

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-711

MEDICAL REVIEW(S)

DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

Secondary Clinical Review Memorandum

Date: December 12, 2008

NDA: 21-711 (Letter date 06-30-08; PDUFA goal date 12-31-08)

Product: Vasovist (Gadofosveset Trisodium)

Drug Class: Magnetic Resonance Angiography (MRA) Imaging Agent

Applicant: EPIX Pharmaceuticals, Inc.

Investigated Use: Evaluation of Aortoiliac Occlusive Disease

Primary Clinical Reviewer: Barbara Stinson, D.O.

Clinical Team Leader: Alexander Gorovets, M.D.

Recommendation

The team leader concurs with the primary clinical reviewer's overall assessment of the sponsor's application and recommends the approval of Vasovist as a gadolinium based contrast agent for use with Magnetic Resonance Angiography (MRA) in evaluation of Aortoiliac Occlusive Disease in adults with known or suspected peripheral vascular disease.

Review Methods

This review is based on the critical appraisal of the primary clinical review, on the sponsor's summary of clinical data and on other excerpts from the application.

Regulatory Background and Product Information

This is the third cycle review of Vasovist application. EPIX originally submitted the NDA 21-711 for Vasovist in December 2003. The first "Approvable" letter was issued by FDA in January 2005. The second cycle review resulted in another "Approvable" letter in November 2005, with both reviews recommending the applicant to conduct additional studies. The cited deficiencies centered on the statistical treatment of uninterpretable images and the apparent inadequacies of the conduct of the blinded reads and reader training. In June 2006, the applicant initiated the process of formal dispute resolution. It resulted in the response from the Deputy Director of CDER which included the

recommendation to conduct a re-read of images from the two trials of Vasovist that focused on the aortoiliac vascular region, to standardize the reader training and to revise the statistical analysis plan to be used in assessing the results of the re-read.

Vasovist, or gadofosveset trisodium, is a stable gadolinium chelate derivative which upon injection binds reversibly to endogenous serum albumin resulting in longer vascular residence time as compared to non-protein binding contrast agents. It has a half-life of approximately 16 hours. The binding to serum albumin increases the relaxivity of gadofosveset and decreases the relaxation time (T1) of water protons resulting in an increase in signal intensity (brightness) of blood.

Vasovist injection is a 0.25 mmol/mL solution administered at a dose of 0.12 mL/kg body weight (0.03 mmol/kg). Vasovist imaging consists of two stages: the dynamic imaging stage and the steady-state imaging stage. Dynamic imaging begins immediately upon injection. Steady-state imaging begins after the dynamic imaging has been completed, generally 5 to 7 minutes following Vasovist administration, and is completed within an hour.

Sources of Clinical Data

The source of clinical data for the efficacy review consisted of a re-read of aorto-iliac images from two Phase-3 multi-center trials, with 424 subjects constituting the primary efficacy population. Safety was not re-evaluated as part of the blinded re-read analysis however a revised, fully Integrated Summary of Safety (ISS) Update 2008 was included in the current NDA submission. ISS 2008 included analysis of 4 additional studies performed since the 2003 summary and a comparison of the safety results from the ISS 2003 to the ISS 2008. The source of clinical data for the integrated review of safety consisted of the entire Vasovist development program. This included five Phase-1 trials, twelve Phase-2 trials, and four Phase-3 trials, and provided an overall safety database of 1763 patients, 1676 receiving the drug and 87 receiving placebo. Doses received ranged from 0.005mmol/kg to 0.15mmol/kg, with 802 subjects receiving the recommended dose of 0.03mmol/kg.

Study Design and Conduct

Efficacy of Vasovist was assessed in two multi-center, open-label Phase-3 clinical trials. In both trials, patients with known or suspected peripheral vascular disease underwent aorto-iliac MRA with and without Vasovist as well as X-ray arteriography of the same vascular region. Diagnostic efficacy was based upon comparisons of sensitivity and specificity between MRA with and without Vasovist, with X-ray arteriography as the standard of truth.

