	09	66/F	0.005 mmol/kg	Cardiac arrest	1 hours call code, 8 days die	Unlikely	?	USA
09/01/14	09	80/M	0.07 mmol/kg	Cardiac arrest	About 72 hours	Possible	agree	USA
18/01/02	18	53/F	0.05 mmol/kg	Cardiac arrest	15 days (HD patient)	Unlikely	?	USA

Source Data: Summary data from annually reports.

Subject 09/14/04: A 66- year- old, morbidly obese white female. She present with severe complications of diabetes and ischemic changes on an ECG. She was being hospitalized for lower extremity ulcers. She received 0.005 mol/ kg study drug on [] at 17: 10 with an unstable clinical condition. A code was being called about one hour post-dosing inside the hospital. She died 8 days later with clinical diagnosis of MI and multiorgan system failure.

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Reviewer's comments: *The primary investigators wrote a detailed report for our review. This reviewer basically agrees with the assessment stated in the submission. The death occurred in the milieu of severe vascular disease. The adverse event (acute myocardial infarction) most likely was the primary event led to the code one hour after MS-325 dosing. However, the patient presented bradycardia (HR 32) 45min post dosing, junctional rhythm, supraventricular tachyarrthmias and non-significant ventricular ectopy that may contribute to her initially homodynamic tenuous. The sponsor argued that that these arrhythmias might be due to morphine use. It was noted, however, most morphine was administrated in morning and noon, but severe bradycardia happened around 6:40 to 8pm when the patient was alert and eating. Therefore morphine was unlikely to trigger this arrhythmia. There are mild inhibitory cardiovascular efforts were observed on both health volunteers and the patient population, which appears to be cholinergic effects in nature.*

The opinion expressed here is based on the review of the following documentation:

- *One page patient summary – ISS, page 8-45587 December-12, 2003*
- *Case Report Form*
- *IND 51, 172 –Serial No. 077 7-Day IND safety report-follow-up.*

Subject 09/01/14:

The patient was an 80- year old, black male with a past medical history of peripheral vascular disease, who had a known abdominal aortic aneurysm (approximately 7 cm) prior to study entry. The patient underwent MRI with MS-325, on [] The patient received one dose of MS- 325 at 0.07 mmol/ kg. He was seen for the 24- hour follow- up exam and vital signs, blood, and urine samples were taken. At the visit the patient was alert, oriented, and denied any physical

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complaints and was in no distress. The patient did not return for the 72- 96 hours post-administration follow-up visit. The date and time of death were _____ 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.

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Reviewer's Comment: *This patient present with a typical story of this population. Being died at home without signs of trauma or distress makes AAA dissection unlikely (which would be marked by excursive pain). This patient received a dose of MS-325, 0.07 mmol/kg. While the causality assessment is challenging without an adequate control group, it is noted, however, by reviewing his hematology tests, 24 hours hemoglobin drops to 10.4 g/dl from baseline 11.5 g/dl. **This reviewer agrees with sponsor's assessment but at the same time believe that this case alone does not constitute a safety signal at this time. This case should be reevaluated after MS-325 in vivo stability data become available. The opinion expressed here is based on the review of the following documentation:***

- *One page patient summary – ISS, page 8-45587 December-12, 2003*
- *Case Report Form*
- *IND 51, 172 –Serial No. 077 7-Day IND safety report-follow-up*

Subject 18/01/02:

The patient was a 53- year old, black female with a medical history of diabetes, end- stage renal disease (on dialysis), hypertension, and anxiety disorder who was administered MS-325 0.05 mmol/kg on [] at an in-house facility. She was discharged from the facility on Day 8, []. She had experienced osteomyelitis of cervical spine and a retropharyngeal infection, received Vancomycin. She was seen at the clinical site on [] for her Day 14 safety visit. **The sub-investigator noted that she “felt better than earlier, but still had the pain”** in her neck with WBC 12.9. Two days later, [] the patient was found dead at home. The Medical Examiner planned to do an autopsy but the family refused to grant permission. The primary nephrologists submitted a Death Notification with cardiac arrest as the primary cause of death and septicemia as the secondary cause. (This information could be found in the IND annual report). In the NDA submission, the sponsor state that **“This AE’s verbatim description was exacerbation neck and back pain duo to retropharyngeal infection, severe in severity, and the investigator determined the AE unlikely related to MS-325.”**

b(6)

Reviewer's Comment: *The MS-325 proposed label states []*

b(4)

] This reviewer considers 5% drug staying in body for more than 14 days an important observation.

There is no data to document long term in vivo stability of MS-325. Total zinc and zinc fosveset excretion in renal impaired patients have not been measured. The possibility of Gd-transchelation cannot be reasonably excluded. Presence of anisocytosis on Day 8 and Day 14 samples is not reassuring though anisocytosis is common in this population. There is a need to demonstrate MS-325's in vivo stability to ensure the safety of MS-325 in renal insufficiency patients.

7.1.2 Other Serious Adverse Events

Table 7.1.2 lists the subjects and serious adverse events by the treatment group. The sponsor has reported that thirteen patients experienced a total of 15 SAEs, including one patient in Study MS-325-07, six in MS-325-09, three in MS-325-12, one in MS-325-13 and one in MS-325-15.

Table 7.1.2 Listing of Subjects with Serious Adverse Events in All Clinical trials

Study	Dose Group (mmol/kg)	Site	Subject Number	Gender Race Age	Event time	Event	Relation To Drug		Out-come
							sponsor	reviewer	
MS-325-09	0.005	USA	09/01/029	M/B/80	24 hours	Syncope with trauma	Unlikely	possibly	2
MS-325-12	0.03	USA	12/04/03	M/B/65	72 hours	Hyperglycemia MI	Unlikely	?	4
MS-325-12	0.03	USA	12/20/12	M/W/72	<24 hours	Gangrene of toes	Unlikely	agree	2
MS-325-12	0.03	USA	12/38/07	M/W/64	25 hours	Chest pain MI	Unlikely	?	2
MS-325-13	0.03	Germany	13/136/003	F/W/66	<1 hours	Anaphylactoid	Probably	agree	2
MS-325-15	0.05	Germany	15/81/02	M/W/75	72 hours	MI	Unlikely	?	4
MS-325-07	0.05	USA	07/02/05	M/W/64	14 days	Abd mass bruit	Unlikely	agree	2
MS-325-09	0.05	USA	09/09/06	F/W/60	24 hours	Chest pain Bradycardia Prolonged QT	Possibly	agree	2
MS-325-09	0.05	USA	09/01/17	M/W/64	<1 hours	Anaphylactoid	Probably	agree	2

Clinical Review
 {Tong Li, M.D.}
 {NDA 21711}
 {Vasovist(MS-325)}

MS-325-09	0.07	USA	09/22/18	M/W/68	72 hours	Syncope with trauma, VT	Unlikely	possible	2
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Source Data: Revised from sponsor's table 7-25 in SSI section p54.

Reviewer's comments: *There are two anaphylactic cases, the sponsor claims probably related with MS-325, one abdominal mass bruit, one gangrene of toes, the sponsor claims unlikely related to the MS-325, this reviewer agrees with above assessment. This reviewer has concerns over cardiac events **even though patient's underlying condition is likely to be responsible for those events.** Since we know that Gd+3 in body may cause cardiac events, there is a need to demonstrate MS-325's in vivo stability before drug-effect can be excluded.*

The following syncope case highlights the need for such a demonstration for in vivo stability.

The summary of patent #09/22/18 in the IND annual report:

The patient, a 69-year old Caucasian male, received 0.07 mmol/kg of MS-325 on 11/21/00 at 12:12 and completed the MRA without incidence. Prior to the 72 hour follow-up visit on 11/24/00, the patient experienced a syncopal episode at home with loss of consciousness. He was admitted to the hospital on [] for observation. A cardiology consult showed no evidence of an MI. The patient experienced a non-sustained episode of ventricular tachycardia rhythms of about 10-15 beats while in the hospital, which suggests that ventricular tachycardia might be the cause for syncope episode. The principal investigator considered this SAE as unexpected, moderate and unlikely related to MS-325.

b(6)

Reviewer's Comments: *This is a stable patient with a medical history of CVA, TIA (1993), HTN and remote aortic dissection surgery in 1993. The patient did not present to 24 hour follow-up. He was being hospitalized for syncope prior to his 72 hour follow-up. If MS-325 is injected into the lateral ventricle of the brain, a cholinergic-like effect could be induced in rat model. Consider history of stroke, the possibility of MS-325 passing BBB in this patient is a possibility. This reviewer is more concerned about VT which may have a wider implication.*

Spontaneous ventricular tachycardia could happen in any patient, particularly in this patient population. The severity of this event and possible correlation with Gd+3 in body (from unstable MS-325) makes it necessary to study the in vivo stability of MS-325 prior to the approval. In addition, this reviewer is concerned that VT was not adequately disclosed in NDA submission.

7.1.3 Dropouts and Other Significant Adverse Events

Three patients discontinued a study because of AE's. Patient 09/01/08 and 09/01/14 have been discussed in the sections above, and the patient 15/81/02 with history of renal mass had the increased creatine from 1.6 to 2.2 mg/dl.

7.1.3.1 Overall profile of dropouts

The same as above.

7.1.3.2 Adverse events associated with dropouts

The same as above.

7.1.3.3 Other significant adverse events

This reviewer conducted an independent search for life-threatening vital sign change and ventricular tachycardia in the submitted data base. Following information is found:

- 17 subjects experienced O2 sat drop to <90% without documented intervention.
- Two cases of non-sustained ventricular tachycardia were noted. One patient had no symptoms and reported as a mild AE. The other was being hospitalized for syncopal episode. The possibility that MS-325 may play a role here cannot be totally excluded.

Reviewer's Comments: Spontaneous ventricular tachycardia happens in any population and hypoxia is not a rare event in MRI suit. The data may just indicate background noise. The issue is the lack of proper evaluation and reporting.

7.1.4 Other Search Strategies

- In addition to reviewing the safety results compiled by the sponsor, an independent safety analysis was conducted based on the original safety databases submitted in the NDA.
- The information about death and SAE for this NDA was compared to that in the original IND 51-172 annual reports.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Based on the study protocols, the adverse events were collected at the baseline and then at 45min, 24 hour and 72-96 hour follow-up. The sponsor provided each study site with a standard open-ended AE collection form, which was filled out for each study subject. Data elements

included description of event, onset and stop dates, severity and seriousness of the event. The relationship to the study drug as judged by the study investigator.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The sponsor has provided in this submission SAS datasets that contain all adverse events recorded in the AE collection form all subjects in all controlled trials. The original description of the adverse event (terms used by investigator and patients) was recoded by using the standard MedDRA dictionary (the Medical Dictionary for Regulatory Activities), the new global standard medical terminology. For each adverse event, there were different levels of MedDRA terms, such as preferred term or verb term.

Reviewer's Comment: *This reviewer had some concerns about AE categorization. For example, in the table below, following AE's may represent CVS toxicity, but the sponsor categorized them in other body systems. As stated early, ventricular tachycardia was being categorized as nervous system disorders. Some significant changes in vital signs may not have been reported as AE's.*

Table 7.1.5.2 MedDRA preferred Term Provided by sponsor

Body-system	Prefterm	Verbterm
<u>General disorders and administration site conditions</u>	Chest pain	Chest pain
<u>Investigations</u>	Blood pressure decrease	Blood pressure decrease
<u>Investigations</u>	EKG abnormal NOS	ECG ST-T abnormalities
<u>Investigations</u>	EKG QT prolonged	Prolonged QT interval
<u>Nervous system disorders</u>	Syncope	Syncope with decrease heart rate
<u>Nervous system disorders</u>	Vasovagal attack	Vasovagal reaction
<u>Investigations</u>	Oxygen saturation decreased	Oxygen desaturation

Source Data: SSI 7.2.1.1. MedDRA Coding for the Integrated Summary of Safety p32.