Out of 493 patients enrolled in these two trials, 424 were included in the comparison of the diagnostic efficacy of Vasovist-MRA to that of non-contrast MRA in detection/exclusion of occlusive vascular disease ($\geq 50\%$ stenosis) in 7 vessel-segments in the aortoiliac region. The interpretation of MRA images from both trials was conducted by three independent radiologist readers who were blinded to clinical data, including the results of X-ray arteriography. In these 424 patients, the median age was 67 years with a range of 29 to 87 years; 58% of the patients were over 65 years of age; 83% were white and 68% were male.

The primary efficacy analyses were designed to demonstrate superiority in sensitivity and non-inferiority in specificity of Vasovist-MRA as compared to non-contrast MRA at the vessel-segment level. In these analyses, the uninterpretable images were assigned an outcome of "wrong diagnosis". The categories of uninterpretable images were pre-specified. In addition to demonstrating the superiority in sensitivity and non-inferiority in specificity, as above, success was also based upon acceptable performance characteristics for the uninterpretable non-contrast MRA vessel segments that became interpretable following Vasovist administration. Specifically, the sensitivity and specificity for these Vasovist images were required to exceed 50%. These pre-specified success criteria were to be achieved by at least the same two readers for all primary analyses.

Efficacy Data Analyses

Superiority in sensitivity and non-inferiority in specificity was demonstrated for Vasovist-MRA by all three blinded readers. On average, 316 vessel segments were

assessed for sensitivity and 2230 for specificity, by each reader. The table below summarizes the efficacy results, by reader.

Performance Characteristics of Vasovist-MRA and Non-contrast MRA

Reader	SENSITIVITY			SPECIFICITY		
	Vasovist-MRA [A]	Non-contrast MRA [B]	[A] – [B] (95% CI)*	Vasovist MRA [A]	Non-contrast MRA [B]	[A] – [B] (95% CI)*
1	89%	69%	20% (15%, 25%)	72%	71%	1% (-3%, 5%)
2	82%	70%	12% (7%, 17%)	81%	73%	8% (4%, 12%)
3	79%	64%	15% (9%, 21%)	85%	85%	0% (-2%, 2%)

*(Based on cluster-corrected McNemar Test)

Among the three readers, 5-12% of the vessel-segments were deemed uninterpretable by non-contrast MRA. For these vessel segments, sensitivity of Vasovist-MRA ranged from 72% [95% CI (54%, 90%)] to 97% [95% CI (93%, 100%)] and specificity ranged from 72% [95% CI (67%, 76%)] to 84% [95% CI (81%, 88%)].

Safety Data Analyses

The 2008 safety update did not appear to reveal any new safety signals as compared to the ISS of 2003. Since 2003, Nephrogenic Systemic Fibrosis (NSF) has been described in association with the use of gadolinium agents in patient with severe renal insufficiency. To date, no cases of NSF have been reported with the use of Vasovist. It has been approved in Europe in 2005 and since then the total postmarketing exposure, at the time of this submission, has been estimated by the sponsor as ≈ 1

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Five deaths have been reported in patients undergoing imaging evaluations involving Vasovist. (Three in 2003, and two in the current submission, but reported separately from the 2008 safety update). None of the deaths appear to have been related to the drug.

Serious Adverse Events in clinical trials included two cases of non-fatal anaphylaxis. The most common adverse reactions (>2%) consisted of pruritis, headache, nausea and Paresthesia.

Conclusion

As a result of the review of the submitted efficacy data (re-read of two trials involving aortoiliac vascular region) and the submitted safety update, the risk and benefit assessment appears to favor the approval of Vasovist for the use with MRA in the evaluation of the aortoiliac occlusive disease in the targeted patient population.

As applicable to all gadolinium agents, there will be a post-marketing requirement involving a clinical trial of Vasovist to assess the risk of NSF in patients with moderate to severe renal insufficiency.

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/s/

Alexander Gorovets
12/18/2008 12:12:47 PM
MEDICAL OFFICER

CLINICAL REVIEW

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Reviewer Name Barbara Stinson, DO
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Established Name Gadofosveset Trisodium
(Proposed) Trade Name Vasovist® Injection
Therapeutic Class Magnetic Resonance
Angiography Imaging Agent
Applicant EPIX Pharmaceuticals, Inc.