7.1.5.3 Incidence of common adverse events

Table 7.1.5.3 List of AEs with a frequency > 1% from all patients received MS-325 regardless of dose

Adverse Events (Preferred Term)	All patients received MS-325 (N=1,321)	All patients received 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%)

Clinical Review
 {Tong Li, M.D.}
 {NDA 21711}
 {Vasovist(MS-325)}

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)

7.1.5.4 Common adverse event tables

Table 7.1.5.4. Number and percent of patients experiencing the most frequently occurring AEs for all patients.

Preferred Term	Placebo N=49	<0.03 N=95	0.03 N=767	0.05 N=348	>0.05 N=111
Any AE	23(46.9)	24(25.3)	276(36)	185(53.2)	86(77.5)
Pruritus NOS	2(4.1)	1(1.1)	38(5)	40(11.5)	20(18)
Paresthesia	1(2.0)	0	21(2.7)	39(11.2)	7(6.3)
Headache NOS	3(6.1)	2(2.1)	33(4.3)	35(10.1)	20(18)
Nausea	0	2(2.1)	32(4.2)	29(8.3)	20(18)
Vasodilatation	1(2.0)	1(1.1)	25(3.3)	20(5.7)	7(6.3)
Burning sensation NOS	0	0	15(2.2)	29(8.3)	7(6.3)
Dysgeusia	6(10.2)	2(2.1)	17(2.2)	20(5.7)	22(19.8)
Dizziness	5(10.2)	0	8(1)	12(3.4)	17(15.3)
Feeling cold	0	2(2.1)	6(0.8)	12(3.4)	5(4.5)
Injection site bruising	0	0	19(2.5)	0	4(3.6)
Venipuncture site bruise	0	0	17(2.2)	4(1.1)	0
Hypertension NOS	1(2)	1(1.1)	11(1.4)	4(1.1)	1(0.9)
Rash NOS	0	0	3(0.4)	11(3.2)	2(1.8)
Diarrhea NOS	0	1(1.1)	4(0.5)	10(2.9)	0

Source Data: SSI Table 7-7, page 37

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7.1.5.5 Identifying common and drug-related adverse events

Table 7.1.5.5. List of most frequently occurring adverse events dose group among patients and Volunteers.

US/CANADA	AE #	Subject #	Ratio
Placebo+ 0 dosing	108	148	0.7
<0.03	64	109	0.6
0.03	538	483	1.1
0.05	636	326	1.9
>0.05	312	147	2.1
Health Volunteers	# AE	# subject	ratio
Placebo	42	30	1.4
<0.03	6	12	0.5
0.05	52	29	1.8
>0.05	107	36	2.9
Total exposure group	165	77	2.14
MS-325-09	# AE	# Subject	Ration
Placebo	50	58	0.86
<0.03	103	78	1.32
0.03	59	39	1.51
0.05	73	43	1.69
>0.05	76	40	1.9

Source Data: Independent analysis from ISS data base.

Reviewer's Comment: Data presented clearly demonstrates MS-325-associated adverse events are dose-dependent.

The most common adverse events that occurred in more than 5% of MS-325 treated subjects are pruritus, paresthesia, headache, nausea and vasodilatation. The sponsor's main conclusion included:

- The incidence of these events are dose-related.
- All of these events were most often considered related to the MS-325.

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7.1.5.6 Additional analyses and explorations

Table 7.1.5.6.1. Comparison of most common Adverse Events with other Gadolinium-based contrast agents

	MultiHance	Magnevist	ProHance	Omniscan	OptiMark	MS-325
Headache	1.7	5.5	-	<3%	8.4	5.8
Nausea	1.5	2.5	1.4	<3%	3	5.3
Vasodilatation	0.9	-	-	-	2.3	5.1
Paresthesia	0.7	-	-	-	2.1	6.1
Pruritus	-	-	-	-	-	7.5

Source data: reviewer summary from the label of each agent. *High frequency of vasodilatation for MS-325 is noted.*

Table 7.1.5.6.2. Onset time of AEs after injection for all patients who received MS-325

Events	0-2 Hours	2-24 Hours	24-48 hours	72 Hours	>72 hours
All events 1292	712(55%)	242(18.7%)	81(6.3%)	68(5.3%)	189(14.6)
Headache 86	19(22.1)	35(40.7)	11(12.8%)	3(3.5%)	18(20.9)
Nausea 76	54 (71.1)	16(21.1%)	2(2.6%)	1(1.3%)	3 (3.9%)
Dizziness 24	13 (54%)	8(33%)	0	1(4.2)	2(8.3%)
Diarrhea 17	0	10(58.8%)	1(5.9%)	1(5.9%)	5(29.4)

Source Data: Revised from SSI table7-9, Page38

Reviewer's Comments: *Approximately 20% AEs occurred after 72 hours. It appears that different type of AEs may have different Emax.*

Table 7.1.5.6.3 Summary of patients who Experienced the most common adverse events by severity for all patients who received MS-325:

Any AE	Mild	Moderate	Severe
N=676	511	137	28
%	76%	20%	4%

Source Data: Revised from SSI Table7-15, page44

For 28 severe adverse events, 15 happened in the 0.03 mmol/kg dose group and 75% of these events might involve symptoms related to the actions of generalized cholinergic stimulation (headache, MI, syncope, chest pain, abdominal discomfort, bradycardia, dyspnea, dysuria, muscle cramps, nausea, pain, vigors, vasodilatation, etc)

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Table 7.1.5.6.4. Total Count of Enrolled and Safety Population Patients Across four Phase 3 Studies

Study	Country	Enrolled	Safety
MS-325-12	US	282 (89%)	244 (89%)
	Non-US	33 (10%)	30(11%)
MS-325-13	US	64(36%)	64(36%)
	Non-US	114(64%)	114(64%)
MS-325-14	US	8(5.5%)	8(5.5%)
	Non-US	137(94.5%)	137(94.5%)
MS-325-15	US	13(7%)	13(7%)
	Non-US	172(93%)	172(93%)
Total	US	367(44%)	329(42%)
	Non-US	456(55%)	453(58%)

Source Data: Sponsor's responses to FDA clinical request 09/09/2004

Table 7.1.5.6.5. Summary of AE's reported by USA and Foreign country

MS-325 Dose	Subjects#	AE#	Ratio
Foreign 0.03 mmol/kg	281	146	0.52
Foreign 0.05 mmol/kg	77	40	0.52
Placebo USA	37	26	0.7
<0.03 mmol/kg USA	92	53	0.58
0.03 mmol/kg USA	458	514	1.12
0.05 mmol/kg USA	81	81	1
>0.05 mmol/kg USA	41	70	1.7
Total	1067	930	0.87

Source: Reviewer summary from original NDASSI data base.

Reviewer's comments: Data from Table 7.1.5.1-5 showed the incidence rate of most common events appears to be slightly higher, as compared to that of other gadolinium agents. It is particularly true for vasodilatation. Most of AEs started within first 2 hours. However, approximately 20% AEs has a delayed onset after 72 hours. Some of those events appear to be generalized cholinergic stimulation (headache, MI, syncope, chest pain, abdominal discomfort, bradycardia, dyspnea, dysuria, muscle cramps, nausea, pain, vigors, vasodilatation, etc). AE reported from foreign countries is lower than that in the US. This may affect general assessment of AE frequency.

7.1.6 Less Common Adverse Events

All significant less common adverse events have been discussed under the section of serious adverse events. Important events included myocardial infarction, syncope, bradycardia, and other cardiac arrhythmias. The causal relationship cannot be established at this time.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Based on the study protocols, routine laboratory testing was conducted at the baseline and then at each of the follow-up visits (2 hours, 24 hours and 72 hours). The laboratory tests included:

- Blood chemistry
- Hematology and coagulation
- Urinalysis
- Metals
- Immunology

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

For each study, blood chemistry, hematology, urinalysis and other laboratory data were collected at baseline and at several time points post-baseline. For the purposes of the summaries of laboratory data, baseline values were defined as the last value recorded prior to dosing. The post-baseline time points at which laboratory data were summarized were 2, 24, and 72 hours post-dosing, as these were the nominal time points for blood sample collection in the Phase 3 studies.

7.1.7.3 Standard analyses and explorations of laboratory data

A clinically significant value was defined as any value that was out of normal range and deemed by the investigator to be clinically significant. Summary statistics are also presented for the change in each laboratory variable from baseline to each post-baseline time point.

7.1.7.3.1 Analyses focused on measures of central tendency

Table 7.1.7.3.1. Summary (mean and sd) of baseline and significant mean change from baseline in general clinical chemistry assays and hematology assays for all patients who received MS-325

Assay	Baseline		2 hours		24 hours		72 hours	
	N	Mean (sd)	N	Mean (sd)	N	Mean (sd)	N	Mean (sd)
Serum glucose	1277	121.1 (56)	1204	+ 9.9 (44)	1178	+6.2 (42)	1168	-0.3 (44)
Creatine Kinase	1045	116.1 (226)	980	-4.9 (64.0.1)	957	+2.4 (198)	952	-13.4 (197.4)

Clinical Review
 {Tong Li, M.D.}
 {NDA 21711}
 {Vasovist(MS-325)}

Norepinephrine	745	400 (227)	664	+54 (247)	600	-8.9 (187)	598	-18.7 (205)
Calcium	1293	9.5 (0.53)	1243	-0.1 (0.46)	1215	0 (0.45)	1203	-0.1 (0.48)
Hematocrit	1232	42.2 (4.9)	1115	-0.4 (2.3)	1088	-0.9 (2.5)	1084	-1.4 (2.8)
Hemoglobin	1253	14.2 (1.58)	1162	-0.1 (0.65)	1137	-0.3 (0.68)	1120	-0.1 (0.79)
RBC	1253	4.5 (0.54)	1162	0 (0.23)	1137	-0.1 (0.24)	1120	-0.10 (0.28)
Platelets	1238	261.92 (85.45)	1133	-3.59 (26.58)	1116	-2.86 (26.48)	1090	-2.46 (33.89)

Source Data: Revised from SSI, Table 8-2 and Table 8-7. page 59 & Page 66

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

There are ten subjects showing hyperglycemia at 0.03 mmol/kg dose. Considered 33% patients with known history of diabetes, this finding is not a safety concern at this time. However, drug-to-drug interaction between MS-325 and anti-diabetic medication should be further evaluated by the sponsor.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

Table 7.1.7.3.3 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 from ISS database.

Reviewer's Comments: 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. This reviewer concerns about hemoglobin drop in patients with renal impairment. Please see discussion the later sections.

7.1.7.4 Additional analyses and explorations

Additional analysis was conducted for mild renal insufficiency patients, detailed results refer to the next section.

7.1.7.5 Special assessments

At FDA's request, special assessments for metals, renal and liver function were conducted.

- Summary of results for Metals:

Table 8-14. Summary of Baseline and Mean Change from Baseline for Serum Calcium by Dose Group for All Patients

	Placebo		Dose Level (mmol/kg)							
	n	mean (sd)	<0.03 n	<0.03 mean (sd)	0.03 n	0.03 mean (sd)	0.05 n	0.05 mean (sd)	>0.05 n	>0.05 mean (sd)
Serum calcium ^a										
Baseline	49	9.4 (0.5)	94	9.5 (0.5)	751	9.5 (0.6)	339	9.4 (0.5)	109	9.4 (0.4)
2-hour change	49	-0.2 (0.4)	90	-0.1 (0.6)	721	-0.1 (0.4)	326	-0.1 (0.6)	106	-0.1 (0.5)
24-hour change	48	-0.1 (0.4)	88	0.0 (0.4)	700	0.0 (0.4)	323	-0.1 (0.5)	104	0.0 (0.4)
72-hour change	48	0.0 (0.4)	88	-0.1 (0.5)	690	-0.1 (0.5)	322	-0.1 (0.5)	103	-0.1 (0.4)

a Normal range: 8.4 - 10.3 mg/dL

Cross-reference: Statistical Table S-5.0, Statistical Table S-5.1

Table 8-15. Summary of Baseline and Mean Change from Baseline for Serum and Urine Iron by Dose Group for All Patients

	Placebo		Dose Level (mmol/kg)							
	n	mean (sd)	<0.03 n	<0.03 mean (sd)	0.03 n	0.03 mean (sd)	0.05 n	0.05 mean (sd)	>0.05 n	>0.05 mean (sd)
Serum Iron ^a										
Baseline	48	96.8 (30.1)	93	89.2 (31.4)	734	91.1 (34.2)	336	91.9 (159.6)	108	91.0 (24.6)
2 Hour Change	46	0.1 (23.3)	86	-1.6 (26.5)	684	-5.6 (19.9)	320	-3.0 (47.9)	105	-1.2 (17.4)
24 Hour Change	47	-8.2 (29.3)	86	16.7 (34.2)	677	4.0 (27.0)	324	-1.4 (73.0)	103	-2.5 (24.9)
72 Hour Change	46	-8.1 (29.3)	88	-5.8 (34.0)	656	-7.8 (27.7)	318	-7.8 (100.1)	102	-10.7 (23.6)
Urine Iron ^b										
Baseline									16	0.2 (0.16)
72 Hour Change									11	0.0 (0.15)

a Normal range: 45 - 160 µg/dL

b Normal range: 0.1 - 0.3 mg/24 hr

Cross-reference: Statistical Table S-5.0, Statistical Table S-5.1, Statistical Table S-7.0, Statistical Table S-7.1

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Table 7.1.7.5 Summary of baseline and Mean changes from baseline for serum and 24-hours urine zinc for patients who received 0.05 mmol/kg MS-325-treated patients

	N	Mean
Serum Zinc (normal 0.6-1.1 ug/kg)		
Baseline	11	0.8
2 hour change	10	0
24 hour change	10	0
72 hour change	10	0
Urine Zinc (normal 300-600 ug)		
Baseline	10	553 ug
24 hour change	10	1302 ug
72 hour change	10	68 ug

Reviewer's Comments: Among all patients treated with MS-325, 5 (0.4%) had hypocalcaemia reported as an AE, including 2 at the proposed clinical dose. One SAE (chest pain) was reported by a patient concomitantly experiencing hypocalcaemia. There is an apparent increase in zinc excreted in urine post dosing. There are only 89% MS-325 were recovered from urine and feces. Those findings are not reassuring. In vivo stability of MS-325 should be adequately demonstrated.

- Liver Safety

Table 7.1.7.6 Number of percentage of patients with abnormal testing results

Laboratory tests	Placebo N=49	0.03 mmol/kg N=767
SGOT	0	1 (0.1%)
SGPT	0	1 (0.1%)
Serum ferritin	0	1 (0.1%)
Bilirubin	0	0

No other clinical chemistry parameter shows a clinically significant trend. Fluctuations were noted in several values, especially ferritin and serum iron, but this variation takes place within the normal range and within a clinically insignificant range of values, and is noted also in the placebo group. MS-325 appears to have no clinically significant effect on clinical chemistry values in any dose group.

- Renal Safety

Please see Section 8.3.1.1.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

For trial MS-325-12, vital signs parameters, including systolic and diastolic blood pressure, pulse, respiration rate, and temperature, were recorded at five time points around the MRA: Baseline, within 45 Minutes, 2 Hours, 24 Hours, and 72-96 Hours post-dose. Pulse oximetry was recorded at two time points; within 10 minutes post-MS-325 dosing and at 2 hours post-dosing.

Vital signs [systolic blood pressure, diastolic blood pressure, pulse rate, respiration rate, and temperature] were measured at baseline and 45 (± 15) minutes, 2 hours (± 15 minutes), 24 (± 4) hours, and 72-96 hours post-dose. Pulse oximetry was measured within 15 minutes before and 15 minutes after dosing for trials MS-325-13; MS-325-14, and MS-325-15.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Table 7.1.8.2 Number of vitals measurements available at baseline and at different time points post baseline (phase 3 studies only)

# of Bp	Baseline	Prior MRA	10 min	45 min	2 h	24 h	72 h
MS-325-12	275	247	105	13	269	265	235
MS-325-13	178	177	NA	178	178	178	175
MS-325-14	144	144	NA	144	145	144	143
MS-325-15	185	185	NA	185	185	185	179

# of OXSAT	baseline	10 -15 min	2 h
MS-325-12	269	268	209
MS-325-13	177	178	NA
MS-325-14	145	143	NA
MS-325-15	185	185	NA

# of pulse	Baseline	Prior MRA	45 min	2 hour	24 h	72-96 h
MS-325-12	277	271	20	269	261	235
MS-325-13	178	177	178	178	178	175

Source Data: Medical reviewer independent analysis of SSI data base.

Reviewer's comments: *The patient blood pressure and pulse were not be monitored for the first 30 minutes post dosing. If patients developed hypoxia post doing, we would not know when they could start to recover. The safety monitoring procedure appears to be suboptimal.*

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Table 7.1.8.3.1 Analysis of mean Change from baseline Vitals signs in Phase 3 studies.

Study #	Baseline Mean SBP (mmHg)	Prior MRA Mean SBP (mmHg)	10 min Mean SBP (mmHg)	45 min Mean SBP (mmHg)	2 h Mean SBP (mmHg)	24 h Mean SBP (mmHg)	72 h Mean SBP (mmHg)
MS-325-12	141 (N=523)	N/A	144.5 N=105	139.4 N=13	139.4 N=249	137.6 N=265	138.4 N=235
MS-325-13	137.8	138	NA	141.7	137	135.5	138.1
MS-325-14	151	150	NA	149.8	147.4	146.6	145
MS-325-15	143.8	142.7	NA	143.3	140.8	139.8	138.8

Study#	Baseline Mean DBP (mmHg)	Prior MRA Mean DBP (mmHg)	10 min Mean DBP (mmHg)	45 min Mean DBP (mmHg)	2 h Mean DBP (mmHg)	24 h Mean DBP (mmHg)	72 h Mean DBP (mmHg)
MS-325-12	75.4 N=523	N/A	79 N=105	70.8 N=13	74.4 N=249	73.1 N=265	74.8 N=235
MS-325-13	74.6	75	NA	76	73.6	73.6	74.8
MS-325-14	85.1	82.6	NA	82.7	82.2	82.2	143
MS-325-15	78.6	77.8	NA	78	77.1	76.7	76.1

Study #	Baseline Mean O2SAT(%)	10 -15 min Mean O2SAT(%)	2 h Mean O2SAT(%)
MS-325-12	95.6	95.1	95.6
MS-325-13	95.8	95.3	NA
MS-325-14	96.4	96.6	NA
MS-325-15	96.1	96	NA

Study #	Baseline Mean Pulse (bpm)	Prior MRA Mean Pulse (bpm)	45 min Mean Pulse (bpm)	2 hour Mean Pulse (bpm)	24 h Mean Pulse (bpm)	72-96 h Mean Pulse (bpm)
MS-325-12	73.8		10 min 72.4 N=248	71.3 N=20	75.1	76.3
MS-325-13	73.6	72.6	72.4	74	73	74
MS-325-14	69.4	68	67.4	67.6	67.4	68.3
MS-325-15	72	72.1	72.3	72.6	72.1	71.2

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.

Reviewer's Comments: *Though mean changes were small, it suggests that the drug may affect homodynamic parameters.* □

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7.1.8.3.2 *Analyses focused on outliers or shifts from normal to abnormal*

The following Sponsor-defined changes from Baseline were used as a guide in determining Clinical significance:

- systolic blood pressure change >20 mmHg
- diastolic blood pressure change >20 mmHg
- heart rate change >15 beats/minute
- respiratory rate change >10 breaths/minute
- temperature change >1.1° C (>1.9° F)
- pulse oximetry change >10%.

Table 9-17. Number and Percent of Patients who Experienced Clinically Significant Vital Signs Abnormalities by Dose Group for All Patients who Received MS-325

	Placebo (N=49)	Dose Level (mmol/kg)				All MS-325 (N=1321)
		<0.03 (N=95)	0.03 (N=767)	0.05 (N=348)	>0.05 (N=111)	
Cardiac disorders	1 (2.0)	1 (1.1)	4 (0.5)	2 (0.6)	1 (0.9)	8 (0.6)
Bradycardia NOS	0 (0.0)	1 (1.1)	2 (0.3)	0 (0.0)	0 (0.0)	3 (0.2)
Tachycardia NOS	1 (2.0)	0 (0.0)	2 (0.3)	2 (0.6)	1 (0.9)	5 (0.4)
General disorders and administration site conditions	0 (0.0)	0 (0.0)	2 (0.3)	5 (1.4)	0 (0.0)	7 (0.5)
Pyrexia	0 (0.0)	0 (0.0)	2 (0.3)	5 (1.4)	0 (0.0)	7 (0.5)
Investigations	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	2 (1.8)	3 (0.2)
Pulse abnormal NOS	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	1 (0.9)	2 (0.2)
Respiratory rate increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.1)
Vascular disorders	2 (4.1)	1 (1.1)	14 (1.8)	4 (1.1)	1 (0.9)	20 (1.5)
Hypertension NOS	1 (2.0)	1 (1.1)	11 (1.4)	4 (1.1)	1 (0.9)	17 (1.3)
Hypotension NOS	1 (2.0)	0 (0.0)	3 (0.4)	0 (0.0)	0 (0.0)	3 (0.2)

Cross-reference: Statistical Table S-2.5

According to sponsor, there is no significant number of vital signs changes identified. However, an independent ISS data base search was conducted with the following findings.

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7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

Table 7.1.8.3.3. List of subject with baseline OXSAT > 90 and post baseline OXSAT <=90

Patient ID	Baseline oxsat(%)	15 min Post dosing oxsat(%)
P09/004/012	93	90
P09/010/019	94	90
P09/025/003	98	89
P12/019/016	95	90
P12/019/017	92	88
P12/020/002	91	90
P12/020/032	96	90
P12/034/012	94	75
P12/040/016	92	88
P12/040/020	96	90
P13/061/007	92	90
P13/066/008	98	90
P13/066/013	96	88
P13/066/014	92	90
P13/075/005	98	74
P13/117/003	94	90
P14/132/002	92	85
P14/145/002	91	87
P15/113/023	94	90

Reviewer's comments: *There are significant variability in vital signs and pulse oximetry data. The sponsor claims that it is not unexpected for at least two reasons: (1) the manner in which these observations were obtained, and (2) the patients' underlying medical conditions. This reviewer agrees. In the clinical setting of the studies, the patient's physical position (recumbent, prone, or sitting) at which the vital signs and pulse oximetry were taken varies from patient to patient and from time to time. Postural changes and the compensatory circulatory changes might account for a wider change in these vital signs in some patients. Additionally, underlying hypertension and relate medical therapy might also have added to the observed variability.*

Without an adequate control group, those explanations may not be sufficient enough to alleviate the concerns for those clinically significant outliers, such as an Oxygen sat drop to 75%, or a drop in diastolic blood pressure to 40 mmHg. This reviewer is particularly concerned about the two subjects with post dosing measurements Oxygen Sat. of below 75%. There is no documentation to show proper evaluation and management.