Priority Designation S

Formulation Injectable Solution, .25 mmol
gadofosveset trisodium/ml
Dosing Regimen Single Dose 12 mL/kg
(0.03mmol/kg) by
intravenous bolus
Indication Diagnosis of Aortoiliac
Occlusive Disease
Intended Population Adults

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1. EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This document is a third-cycle FDA review of Vasovist, (MS-325, [generic name Gadofosveset Trisodium]), which is a gadolinium containing contrast agent intended for use in magnetic resonance angiography. Two prior "Approvable" letters were issued in 2005. This document references the two prior clinical reviews written in support of these actions. The Introduction and background section of this document contains a summary of regulatory actions from the time of initial submission of the NDA to the present. The current review concentrates on the review of the re-read of two prior studies performed to determine efficacy and references the two prior clinical reviews, especially as they relate to safety.

Based on the comments below referencing efficacy and safety, this reviewer recommends the approval of NDA # 21711 for the use of Vasovist (MS-325) as a magnetic resonance angiography imaging agent in the diagnosis of Aortoiliac Occlusive Disease.

The re-read of two prior efficacy trials submitted in support of the NDA (Study MS-325-12 and Study MS-325-13) achieved the two conditions agreed upon to achieve the primary efficacy endpoint by demonstrating that the sensitivity for disease using Vasovist-enhanced MRA is greater than that of non-contrast MRA and that the specificity for disease detection using Vasovist-enhanced MRA is non-inferior to non-contrast MRA. In addition, the re-read met the second condition for efficacy for which segments deemed uninterpretable on non-contrast MRA but interpretable with Vasovist achieved a sensitivity and specificity of greater than 50%.

This reviewer finds the safety profile of MS-325 to be acceptable. The current Integrated Summary of Safety shows that the safety database is stable with no alteration in the safety profile since the ISS 2003 report. Since the original submission, Vasovist has been marketed in a number of countries outside of the US with no reports of NSF in the approximately _____ patients who have received the product.

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1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

In view of the current safety reports for this NDA, the reviewer recommends routine safety surveillance reports, including such reports as Adverse Event Reports (MedWatch Reports), Periodic Safety Updates and Annual Reports, as required for compliance with regulatory standards. This application will be subject to the Post-Marketing Requirement (PMR), same as all approved gadolinium products to date, to conduct a clinical trial to

collect clinical data sufficient to assess the magnitude of risk for the development of NSF among patients with moderate ($\text{GFR} < 60 \text{ mL/min/1.73m}^2$) to severe renal insufficiency.

1.2.2 Required Phase 4 Commitments

Apart from the NSF related PMR, no other Phase-4 commitments are being recommended at this time.

The sponsor has requested a full pediatric waiver, and the recommendation of this reviewer is to grant the request. Aortoiliac Occlusive disease is a manifestation of atherosclerotic arterial disease which rarely, if ever, occurs in children.

1.2.3 Other Phase 4 Requests

No other Phase-4 requests are being considered at this time.

1.3 Summary of the Re-read Findings

1.3.1 Brief Overview of the Clinical Program and the Re-Read Program

Gadofosveset Trisodium (MS-325) is a gadolinium-based blood pool contrast agent that was developed as a new magnetic resonance angiography (MRA) imaging agent for the evaluation of arterial vascular disease in the aortoiliac region. It is a stable gadolinium DTPA chelate that is injected in an aqueous solution. The product's Established Name is Gadofosveset Trisodium (MS-325). The product's proposed Trade Name is Vasovist™. The drug product is administered by a single intravenous bolus injection, either manually or via injector. Following intravenous injection, gadofosveset binds reversibly to endogenous serum albumin resulting in longer residence times than non-protein binding agents and thus allowing for imaging up to one hour following injection. According to the Sponsor, the binding to serum albumin also increases the magnetic resonance potency (relaxivity) of gadofosveset and decreases the relaxation time of water protons (T1) thereby resulting in an increased signal intensity of blood. Protein binding enhances this relaxivity compared to non-protein bound gadolinium chelates.

The sponsor has proposed the following indication:

"Vasovist Injection is a gadolinium-based [] contrast agent indicated for use with magnetic resonance angiography (MRA) to evaluate aortoiliac occlusive disease (AIOD) in adults with known or suspected peripheral vascular disease."

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The recommended dose is 0.12 mL/kg of a 0.25mmol/mL solution (0.03mmol/kg) administered as an intravenous bolus over 30 seconds, either manually or via power injector. The injection is followed with a 25-30 mL saline flush.

There have been 21 clinical trials with MS-325. A total of 1379 subjects have been exposed to the agent and 802 patients have been exposed to the proposed clinical dose of 0.03 mmol/Kg. A summary of exposure to Vasovist or placebo in MS-325 clinical trials is presented in the ISS section.

The source of clinical data for the review of efficacy consisted of a re-read (R) of two Phase-3 multi-center trials (protocol MS-325-12R and MS-325-13R). The primary efficacy population included 424 subjects and was defined for the Evaluable population as those subjects with an interpretable x-ray angiography (XRA) used as the standard of reference (SOR) and both a Vasovist-enhanced and non-contrast MRA. Safety was not re-evaluated for the Blinded Re-read analysis however a revised, fully Integrated Summary of Safety (ISS) Update 2008 was included in the current NDA submission. ISS 2008 includes analysis of 4 additional studies performed since the 2003 summary and a comparison of the safety results from the ISS 2003 to the ISS 2008. The source of clinical data for the integrated review of safety consisted of the entire Vasovist development program. The program consisted of five Phase-1 trials, twelve Phase-2 trials, and four Phase-3 trials. This provided an overall safety database of 1763 patients, 1676 receiving treatment with MS-325 and 87 receiving placebo. Doses received ranged from 0.005 mmol/kg to 0.15 mmol/kg with only healthy volunteers receiving doses of 0.10 mmol/kg or greater.

NDA 21,711 was initially submitted on December 12, 2003 and filed on February 13, 2004. The first Approvable Letter was issued on January 12, 2005 requiring the conduct of additional studies. The Sponsor, EPIX, received a second Approvable Letter on November 21, 2005. On June 30, 2006, EPIX appealed this action, requesting formal dispute resolution. The outcome was a letter from the Deputy Director of CDER dated June 15, 2007, providing recommendations for a path forward for the approval of Vasovist. EPIX incorporated these recommendations resulting in a re-read protocol and a revised statistical analysis plan which form the basis for this submission.

1.3.2 Efficacy

Two studies were identical for the purpose of the re-read. Combined efficacy analyses were performed on all available images from both studies. Measures were taken to standardize and improve reader training. The core lab selected three newly trained blinded readers for the new efficacy assessment. Both the efficacy endpoints and the statistical analysis plan were pre-specified prior to submission of the NDA.

The sponsor evaluated the efficacy of Vasovist injection by assessing the diagnostic performance of Vasovist Injection, measured by sensitivity and specificity, by the re-

reading the images obtained in two multi-center, open label, parallel, Phase-3 clinical trials. Studies MS-325-12R and MS-325-13R were designed to compare the efficacy for the diagnosis of aortoiliac occlusive disease by comparing both Vasovist MRA contrast images and non-contrast MRA images to X-ray angiography (XRA) as the Standard of Reference (SOR) with primary efficacy endpoints to be met simultaneously by two of three blinded readers. Sensitivity and specificity were defined by comparison of MRA images of 7 vessel segments in the aortoiliac region to these same segments on x-ray angiography. The first efficacy endpoint was defined as statistically significant superiority in sensitivity of the MRA contrast images compared to non contrast images and the non-inferiority in specificity. An additional primary efficacy endpoint requirement was for all vessel-segments for which non-contrast MRA was uninterpretable but Vasovist MRA was interpretable and required that the sensitivity and specificity of Vasovist were to be greater than 50% for the same two readers satisfying the first criterion.

The sponsor has achieved the paired criteria for success in the re-read of the combined aortoiliac studies by all 3 blinded MRA readers. The Vasovist-enhanced vessel-weighted sensitivity (ranging from 79% to 89%) was significantly increased as compared with the non-contrast vessel-weighted sensitivity. The differences between Vasovist-enhanced sensitivity and non-contrast sensitivity ranged from 12.2% to 20.4%. For all readers, Vasovist-enhanced vessel-weighted specificity (ranging from 72% to 85%) was non-inferior to non-enhanced vessel-weighted specificity, with differences (enhanced minus non-enhanced) showing 95% CIs overlapping or exceeding 0 in favor of Vasovist-enhanced specificity. The analysis of sensitivity and specificity of Vasovist-enhanced MRA, where the corresponding non-contrast MRA vessel segment was deemed uninterpretable, showed these measurements exceeding 50% on Vasovist-enhanced images.