7.1.8.4 Additional analyses and explorations

None

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Table 9-1. Number of 12-lead ECG Results for Patients by Time Relative to Dosing

Pre-dose Time Points		Post-dose Time Points	
Time Point	Number of Subjects	Time Point	Number of Subjects
Screening	189	45 min post-dose	886
Baseline	770	1 hr post-dose	41
24 hrs prior to dose	388	2 hrs post-dose	252
12 hrs prior to dose	70	8 hrs post-dose	53
45 min prior to dose	19	24 hrs post-dose	610
		72 hrs post-dose	21
		72-96 hrs post-dose	1109
		120 hrs post-dose	1
		168 hrs post-dose	103
		10 days post-dose	72
		14 days post-dose	103
		20 days post-dose	1
		21 days post-dose	18
		Unscheduled/Early Term	48

Cross-reference: Appendix 20.3.9

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7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Table 7.1.9.2 QTc changes from two placebo-controlled phase 1 studies

MS-325-01A & 01C QTcB Time	Placebo N=30	<0.03 N=12	0.05 N=12	>0.05 N=36
0.25	3.9	1.75	5.3	10.4
1	1.9	0	2.9	4.56
3	-0.3	-2.9	5.3	2.14
6	17.5	18.8	21.5	8.16
36	1.8	10.25	16.2	2.17
72	5.6	10.95	19.3	5.9
144	13.9	8.15	22	N/A
168	4.6	N/A	7.9	11.5

Source: reviewer summary from original NDA submission

7.1.9.3 Standard analyses and explorations of ECG data

Table 9-5. Summary of Post-Dosing Changes in QTc (msec) on 12-lead ECG for All Patients

Dose Group	Baseline		Change from Baseline					
	n	Mean (sd)	45 minutes		24 hours		72 hours	
			n	Mean (sd)	n	Mean (sd)	n	Mean (sd)
Placebo	49	424.7 (21.5)	38	3.2 (14.9)	11	2.0 (26.9)	48	-2.0 (21.1)
< 0.03 mmol/kg	94	430.9 (26.8)	93	-2.9 (34.0)	0	-	90	-2.3 (14.6)
0.03 mmol/kg	731	407.7 (32.1)	702	2.8* (25.6)	406	0.7 (19.9)	675	0.6 (22.4)
0.05 mmol/kg	290	408.9 (27.0)	201	1.4 (26.8)	180	-4.5* (20.5)	275	-2.9* (22.8)
> 0.05 mmol/kg	111	414.1 (23.5)	107	8.8* (14.7)	1	4.5 (-)	107	0.9 (16.4)
All doses combined	1226	410.3 (30.5)	1103	2.7* (25.9)	587	-0.9 (20.2)	1147	-0.4 (21.5)

Note: n = number of patients

a p < 0.05 (t-test)

Cross-reference: Statistical Table S-3.1

7.1.9.3.1 Analyses focused on measures of central tendency

Table 7.1.9.3.1 Mean change in QTc and PR from baseline in Phase 3 program

	45 min	24 h	72 h
PR change			
MS-325-12	1.74	n/a	0.86
MS-325-13	1.91	2.19	2.62
MS-325-14	0.27	-1.2	-0.84
MS-325-15	0.53	0.13	0.55
QTc change			
MS-325-12	3.15	n/a	-1.544
MS-325-13	4.5	2.77	6.5
MS-325-14	2.24	0.85	0.94
MS-325-15	0.04	-1.55	-0.23

Table 7.1.9.3.2 Mean changes in QTc by dose groups in a phase 2 study

MS-325-09	Placebo	<0.03	0.03	0.05	>0.05
QTc_CH 45 min	3.23	1.13	2.41	2.67	7.75
QTc_CH 72 HR	-3.5	-2.22	3.19	0	0.21
HR_CH 45 min	-1.31	-1.97	-2.72	-2.65	-0.28
HR_CH 72 HR	2.86	-1.08	2.72	1.27	1.32
PR_CH 45 min	0.94	-5.9	2.51	-1.06	-1.72
PR_CH 72 HR	2.44	0.93	1.05	-1.71	1.62

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Table 4.1B
 QTcB (Bazzet's) Changes from Baseline ≥ 30 ms or ≥ 60 ms at Each Time Point Post-baseline
 (Studies MS-325-01A and MS-325-01C, All Doses Combined)

QTcB Interval Change from Baseline				
MS-325 (N: 60)			Placebo (N: 30)	
Mean (Std) QTcB (ms) at Baseline: 375.5 (19.9)			Mean (Std) QTcB (ms) at Baseline: 373.8 (18.8)	
Time Post Dosing (hr)	QTcB change from baseline ≥ 30 ms	QTcB change from baseline ≥ 60 ms	QTcB change from baseline ≥ 30 ms	QTcB change from baseline ≥ 60 ms
	n (%)	n (%)	n (%)	n (%)
0.25	3 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
1	5 (8.3)	0 (0.0)	2 (6.7)	0 (0.0)
3	0 (0.0)	0 (0.0)	1 (3.3)	0 (0.0)
6	8 (13.3)	1 (1.7)	5 (16.7)	3 (10.0)
24	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
36	5 (8.3)	1 (1.7)	0 (0.0)	0 (0.0)
72	7 (11.7)	0 (0.0)	1 (3.3)	0 (0.0)
144	3 (5.0)	0 (0.0)	1 (3.3)	0 (0.0)
168	2 (3.3)	1 (1.7)	3 (10.0)	0 (0.0)

Program/Output (Date): T_ECGOUT_FDA/T_ECGOUT_FDA_4_1B.LST (26APR04)

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MS-325-12:

22 patients (8.4 %) had a total of 25 increases in QTc interval that were >30 ms including 19 patients with increases that were 30-60 msec, and 4 patients had a single increase that was > 60 msec.

MS-325-13:

26 patients had a total of 37 increases in QTc interval that were >30 ms: 25 patients had a total of 35 increase that were >30 and <60 ms, and 2 patients each had a single increase that was >60 ms.

MS-325-14:

18 patients (13%) had QTc increases from baseline >30 ms to <60 msec, 5 patients (4%) experienced a maximum increases from baseline in QTc of > 60 msec. One patient was an increase greater than 100msec and a result of over 500 msec.

MS-325-15:

10 patients had a total 14 QTc values that increased >30 ms, one was >60 ms.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

Table 7.1.9.3.3 Number and Percentage of Patients who Experienced Clinically Significant ECG Abnormalities by Dose Group for All Patients who Received MS-325

Dose Level	Placebo (N=49)	<0.03 (N=95)	0.03 (N=767)	0.05 (N=348)	>0.05 (N=111)	All MS-325 (N=1321)
EKG abnormalities	2 (4.1)	3 (3.2)	14 (1.8)	13 (3.7)	6 (5.4)	36 (2.7)

Data source: Reviewer summary from Statistical Table S-3.4

7.1.9.4 Additional analyses and explorations

None

7.1.10 Immunogenicity

The immunology laboratory panel consists of complement C3 and C4, histamine, IgE, and tryptase measurements and was used to detect any response in the immunological system which might be induced following dosing with MS-325. There is no apparent safety signal that may suggest a drug-related acute change in those parameters within 72 hours post dosing.

7.1.11 Human Carcinogenicity

Since MS-325 is administered as a single intravenous bolus injection, long-term carcinogenicity studies in animals were not conducted. The following genotoxicity assays, however, were performed: Salmonella/*E. coli* reverse mutation assay (Ames), mouse lymphoma assay, chromosome aberration test in CHO cells, and in vivo mouse micronucleus assay. None of the performed studies showed any positive signals.

7.1.12 Special Safety Studies

- **There is no “thorough” QT study conducted.** The potential drug-related QT effect cannot totally excluded from the data from three Phase 1 QT studies.
- There is no special study to demonstrate the in-vivo stability of MS-325 given its long half-life, compared to that of other Gd-based products.
- **The studies that evaluated drug’s potential to affect hemoglobin, platelet, etc dose not appear to be sufficient due to relative short follow-up period**
- Free gadolinium has the potential to delay cardiac repolarization and cause serious cardiac arrhythmias. A special safety study is needed to ensure in-vivo stability of MS-325 to rule out MS-325’s potential to cause QT cardiac arrhythmias.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There are no data available on this section. MS-325 is not a candidate for scheduling under the Controlled Substances Act, and it is not pharmacologically or structurally related to another drug that is know to have abuse potential.

7.1.14 Human Reproduction and Pregnancy Data

No human studies have been performed to assess excretion of MS-325 into human milk. However, excretion into milk has been studied with lactating rats at doses of up to 0.3 mmol/kg. Less than 1% of the dose was excreted into the milk.

Adequate and well-controlled studies were not conducted in pregnant women. The effect of MS-325 on fertility, however, was tested in rats up to a dose of 1.5 mmol/kg (8.3 times the human dose based on body surface area) for at least 4 weeks (males) and two weeks (females). No effects on male or female fertility were observed. The compound had no effect on early embryonic development at this dose. Please see Pharmacology and toxicology review for more information.

Because animal reproduction studies are not always predictive of human response, MS-325 should be used during pregnancy only if clearly needed and the potential benefit justifies the potential risk to the fetus.

7.1.15 Assessment of Effect on Growth

Safety and effectiveness of MS-325 in pediatric patients have not been established.

7.1.16 Overdose Experience

Ms-325 has been tested in human up to a dose of 0.15 mmol/kg. There are safety concerns from the overdose data.

- In MS-325-1C single rising dose safety and PK study showed that at higher doses (0.125 and 0.15 mmol/kg) renal tubular cells were seen in urinary sediments. Renal tubular cells were also observed in urinary sediments in placebo group as well. The appearance of renal tubular cells and inclusion bodies in the urinary sediments is of concern. A few renal cells were also **observed approximately "24 hours" post-dose in** one individual (Subject No. 608) in dose group 0.100 mmol/kg. The sponsor failed to find out the reason behind these findings and **simply attributed it to "some other as yet unidentified study procedure."** This caused revise of 1C protocol, from dose 0.225 reduce to 0.125 mmol/kg. There were no clinically significant changes in any other parameters of renal functions. No renal cells were found in subjects receiving lower dose (0.05 and 0.075 mmol/kg) of MS-325 and proposed clinical dose of 0.03 mmol/kg. Considering the clinical effective dose for dynamic images is 0.1 mmol/kg, current approved dose range is 0.1 mmol/kg to 0.3 mmol/kg. This safety issue need further evaluated.
- The frequency of adverse events appears to be dose-related.
- While some serious events, including death, occurred in a dose higher than that of clinically proposed one, there is no clear evidence that those events are drug-related.