1.3.3 Safety

The current document submitted for review is a revised Integrated Summary of Safety (ISS). This ISS Update 2008 extends the ISS submitted with the original NDA (ISS 2003) and includes 21 clinical studies with Studies MS-325-18, MS-325-19, MS-325-20, and 305608 added since the prior update. In addition to presenting integrated data from all 21 clinical studies, ISS Update 2008 compares the safety results with ISS 2003. MS-325-12/13R is not included in ISS Update 2008 since it represented an analysis of efficacy data only, with no additional subject exposure to Vasovist.

Of the 21 studies included in the summary, there are 5 Phase 1 studies which were all conducted in normal healthy volunteers, 12 Phase 2 studies, and 4 Phase 3 studies. 1676 subjects received MS-325 in a dose ranging from 0.005 mmol/kg to 0.15 mmol/kg. 87 subjects in these studies received placebo.

Three subject deaths occurred during the Vasovist clinical trials, 2 in Study MS-325-09 and one in Study MS-325-18. Two of these appear to be unrelated to the product and one, according to the Sponsor, is possibly related. All of these were previously reported in ISS 2003 and reviewed by the FDA.

This reviewer finds the safety profile of MS-325 to be acceptable. (Please see the FDA reviews by Dr. Tong Li and Dr. Melanie Blank for greater detail).

1.3.4 Dosing Regimen and Administration

Vasovist Injection is administered to adults as an intravenous bolus injection, either manually or by power injector. The recommended dose is 0.12 mL/kg body weight (0.03 mmol/kg) of 0.25mmol/mL solution to be administered as a bolus injection up to 30 seconds. The product is available as single use vials.

1.3.5 Drug-Drug Interactions

No information on drug-drug interaction was assessed in this review.

1.3.6 Special Populations

No studies in Special Populations have been assessed during this review.

2. INTRODUCTION AND BACKGROUND

2.1 Product Information

2.1.1 Description of the Product

The product under the Laboratory Code of MS-325 was developed (under IND 51172) as a new magnetic resonance angiography imaging agent for the evaluation of aortoiliac occlusive disease (AOID) in patients with known or suspected peripheral vascular disease (PVD). It is engineered to act as a blood pool agent that binds reversibly to endogenous serum albumin which allows for imaging up to one hour following injection.

The product's Established Name is Gadofosveset Trisodium.

The product's proposed Trade Name is VASOVIST® 0.25 mmol/L Solution for Injection.

Vasovist Injection is a formulation of a stable gadolinium diethylenetriaminepentaacetic acid (GdDTPA) chelate derivatized with a diphenylcyclohexylphosphate group. The structural formula in aqueous solution consists of the stable gadolinium chelate (C^3

charge) attached to 3 sodium ions (3Na^{+3}). Each mL of Vasovist Injection contains 244 mg of gadofosveset trisodium (0.25 mmol), 0.27 mg of fosveset, and water for injection along with [] excipients. It is supplied as a solution with dosage volume dependent on patient body weight. It is supplied in a glass vial at a single strength, 0.25 mmol/mL, as a sterile solution for intravenous injection, either by manual or power injector bolus injection.

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2.1.2 Description of the Imaging Method

Magnetic Resonance Angiography with Vasovist is a non-invasive method for imaging blood flow in the aortoiliac vasculature. The gadofosveset binds reversibly to human serum albumin. Protein binding enhances T1 relaxivity of gadofosveset up to 10 fold compared to non-protein bound gadolinium chelates. Dynamic imaging of vascular structures begins immediately upon injection with high resolution MRA scans obtained up to one hour after administration of the product. The shortened T1 value (relaxivity) of the water protons which is demonstrated as an increase in signal intensity (brightness) of the blood lasts up to 4 hours after intravenous bolus injection. When evaluating the vascular system with MRI, several aspects of blood flow are considered. Flow patterns are important considerations in interpreting MR angiograms and must be differentiated from true disease processes. The quality of non-contrast MR angiograms may be compromised by flow patterns, for example when blood vessels run parallel to the imaging plane, the blood experiences multiple RF pulses and eventually becomes saturated or tortuous vessels with areas of complex flow to include signal obliteration. Contrast-enhanced (Gadolinium-enhanced) MRA yields images which are dependent on the presence of contrast in blood rather than on blood flow. The sponsor postulates that the ability to use image manipulation of 3D dynamic phase and static phase of the contrast-enhanced images would improve the sensitivity and specificity of MRA for detection of peripheral vascular disease.

Dynamic imaging begins immediately upon injection. Steady-state imaging can begin after the dynamic scan has been completed. In clinical trials, steady-state imaging began within 15 minutes after injection and was completed within approximately one hour following injection.

2.1.3 Proposed Indication and Dosing Regimen of the Imaging Product

The sponsor seeks the following indication for VASOVIST® Injection:

“Vasovist Injection is a gadolinium-based [] contrast agent indicated for use with magnetic resonance angiography (MRA) to evaluate aortoiliac occlusive disease (AIOC) in adults with known or suspected peripheral vascular disease.”

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The recommended dose is 0.12 mL/kg administered by intravenous bolus injection of duration not exceeding 30 seconds and followed by a 25-30 mL normal saline flush.

2.2 Currently Available Treatment for Indications

2.2.1 Currently Available Products for the Imaging Method of the Proposed Indication

There is currently no magnetic resonance imaging agent available for diagnosis of peripheral vascular disease in the aortoiliac region. There are other Gadolinium chelates for this use which are not approved in the US. See previous Agency reviews for further information.

2.2.2 Currently Available Diagnostic Modalities for the Proposed Indication

X-Ray Angiography

X-ray angiography (XRA) has been used historically to detect arterial lesions and stenoses in patients with suspected vascular disease. Although it produces excellent examinations, the procedure is invasive as well as onerous and lengthy for patients and involves multiples injections of iodinated contrast. The procedure involves patient exposure to ionizing radiation also. Among risks of the procedure are those associated with catheterization such as injury to the vessel wall, allergic reactions to contrast, and contrast-induced nephropathy. This technique is presently considered the “gold standard” or Standard of Reference (SOR) for evaluation of peripheral vascular arterial disease. In general, stenosis $\geq 50\%$ is considered for medical or interventional therapy.

Computed Tomographic Angiography

Peripheral Computed Tomographic Angiography (CTA) uses multidetector CT technology (MDCT) to scan the entire lower extremity inflow and runoff vessels in a single CT acquisition with a single contrast-medium injection at adequate spatial resolution. Peripheral CT angiograms can be obtained with any scanner in a short time period and the risks associated with catheter-related complications are avoided. High resolution images may be obtained with post-processing reconstruction techniques. There are various pitfalls of interpretation of the images related to window/level settings and while the technique is valuable in the emergency department situation and for the demonstration of chronic/multiple site disease (as in a pre-surgical work-up) and widely used otherwise, its use has not supplanted the gold standard XRA.

Ultrasound

Duplex ultrasonography is used to evaluate arterial blood flow patterns and velocity superimposed on anatomical (B-mode) images. Localization and determination of disease severity is based on peak-systolic and end-diastolic velocity measurements. Although non-invasive and relatively quick to perform, the procedure is highly operator dependent and as well depends upon patient body habitus. Interpretation is subjective. In addition, only larger vessels are visualized and only portions of vessels may be visualized.

2.3 Availability of Proposed Active Ingredient in the United States

Vasovist® was approved for supply to the European Union in October 2005. Since the initial filing of the NDA, additional batches of gadofosveset trisodium, fosveset, and MS-325 were manufactured to support commercialization of the product outside of the US. Manufacturing sites, materials, and process of synthesis have remained unchanged although there have been minor changes in the manufacturing process due to increases in product production. To maintain a consistent global manufacturing process, these changes in manufacturing are proposed for commercialization within the United States.

The name of the previous manufacturer, Tyco/Mallinckrodt, has been changed to Covidien. The administrative site address of the manufacturing facility is in Hazelwood, Missouri. The facility is also responsible for all testing during drug substance manufacture with the exception of [] which may be performed at a Covidien facility in St. Louis, Missouri and Bacterial Endotoxin and Total Aerobic Microbial Count testing which is performed at [] and which is a contract laboratory. Bayer Schering Pharma AG (Bayer) is responsible for all ex-US regulatory and marketing activities. Bayer HealthCare Pharmaceuticals Inc. in Wayne, New Jersey is the product distributor. Please see CMC reviews for further information.