7.1.17 Postmarketing Experience

There is no information available.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

This NDA contain data from 18 clinical trials and Table 7.2.1.1 summarizes the level of drug exposure. One thousand three hundred twenty-one (1,321) patients and 117 healthy volunteers were administered with MS-325. The post-dosing safety monitoring period ranged from 3-4 days in the Phase 3 studies and to up to 21 days in some Phase 1 and 2 studies.

Table 7.2.1.1 Summary of Exposure to MS-325 or Placebo in MSA-325 Clinical Trials

Group Number	Group Description	Number of Subjects
1	All patients who received MS-325	1321
2	All healthy volunteers who received MS-325	117
3	All patients with vascular disease who received MS-325	1203
4	All placebo-treated subjects 30 healthy	49 patients, 30 healthy volunteers
5	All patients who received the proposed clinical dose of MS-325 (0.03 mmol/kg)	767

Groups 1 and 2 comprise all 1,438 subjects who received MS-325 in all studies.

7.2.1.2 Demographics

1,321 patients received MS-325, ranging from 0.005 to 0.10 mmol/kg. 865 (65.5%) were men and 456 (34.5%) women with a mean age of 62.8 years (**range 21 – 91 years**). **In this population**, there were 1055 (79.9%) White, 158 (12.0%) Hispanic, 95 (7.2%) Black, 7 (0.5%) Asian, and 6 (0.5%) patients of other racial groups.

A total of 767 patients received MS-325 at the proposed clinical dose (0.03 mmol/kg) and 49 patients received placebo. Of the 767 patients, 505 (65.8%) were men and 262 (34.2%) were **women with a mean age of 64.4 years (range 21 – 91 years)**. In this population, there were 604 (78.7%) White, 113 (14.7%) Hispanic, 46 (6.0%) Black, 1 (0.1%) Asian, and 3 (0.4%) patients of other racial groups.

Of 49 patients who received placebo, 36 (73.5%) were men and 13 (26.5%) were women with a **mean age of 62.5 years (range 46 – 79 years)**. In this population, there were 44 (89.8%) White, 4 (8.2%) Black, and 1 (2.0%) patient of other racial groups.

7.2.1.3 Extent of exposure (dose/duration)

Table 7.2.1.3 Numbers of Patients by Dose and Dose Group for All Patients who Received MS-325

Dose Group	<0.03	0.03	0.05	>0.05	All MS-325
Number of patients	95	767	348	111	1321
Number of Volunteers	14	10	57	36	117

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

There is no data available for review.

7.2.2.2 Postmarketing experience

There is no data available for review.

7.2.2.3 Literature

See references section

7.2.3 Adequacy of Overall Clinical Experience

- The number of subjects exposed to MS-325 appears to be consistent with that required for single use contrast agents;
- There is an evidence of underreporting from some of the clinical sites outside of the US. But it may not change overall assessment of this drug;
- There is no comparator group in phase 3 trials. For the future trials, there might be a need to demonstrate a comparative safety by including a control group of other Gd-based contrast agent;
- **There is insufficient information on MS-325's potential affect in renal insufficient patients**

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Please refer to toxicity review.

7.2.5 Adequacy of Routine Clinical Testing

- In isolated cases involving a death case and two subjects with lower O2Sat (75%), there was no appropriate documentation of vital signs monitoring.
- Since majority of acute hemoglobin drop occurred at 72 hours post dosing, some lab. tests should be collected at a later time point.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

MS-325 was incubated with human microsomes at various concentrations. This study showed that MS-325 levels were unchanged, which implies that cytochrome P450 enzymes are not involved in the disposition of MS-325.

Renal excretion is the principle route of elimination for MS-325. In healthy subjects following an IV dose of 0.03 mmol/kg (CSR MS-325-16), the mean percent dose excreted in urine was 83.7% (range 79.0 to 94.0%). A small proportion of the dose (4.7%; range 1.1 to 9.3%) was eliminated in the feces. This indicates a minor role of biliary excretion.

Reviewer's Comments: *While MS-325 is not metabolized, data dose not provide adequate support for in-vivo stability of MS-325. The primary data suggest increased zinc excretion through urine within 72 hours post dosing.* [

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7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Free gadolinium has the potential to delay cardiac repolarization and cause serious cardiac arrhythmias. In vitro animal models have shown that gadolinium cations affect cardiac ion

channels. Gadolinium inhibits stretch-activated channels and blocks L-type calcium channels. Blockade of the delayed rectifier potassium current (I_{Kr}) in isolated guinea-pig ventricular myocytes has also been demonstrated with gadolinium. In the clinical trials, there were a few cases of non-sustained ventricular tachycardia and other cardiac events. While there cases are **likely to be caused by patient's underlying** conditions, a study to demonstrate the in-vivo stability of MS-325 is recommended to provide a high assurance on cardiac safety of MS-325. Such an assurance is particularly important given the long half-life of MS-325 and lack of the demonstration of the value steady-state images.

7.2.8 Assessment of Quality and Completeness of Data

There was evidence of lack of adequate monitoring and documentation of safety monitoring, especially in cases where a serious events occurred. In some cases, the data may not be complete to assess whether and when an AE was resolved or an abnormal lab. result returned to the normal. In any future trials, the safety monitoring needs to be enhanced.

7.2.9 Additional Submissions, Including Safety Update

This reviewer also evaluated the following amendments:

2004-03-30 – Response to QT issue

2004-04-14 – 120 day Safety Update

2004-05-14 – Response to syncope issue

2004-06-11 – Response to O2Sat issue

2004-07-16 – Response to ST depression issue

2004-10-22 – Response to hemoglobin issue

All about additional submissions did not address critical safety concerns expect ST-T evaluation.

- In the 120-day safety update, for two serious cardiac events, the outcome was still recoded as ONGOING.
- For the two subjects who experienced O2Sat drop to below 75%, the sponsor provided two letter of support from the original PI, certifying that the reading might be machine error and there was no AE occurred. However, vital signs were not documented to support the claims.
- QT data appears to be reasonable but the potential QT effect cannot be totally excluded.
- There is no clear evidence that drug causes syncope. However there will be a concern over the case of syncope with non-sustained ventricular tachycardia if MS-325 in vivo stability can not be adequately demonstrated;
- 17 subjects had significantly ST-T decreases post dosing, the sponsor claimed it most likely related to the methodology. This reviewer concurs with the explanation.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

- There were two cases of non-sustained ventricular tachycardia. Though those events can be due to the underlying cardiac conduction, there is a need to demonstrate the in vivo stability of MS-325;
- There were three cases of MI/sever chest pain (SAEs) and other cardiac arrhythmias. There is no clear evidence that those events are drug-related. The final decision regarding the causality should be deferred to a later time when the study of demonstrating the in vivo stability of MS-325 is conducted;
- There were 19 subjects with O2Sat changes post dosing. Since those events occurred within 15 minutes of post dosing, it can be handled via product labeling;
- In clinical trials, 34 and 71 subjects, respectively, had experienced an acute hemoglobin drop (>2 gm/dL decrease from baseline) or hypocalcaemia episode (< 8.5 mg/dL). Within 72 hours of dosing. The majority of acute hemoglobin drop occurred at 72 hours post dosing. The new study is needed to assess the effect beyond 72 hours pose dosing;
- There were renal tubular cells seen in urine specimen of a high dose administration (0.125 and 0.15 mmol/kg). Similar findings were also observed in placebo group. Though the **sponsor's explanation is not satisfactory**, the final decision regarding whether or not to pursue this issue should be deferred to a later time when in vivo stability evaluation is conducted. In the future studies, the urine specimen should be routinely collected and examined.
- The common adverse events profile of MS-325 appears to be dose-related and higher than that of other marketed gadolinium based drugs. However, there is no direct comparison data to support this at this time. The adverse event profile of MS-325 appears to generalize cholinergic stimulation in nature. Headache (112); nausea(110); vasodilatation(88); dizziness (39) & syncope(10); an abdominal cramps, diarrhea, vomiting(59); chest pain (25) respiratory syndrome (40) (dyspnea, running nose, wheezing, cough) were the most frequently reported events. There is a possibility that those were related to potential in vivo instability.
- There were some cases of QTc increases over 60 ms in Phase 3 clinical trials. Data from phase 1 clinical trials provide a reasonable assurance over QT safety. However, the drug induced QT effect cannot be totally excluded at this time due to lack of positive control.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

The incidences of common AEs were calculated from all patients from four phase 3 studies. There was evidence of underreporting from some of the clinical sites outside of the US. Such an underreporting does not appear to affect the overall safety profile of MS-325.

Table 7.4.1 Summary of AE's reported by USA and Foreign country

MS-325 Dose	Subjects#	AE#	Ratio
Foreign 0.03 mmol/kg	281	146	0.52
Foreign 0.05 mmol/kg	77	40	0.52
Placebo USA	37	26	0.7
<0.03 mmol/kg USA	92	53	0.58
0.03 mmol/kg USA	458	514	1.12
0.05 mmol/kg USA	81	81	1
>0.05 mmol/kg USA	41	70	1.7
Total	1067	930	0.87

Source: Reviewer summary from original NDASSI data base.

7.4.1.1 Pooled data vs. individual study data

See above

7.4.1.2 Combining data

See above

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Table 7.4.2.1 Number and percent of patients experiencing the most frequently reported AEs for all patients.

Preferred Term	Placebo N=49	<0.03 N=95	0.03 N=767	0.05 N=348	>0.05 N=111
Any AE	23(46.9)	24(25.3)	276(36)	185(53.2)	86(77.5)
Pruritus NOS	2(4.1)	1(1.1)	38(5)	40(11.5)	20(18)
Paresthesia	1(2.0)	0	21(2.7)	39(11.2)	7(6.3)
Headache NOS	3(6.1)	2(2.1)	33(4.3)	35(10.1)	20(18)
Nausea	0	2(2.1)	32(4.2)	29(8.3)	20(18)
Vasodilatation	1(2.0)	1(1.1)	25(3.3)	20(5.7)	7(6.3)
Burning sensation NOS	0	0	15(2.2)	29(8.3)	7(6.3)
Dysgeusia	6(10.2)	2(2.1)	17(2.2)	20(5.7)	22(19.8)

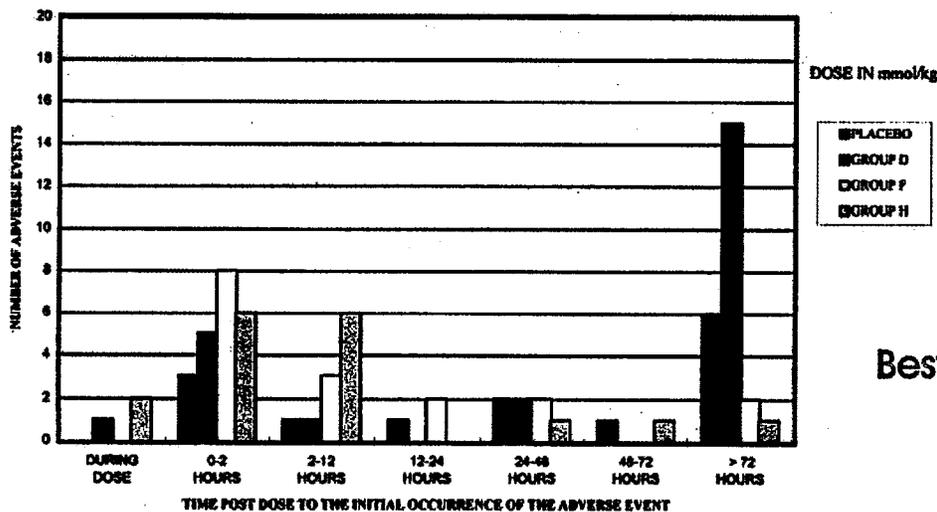
Clinical Review
 {Tong Li, M.D.}
 {NDA 21711}
 {Vasovist(MS-325)}

Dizziness	5(10.2)	0	8(1)	12(3.4)	17(15.3)
Feeling cold	0	2(2.1)	6(0.8)	12(3.4)	5(4.5)
Injection site bruising	0	0	19(2.5)	0	4(3.6)
Venipuncture site bruise	0	0	17(2.2)	4(1.1)	0
Hypertension NOS	1(2)	1(1.1)	11(1.4)	4(1.1)	1(0.9)
Rash NOS	0	0	3(0.4)	11(3.2)	2(1.8)
Diarrhea NOS	0	1(1.1)	4(0.5)	10(2.9)	0

Source Data: SSI Table 7-7, page 37

7.4.2.2 Explorations for time dependency for adverse findings

Temporal relationship between onset of adverse event and MS-325/Placebo IV bolus dose was studied in MS-325-1C. Please see graph below:



Best Possible Copy

FIGURE C-59 NUMBER OF ADVERSE EVENTS OVER TIME BY DOSE
 (30 SECOND IV BOLUS DOSE)

Reviewer's Comments: *These results indicate that the majority of the AE's were reported within the first 24 hours following IV bolus dose infusion, with most of these occurring within the first 2 hours following dose infusion. However, there appear to be a second peak after 72 hours, which is consistence with animal findings. These delayed AE's (diarrhea, headache, and arrhythmias) appears to be cholinergic in nature.*

7.4.2.3 Explorations for drug-demographic interactions

No information available.

7.4.2.4 Explorations for drug-disease interactions

- Vascular Disease: There are no apparent differences in the PK behavior between patients and healthy volunteer. However, there is a tendency of increasing severity of hematology toxicity.
- Renal Insufficiency: Renal insufficiency significantly increases systemic exposure. In vivo stability and toxicity level has not established yet.
- Hepatic Insufficiency: Moderate hepatic impairment could reduce biliary excretion of gadolinium although the total amounts excreted via fecal elimination.

7.4.2.5 Explorations for drug-drug interactions

Since MS-325 may affect blood pressure and blood sugar levels, MS-325 may have some impact on anti-hypertensive and anti-diabetic treatments. Although in vitro studies shows MS-325 increased the warfarin free fraction by 50%, and Ibuprofen decreases MS-325 binding by 10-53%, there is no concern from in vivo data.

7.4.3 Causality Determination

Without an adequate placebo control, it is difficult to assess causality. Unlike the clinical trials of a drug for the chronic use, a contrast agent is designed for a single use and it is common that the drug is tested without large number of placebo control subjects in the Phase 3 development program. In this case, the level of safety concern and interpretation of any safety signal will be greatly affected by presence of the biological possibility.

As stated under section of 7.3, there were observations of adverse events such as non-sustained ventricular tachycardia, acute hemoglobin drop, hypocalcaemia and acute O2Sat drop. They can **be related to the patient's underlying conditions** or due to the drug effect. Since the studied population is prone to those events, this reviewer would like to defer the final decision on the causality until the in vivo stability data is available.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

In the phase 3 clinical trials, patients received one dose of 0.03 mmol/kg of MS-325 as a single intravenous bolus injection (manually or by power injection), over a period of up to 30 seconds followed by a 25- 30 mL normal saline flush. Imaging procedure began within 15 minutes after injection and was completed within approximately one hour following injection. Dynamic imaging began immediately upon injection. Steady state imaging began after the dynamic scan was completed.

0.03 mmol/kg dose selection was based on MRA literature” **A single bolus of 0.1 mmol/kg of gadolinium** has been shown to well visualize all iliac, renal, femoral, and lower limb vessels with **a 3D subtraction MRA technique.” Using a 4:1 dose correction** for the enhanced relaxivity of MS-325 compared to conventional Gd MRA agents (MS-325 $16-22\text{S}^{-1}\text{mM}^{-1}$ VS. Gd-ECS agents about $4.5\text{ s}^{-1}\text{mM}^{-1}$), the 0.1 mmol/kg dose of conventional contrast is consistent with a 0.03 mmol/kg dose of MS-325.

Reviewer’s Comments: *Adequate dosing is one of key components of efficacy determination. Selection of 0.03 mmol/kg for dynamic scan appears to be suboptimal.*

It is essential to inject sufficient paramagnetic contrast to reduce the arterial blood T1 to well under the T1 of surrounding tissues. This would result in arterial blood appearing bright on the image compared to all other tissues. Shortening the arterial blood T1 relaxation time also increases the image signal-to-noise ratio. Currently available first pass agents have a T1 relaxivity of around 4.5/mMolar.sec. The blood gadolinium concentration of at least 1 mMolar is required to achieve a T1 shorter than 270ms, that representing T1 of Fat. The patients with cardiovascular disease would require higher doses of contrast than normal volunteers to optimally visualize vascular pathology. This is because higher signal-to-noise ratio is required to resolve the fine details of severe stenoses and atherosclerotic irregularities. Therefore, most investigators propose doses range from 0.1 to 0.3 mmol/kg.

MS-325 has two phase of early distribution following injection, that is bolus phase and the steady-state phase. The r1 relaxivities were 6 seconds⁻¹.mmol/L⁻¹ and 33 seconds⁻¹.mmol/L⁻¹ for the albumin bound form. At the peak of the bolus, 74% of MS-325 was in free form. This proportion decreased progressively during the steady-state phase. The free form of MS-325 would rapidly diffuse into the interstitial space. However, one of the key requirements for blood pool agents is minimal interstitial diffusion. The extravasation of the free form of MS-325 during the bolus phase leads to tissue enhancement by binding to any interstitial protein.

According to the affinity contrast of MS-325, the blood pool activity of the agent is limited by the plasma albumin concentration; modulation of this effect is not possible since an increase in the injected dose leads to an increase of the free form due to saturation of the albumin binding. This division require that the optimal contrast dose achieved for each vascular territory. However, both carotid and foot trials show that extravasation limits the contrast-to-noise with dose increase. In addition both of them suffer from rapid venous contamination.

In the published MS-325 phase II carotid trial, 10% carotid arteries were not depicted separately from the internal jugular vein on the 5-minute MS325-enhanced images; an additional 24% of vessels were obscured.

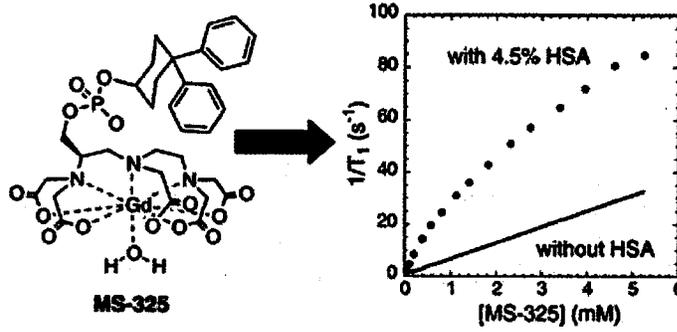


Figure 1

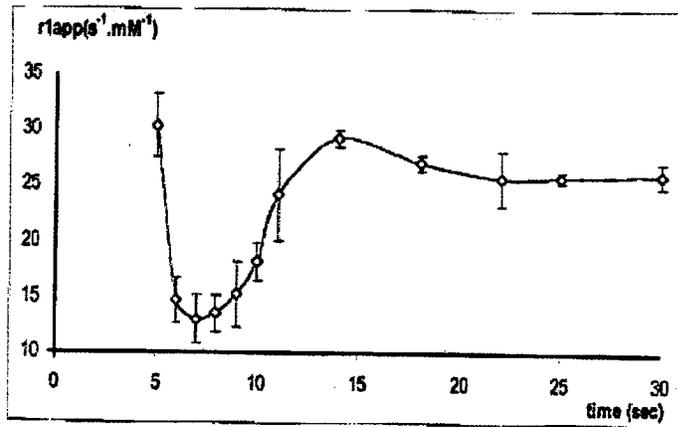


Figure 2. Apparent relaxivities of MS-325 during the bolus phase. (Corot et al. 311-19)

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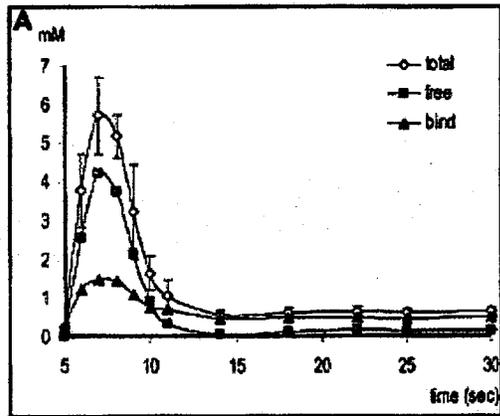


Figure 3. Plasma concentration of the total, free, and bound forms of MS-325 during the bolus phase. (Corot et al. 311-19)

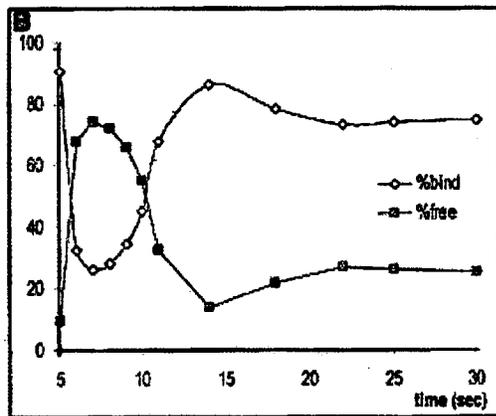


Figure 4. Proportion of the free and bound forms of MS-325 during the bolus phase. (Corot et al. 311-19)

The sponsor attempted to use a 4:1 dose correction for the enhanced relaxivity of MS-325 compared to conventional Gd MRA agents. 0.03 mmol/kg dose of MS-325 may not be comparable to that of 0.1 mmol/kg dose of conventional contrast because during bolus phase, 74% MS-325 is in free form. MS-325 only shows 4 folds enhanced relaxivity after binding to albumin.

It appears that

1. *For dynamic imaging, 0.03 mmol/kg may be one of the factors that led to suboptimal performance in the clinical trials. The increase in dosing may be limited by the lack of demonstration of in vivo stability;*
2. *For steady-state imaging, both venous and background enhancement may affect the performance. Currently, there are no artery-vein separation techniques available.*
3. *The background enhancement may be more prominent due to its ability to bind to any of interstitial protein.*

8.2 Drug-Drug Interactions

Warfarin may be used in subjects with vascular disease requiring diagnostic MR imaging, and because both warfarin and MS-325 bind to human serum albumin (HAS), a study was undertaken in subjects with arterial vascular disease to assess potential PK/PD interactions of MS-325 and warfarin. The results showed that the PK profile of MS-325 was unaltered in subjects on concurrent warfarin therapy as compared to those who did not receive warfarin.

In the presence of the commonly prescribed, highly albumin-bound drugs, warfarin, ibuprofen, digitoxin, propranolol, and verapamil, results from in vitro studies indicated no significant protein binding interactions with MS-325. A series of in vitro studies were performed to investigate the potential effect of commonly used drugs (digitoxin, propranolol, verapamil, warfarin, phenprocoumon, ibuprofen, diazepam, ketoprofen, naproxen, diclofenac, and piroxicam) on MRI efficacy using the pharmacodynamic parameter $1/T1$ (relaxation rate) as a surrogate. Results showed that MS-325 does not adversely interact with these drugs at clinically relevant concentrations.

Reviewer's Comments: *Interaction with anti-hypertensive and anti-diabetic drugs have not been studied.*

8.3 Special Populations

Age, gender and ethnicity:

Evaluation of pharmacokinetic results obtained across 5 studies (46 males and 18 females), $T_{1/2}$ for male and female is 18.98 hours and 17.31 hours, respectively.

Evaluation of pharmacokinetic results obtained across 5 studies (64 subjects; 57 less than 65 years and 7 greater than or equal to 65 years of age) indicated $T_{1/2}$ for elderly was longer than adult <65.

Pharmacokinetic differences by race after intravenous MS-325 dosing have not been studied.

Table 8.3.1 Summary Pharmacokinetics of MS-325 by Gender and Age

Group	V(ss) (mL/kg)	T (1/2 term) (hr)	Cl (r) (mL/hr/kg)
Males N=46	168.8	19.63	5.55
Female N=18	160.6	17.31	6.07
Adult (<65) N=57	165.38	18.71	5.72
Elderly(>65) N=7	175.57	21.14	5.69
All Normal N=64	166.49	18.98	5.49

Source Data: Proposed Labeling Page 6. Table3

Reviewer's Comments: *In animal studies, male animal appeared to be more sensitive to MS-325 showing a higher frequency of toxicity, compared to that of female animals..*

Pregnancy and Nursing Mothers:

Adequate and well- controlled studies were not conducted in pregnant women. Mutagenicity studies shows MS-325 does not appear to be genotoxic in Ames Test; Chromosomal aberration in CHO cells assay and in vivo mouse micronucleus assay. But animal reproduction studies are not always predictive of human response.

Renal Insufficiency:

Pharmacokinetics and safety of MS-325, after intravenous bolus injection (1.5 mL/ sec) at a dose of 0.05 mmol/ kg, (1.7 times the clinical dose) were investigated in groups of patients with mild (n= 11), moderate (n= 12) and severe (n= 9) renal impairment in comparison to a group of subjects with normal renal function (n= 20). Systemic drug exposure increases 2-3 folds with renal impairment. A prolongation of the elimination half, increases in AUC and MRT, and decreases in CL(t) and Cl(r) were seen with decreasing renal function.

Table 8.3.2 Summary of Key MS-325 Pharmacokinetic Parameter Results from trial MS-325-07

Parameter	Normal Group N=20 Mean	Mild Group N=11 mean	Moderate Group N=12 mean	Severe Group N=9 mean
AUC (0-inf), mg.hr/mL	1128	1210	2168	2893
T(1/2 term),	18.9	22.5	49	69.5

Clinical Review
 {Tong Li, M.D.}
 {NDA 21711}
 {Vasovist(MS-325)}

hours				
V(ss), mL/kg	161	169.9	193	181
MRT, hours	23	26.4	53.9	68.2
Cl(t), mL/hr/kg	7.1	7	4.1	3
Cl(r), mL/hr/kg	5.3	5.7	3	2.2

Source Data: MS-325 proposed labeling. Revised from table 2 on page 5.

Reviewer's Comments: *One of the potential advantages of MRA is its use in renal insufficient patients, MS-325 long half-life and lack of demonstration of in vivo stability may limit its use in this special population.*

8.3.1.1 Additional analyses and explorations for mild renal insufficiency patients

An analysis for the mild renal insufficiency patients was summarized as follows:

- In trial MS-325-12, protocol requires that the patients have a serum creatinine level within the normal range for the site laboratory immediately prior to MS-325 administration. The patient has a history of abnormal renal function including but not limited to severe renal impairment, renal transplant, or hemodialysis would be excluded. There was only one subject with a baseline creatinine level >1.5 mg/dl from that trial. Other three trials requires baseline serum creatinine level <2.0 mg/dl.
- Classifications: Based on current clinical standard, patients were categorized according initial serum creatinine level as following:
 - No renal insufficiency group: Baseline creatinine level < 1.5 mg/dl.
 - Mild renal insufficiency group: Baseline creatinine level 1.5 to 2.4 mg/dl

There are total 16 subjects with initial creatinine level >1.5 mg/dl at baseline. One subject had two values, 1mg/dl and 2 mg/dl. This subject was categorized as having no renal insufficiency. The other 15 subjects were further searched for their medical history, serum creatinine, calcium, hemoglobin, platelets and efficacy results.

- Results:
 - There are total 15 subjects with baseline creatinine level >1.5 mg/dl (Aged 48-88 years), including 11 males and 4 females. Five of them were enrolled from USA or Canada sites. 6 subjects had known history of renal disease (Table 8.3.1.1.1).
 - 80 % (12/15) subjects had a decrease in hemoglobin (average 4.4%), most of which did not return to baseline by 72 hours. Patient P15/146/007 was a 88 years old male with right foot ischemia. He had acute drop of Hb (17%) to a level of 10 gm/dl with serum calcium dropping to 8.4 mg/dl.
 - There is a general trend of a decrease in serum calcium, platelets and an increase in creatinine level. The decrease appears to be more prominent in mild renal

insufficient patients than that of the subjects with normal renal function (pooled data) - Table 8.3.1.1.3;

- This analysis is limited by sample size and the current Phase 3 studies did not appear to be adequate to assess safety of mild renal insufficiency patients.

Table 8.3.1.1.1 Summary of demographic information of 15 renal insufficiency patients.

Subject ID	Gender	Age	Country	Medical history	History of renal disease
P13/052/003	M	62	US/CA	PVD	
P13/083/003	M	68	F	DM, COPD, MI, S/p AVR	
P13/114/014	M	75	F	DM, HTN	
P13/068/028	F	81	US/CA	CVA, CABG, MI	
P13/083/018	F	75	F	CAD, CABG, MI	Yes, Renal Inflammation
P13/108/007	M	77	F	CAD, CABG, HTN	
P14/070/009	F	74	US/CA	AAA, arthritis	Yes, Renal Insufficiency
P14/129/011	F	73	F	CDA, HTN, obesity	
P14/130/022	M	72	F	HTN	Yes, PTA renal artery
P14/111/007	M	66	F	DM, Anxiety, dizziness	Yes, Left renal atrophy
P14/130/003	M	75	F	HTN	Yes, Right renal atrophy
P15/084/004	M	48	US/CA	HTN, Feet Numbness	
P15/115/001	M	53	F	DM, Atrial Fibrillations, HTN	
P15/138/002	M	79	US/CA	Blind, BPH	Yes, mild renal insufficiency
P15/146/007	M	88	F	CAD, DM, Right foot ischemia	

Source Data: Medical reviewer summary from SSI database.

Table 8.3.1.1.2 Test results from SSI database.

Patients ID	Creatinine (mg/dl)			Platelet count (mm ³)			Hemoglobin (g/dl)				Calcium (mg/dl)		
	B	24H	72H	B	24 H	72 H	B	24 H	72 H	B	24 H	72 H	
P13/052/003	1.6	1.6	1.8	314	306	n/a	13.5	12.9	-4.4%	n/a	9.7	9.4	8.9
P13/083/003	1.6	1.7	1.7	136	134	n/a	11.9	11.2	-5.9%	n/a	8.9	9.1	9.9
P13/114/014	1.6	1.6	1.7	225	249	299	13.9	13.6	-2.2%	14.4	10.3	10.1	10.3
P13/068/028	1.7	1.6	1.5	223	234	221	13.2	13.0	-1.5%	12.7	9.7	9.5	9.5
P13/083/018	1.8	1.8	1.8	253	260	245	13.1	13.1	0	13.4	9.3	9.3	9.1
P13/108/007	2.0	2.0	2.0	226	199	197	11.9	11.4	-4.2%	10.9	9.4	9.1	8.8
P14/070/009	1.6	1.4	1.8	205	185	207	13.6	13.6	0	12.5	10.0	9.8	10.0
P14/129/011	1.8	2.4	1.8	<i>1170</i>	<i>1170</i>	<i>n/a</i>	13.9	13.1	-5.7%	n/a	10.5	10.5	10.5
P14/130/022	1.8	1.9	1.7	233	223	241	16.7	15	-10.2%	16.3	10.1	9.7	9.9

Clinical Review
 {Tong Li, M.D.}
 {NDA 21711}
 {Vasovist(MS-325)}

P14/111/007	1.9	1.9	1.8	263	238	231	14.7	14.5	-1.3%	14.3	9.7	10.0	10.1
P14/130/003	1.9	2.5	2.0	266	273	268	14.3	13.1	-8.4%	13.8	10.2	10.2	10.2
P15/084/004	1.6	1.6	2.0	209	258	238	16.4	17.5	+6.7%	18.3	10.1	10.0	10.1
P15/115/001	1.7	1.7	1.5	100	91	98	12.6	12.2	-3.2%	12.7	9.5	9.5	9.9
P15/138/002	1.8	1.6	1.5	151	177	151	13.9	12.7	-8.6%	13.5	11.0	10.3	11.0
P15/146/007	2.1	2.0	2.1	515	443	487	12.0	10.0	-16.7%	10.8	8.8	8.4	9.0
Mean value	1.76	1.82	1.78	237	233	240	13.7	13.1	-4.4%	13.5	9.8	9.6	9.8

Data source: Reviewer's independent analysis based on the dataset provided in NDA.

Table 8.3.1.1.3. Comparison of mean changes with pool data from all MS-325 exposure population

Assay	Baseline				24 hours				72 hours			
	Pool data		Cr>1.5 mg/dl		Pool data		Cr>1.5 (mg/dl)		Pool Data		Cr>1.5 (mg/dl)	
	N	Mean	N	Mean	N	Mean change	N	Mean change	N	Mean change	N	Mean change
Calcium (mg/dl)	1293	9.5	15	9.8	1215	0	15	-0.2	1203	-0.1	15	0
Platelets(mm3)	1238	261.9	14	233	1116	0	14	-4	1090	-2.46	12	+3
Hemoglobin (g/dl)	1253	14.2	15	13.7	1137	-0.3 (2.1%)	15	-0.6 (4.3%)	1120	-0.1	12	-0.2

Source Data: reviewer summary from SSI database.

Table 8.3.1.1.4. Comparison of mean hemoglobin change by renal functions

Trial # & dose group	# of subject	Baseline Hemoglobin Mean value (g/dl)	24 hours Hemoglobin Mean value (g/dl)	Changes Mean (g/dl)	Changes %
MS-325-07 Normal group 0.05 mmol/kg	22	14.1	13.3	-0.8	-5.6%
MS-325-07 Mild renal group 0.05 mmol/kg	12	13.6	12.6	-1	-7.3%
MS-325-07 Moderate renal group 0.05 mmol/kg	18	12.6	11.8	-0.8	-6.3%

Hemodialysis:

MS-325 can be removed from the body by hemodialysis. After 0.05 mmol/ kg (1.7 times the clinical dose) of MS-325 was administered as a bolus intravenous injection (1.5 mL/ sec) to a group of 6 patients undergoing hemodialysis using a high flux dialysis filter, 73 ± 5% of the dose was recovered in the dialyzate following three dialysis sessions that occurred at 30 minutes, 48 hours and 96 hours after injection. After 14 days the plasma concentration declined to 5 ± 2% of the Cmax.

Reviewer's comments: In MS-325-18, 7 patients were enrolled (aged 18 to 64, and 3M/4F). 21 AEs were reported from 5 subjects. 7/21 AEs belonged to the cardiovascular

system, which included chest pain, dizziness and vasodilatation. One patient (P18/001/002) dies at home due to cardiac arrest 15 days post dosing. This patient was found to be anemic post dosing (9.4 g/dl). RBC morphology examination showed Anisocytosis in her blood smear on post-dosing Day 7 and 14. Five out of seven subjects ere found anisocytosis in their post-dosing samples. Although it is not uncommon to have anisocytosis in hemodialysis patients, the cluster of anisocytosis post dosing causes concerns. It is known that gadolinium contrast can cause hemolysis. For that reason, patients with sickle cell diseases are contraindicated for the gadolinium contrast.

Conclusion: The findings reconfirmed the need to demonstrate the in vivo stability of MS-325, especially in renal insufficient patients.

Hepatic Insufficiency:

The pharmacokinetics of a single bolus intravenous dose of 0.05 mmol/ kg MS-325 (1.5 mL/sec) was evaluated in a group of patients (n= 8) with moderate hepatic impairment (Child- Pugh Class B), and compared to a group of age- matched healthy subjects (n= 10). Pharmacokinetics and plasma protein binding of MS-325 was not significantly influenced by moderate hepatic impairment. A slight decrease in fecal elimination of MS-325 was seen for the hepatic impaired subjects (2.7%) compared to normal subjects (4.8%).

Reviewer's Comments: *Decreased plasma albumin is the known characteristic of hepatic impairment. One Patient, Child-Pugh score 9 with albumin score of 3 exhibited a shorter T (1/2-elim) (8.89hrs VS 20.5 for the group). This patient also had a higher fraction of MS-325 unbound to protein. Both the shorter kinetics and higher unbound fraction of MS-325 are consistent with the known mechanism of action of MS-325.*

8.4 Pediatrics

The sponsor has not conducted clinical studies with MS-325 in the pediatric population. A waiver has been filed with the Agency.

Reviewer's comments: *This reviewer does not recommend pediatric study at this time due to unresolved safety and efficacy issues in adult population.*

8.5 Advisory Committee Meeting

There was no advisory committee meeting planned. However, this reviewer suggests that clinical indication for MRA blood pool agents should be discussed.

8.6 Literature Review

Refer to Appendix 1.3

8.7 Postmarketing Risk Management Plan

N/A

8.8 Other Relevant Materials

There are currently no other data available for review.

9 OVERALL ASSESSMENT

9.1 Conclusions

From a clinical standpoint, the evidence presented in this NDA submission is not substantial and not adequate in support of the effectiveness and safety of MS-325 for a MRA application. All four Phase 3 studies have failed to demonstrate the improvement in sensitivity and specificity of MS-325 enhanced MRA, compared to that of non-contrast MRA. In addition, MS-325 enhanced **MRA's performance appears to be sub-optimal** and the studies were not designed to demonstrate efficacy of steady state images. Such a deficiency is important given the prolonged half-life of MS-325 in human body.

The drug may affect blood hemoglobin and calcium level. 34 subjects had experienced an acute hemoglobin drop, and 5 had a hypocalcaemia episode being reported as an adverse event (not by the measurement of serum calcium level), within 72 hours of dosing. Those observations, combined with the observed increase in urine Zinc level post dosing, raised a question of MS-325 in-vivo stability. The answer to this question is important because the serious cardiac events, including cardiac death, were reported from clinical trials, and there were patients with significant QTc increases of > 60 ms from the clinical trials. Unacceptable levels of Gd+3 dissociated from unstable MS-325 may contribute to those events and outcomes though those patients were at a higher risk for those cardiac events themselves due to their underlying cardiac conditions. Because of a lack of the adequate control group, the sub-optimal safety monitoring and follow-up in some cases and the evidence of AE underreporting from some of the clinical sites, the demonstration of in vivo stability will provide the **needed assurance on the product's** safety. This assurance is particularly important for the patients with renal insufficiency.

9.2 Recommendation on Regulatory Action

From a clinical perspective, this reviewer recommends that MS-325 for the MRA application receive an **Approvable** for the current indication.

9.3 Recommendation on Postmarketing Actions

N/A

9.3.1 Risk Management Activity

N/A

9.3.2 Required Phase 4 Commitments

N/A

9.3.3 Other Phase 4 Requests

N/A

9.4 Labeling Review

Deferred

9.5 Comments to Applicant

The deficiency may be corrected by conducting new adequate, prospectively designed safety and efficacy studies. Prior to the new study design, the sponsor should consider the means of reducing background enhancement, and venous signal contamination. Demonstrating efficacy and safety in different vascular territories is also an option.

The following issues should be considered in the new clinical trials:

- Adequate evaluation of MS-325 stability in patients with and without renal insufficiency.
- Standardization of the non-contrast imaging protocol at baseline to achieve an optimal performance level.
- [
- Ensuring the validity of data imputation method used in the primary efficacy analysis. In the current studies, all uninterpretable MRA images were treated as either false negative in sensitivity calculation, or false positive in specificity calculation. Since a much higher percentage of non-contrast MRA images (up to 41% for some arterial regions) at baseline were considered as the uninterpretable, compared to that (<3%) of MS-325 enhanced MRA images, this so-called “conservative treatment of uninterpretable MR images” is problematic because it greatly underestimated both sensitivity and specificity of non-contrast MRA at baseline, compared to that of MS-325 enhanced MRA. As a result, it may create a false impression of an improvement of post-contrast images in both sensitivity and specificity.

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10 APPENDICES

10.1 Review of Individual Study Reports

N/A

10.2 Line-by-Line Labeling

N/A

10.3 References

Bluemke, D. A. et al. "Optimal characterization of myocardial perfusion with AngioMARK."

Acad.Radiol 9 Suppl 1 (2002): S78.

Caravan, P. et al. "The interaction of MS-325 with human serum albumin and its effect on proton relaxation rates." J.Am.Chem.Soc 124.12 (2002): 3152-62.

Caravan, P. et al. "Thermodynamic stability and kinetic inertness of MS-325, a new blood pool agent for magnetic resonance imaging." Inorg.Chem. 40.9 (2001): 2170-76.

Carroll, T. J. et al. "The effect of injection rate on time-resolved contrast-enhanced peripheral MRA." J.Magn.Reson.Imaging 14.4 (2001): 401-10.

Earls, J. P. and D. A. Bluemke. "New MR imaging contrast agents." Magn.Reson.Imaging Clin.N.Am. 7.2 (1999): 255-73.

Foo, T. K., V. B. Ho, and P. L. Choyke. "Contrast-enhanced carotid MR angiography. Imaging principles and physics." Neuroimaging.Clin.N.Am. 9.2 (1999): 263-84.

- Foo, T. K. et al. "Preferential arterial imaging using gated thick-slice gadolinium-enhanced phase-contrast acquisition in peripheral MRA." J.Magn.Reson.Imaging 13.5 (2001): 714-21.
- Frangi, A. F. et al. "Quantitative analysis of vascular morphology from 3D MR angiograms: In vitro and in vivo results." Magn.Reson.Med. 45.2 (2001): 311-22.
- Goyen, M. and J. F. Debatin. "Gadopentetate dimeglumine-enhanced three-dimensional MR-angiography: dosing, safety, and efficacy." J.Magn.Reson.Imaging 19.3 (2004): 261-73.
- Goyen, M., S. G. Ruehm, and J. F. Debatin. "MR-angiography: the role of contrast agents." Eur.J.Radiol 34.3 (2000): 247-56.
- Grist, T. M. et al. "Steady-state and dynamic MR angiography with MS-325: initial experience in humans." Radiology. 207.2 (1998): 539-44.
- Herborn, C. U. et al. "Whole-body 3D MR angiography of patients with peripheral arterial occlusive disease." AJR.Am.J.Roentgenol. 182.6 (2004): 1427-34.
- Ho, V. B. et al. "Contrast-enhanced magnetic resonance angiography: technical considerations for optimized clinical implementation." Top.Magn.Reson.Imaging 12.4 (2001): 283-99.
- Kirchin, M. A. et al. "Safety assessment of gadobenate dimeglumine (MultiHance): extended clinical experience from phase I studies to post-marketing surveillance." J.Magn.Reson.Imaging 14.3 (2001): 281-94.

Knopp, M. V. et al. "Contrast agents for MRA: future directions." J.Magn.Reson.Imaging 10.3 (1999): 314-16.

Kroft, L. J. and A. de Roos. "Blood pool contrast agents for cardiovascular MR imaging." J.Magn.Reson.Imaging 10.3 (1999): 395-403.

Lauffer, R. B. et al. "MS-325: albumin-targeted contrast agent for MR angiography." Radiology. 207.2 (1998): 529-38.

Lei, T. et al. "3DVIEWS-NIX-AVS: a software package for the separate visualization of arteries and veins in CE-MRA images." Comput.Med.Imaging Graph. 27.5 (2003): 351-62.

Li, D. et al. "Three-dimensional MRI of coronary arteries using an intravascular contrast agent." Magn.Reson.Med. 39.6 (1998): 1014-18.

Parmelee, D. J. et al. "Preclinical evaluation of the pharmacokinetics, biodistribution, and elimination of MS-325, a blood pool agent for magnetic resonance imaging." Invest.Radiol 32.12 (1997): 741-47.

Perreault, P. et al. "MR angiography with gadofosveset trisodium for peripheral vascular disease: phase II trial." Radiology. 229.3 (2003): 811-20.

Prasad, P. V. et al. "First-pass renal perfusion imaging using MS-325, an albumin-targeted MRI contrast agent." Invest.Radiol 34.9 (1999): 566-71.

- Ruehm, S. G. et al. "Pelvic and lower extremity arterial imaging: diagnostic performance of three-dimensional contrast-enhanced MR angiography." AJR.Am.J.Roentgenol. 174.4 (2000): 1127-35.
- Shetty, A. N. et al. "Contrast-enhanced breath-hold three-dimensional magnetic resonance angiography in the evaluation of renal arteries: optimization of technique and pitfalls." J.Magn.Reson.Imaging 12.6 (2000): 912-23.
- Swan, J. S. et al. "Magnetic resonance angiography of aorto-iliac disease." Am.J.Surg. 180.1 (2000): 6-12.
- Weinmann, H. J. et al. "Comparative studies on the efficacy of MRI contrast agents in MRA." Acad.Radiol 9 Suppl 1 (2002): S135-S136.
- Yucel, E. K. et al. "AHA scientific statement. Magnetic resonance angiography : update on applications for extracranial arteries." Circulation 100.22 (1999): 2284-301.
- Patel, M. R. et al. "Preoperative assessment of the carotid bifurcation. Can magnetic resonance angiography and duplex ultrasonography replace contrast arteriography?" Stroke. 26.10 (1995): 1753-58.
- Quinn, S. F. et al. "Evaluation of the iliac arteries: comparison of two-dimensional time of flight magnetic resonance angiography with cardiac compensated fast gradient recalled echo and contrast-enhanced three-dimensional time of flight magnetic resonance angiography." J.Magn.Reson.Imaging 7.1 (1997): 197-203.
- Corot, C. et al. "Comparison of different types of blood pool agents (P792, MS325, USPIO) in a rabbit MR angiography-like protocol." Invest.Radiol 38.6 (2003): 311-19.

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