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2.4 Important Issues with Pharmacologically Related Products

There are no other Gadolinium chelates approved for use in the United States for the indication of Magnetic Resonance Angiography. However, Nephrogenic Systemic Fibrosis (NSF) has been reported with other gadolinium-based contrast agents that are approved for other uses. These agents increase the risk of NSF in patients with acute or chronic severe renal insufficiency (glomerular filtration rate $<30\text{mL}/\text{min}/1.73\text{m}^2$) or acute renal insufficiency of any severity due to hepato-renal syndrome or in the perioperative transplantation period. The mandatory black box warning on all gadolinium-based contrast agents warns that all patients should be screened for renal function, that the recommended dose should not be exceeded, and that a sufficient time is allowed for elimination of the agent from the body prior to any re-administration.

2.5 Presubmission Regulatory Activity

Original NDA #21711 was submitted on December 12, 2003 and received an Approvable Letter on January 12, 2005. A second Approvable Letter was received on November 21, 2005. On June 30, 2006, the Sponsor launched a request for formal dispute resolution. This request was escalated and on May 8, 2007, a meeting was held between officials of CDER and EPIX (the Sponsor). The Agency provided EPIX with recommendations for a path forward for the approval of Vasovist. After subsequent meetings between the Division of Medical Imaging and Hematology (DMIHP) and EPIX, the current submission was submitted on June 30, 2008 with a PDUFA date of December 30, 2008.

The current submission represents a re-read of two large phase 3 protocols. In addition to a revision of the re-read process, the statistical analysis plan has been revised.

2.6 Other Relevant Background Information

This review will focus on updated efficacy reports (the blinded re-read of two previous Phase 3 trials), the updated safety report (Integrated Summary of Safety 2008), interval changes to the CMC section, and the Statistical Analysis report.

Of note, this reviewer has noted the following differences between the studies with regards to study enrollment and study populations evaluable for efficacy. Study MS-325-12 enrolled 315 patients. 274 of these were included in the safety analysis, (41 early discharge, 3 XRA drop-outs, 12 withdrew consent, 19 non-compliant, and 7 "other"). 266/274 patients underwent all procedures, (8 discontinued from the study, 1 withdrew consent, 3 non-compliant, 3 "other", and 1 no disposition data). There were 268 patients in the intent-to treat (ITT) population and 2 of these discontinued after all imaging was performed. Of these, 12 patients were missing XRA data and 5 patients had XRA examinations that were considered uninterpretable by the blinded readers. Thus 251 patients had data that were analyzed for efficacy.

Study MS-325-13 enrolled 178 patients. 178 were included in the safety population and 175 were in the ITT population. Two patients in the ITT population had XRA exams considered uninterpretable and therefore 173 patients were evaluated for efficacy.

3. SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Please see previous agency clinical review by Dr. Tong Li and CMC review.

Since the initial filing of the NDA and approval for supply to European Union in October 2005, additional batches of gadofosveset trisodium, fosveset and MS-325 were manufactured to support commercialization of Vasovist® outside the United States. The manufacturing sites, starting materials, inactive and active components, and container/closure systems all remain unchanged. Minor manufacturing process changes have been made as a result of the increase in the scale of the manufacture. To maintain a consistent global manufacturing process, the manufacturing changes are proposed for commercialization within the United States.

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In addition, based on a review of quality data, both the drug substance and ligand acceptance criteria were reviewed with proposed modifications to the existing specifications to include changes in specifications for impurities, changes in in-process controls, and minor changes in testing methods and specifications.

Primary and supportive stability studies on gadofosveset trisodium, fosveset, and MS-325 which were active at the time of initial filing have been completed and data is provided. This data supports post-marketing approval commitments in the EU.

The name of the company responsible for the drug substance, ligand excipient, and drug product manufacture has been changed from Tyco/Mallinkrodt to Covidien.

A summary of the list of the changes is contained in Section 4.0 CMC, pages 10-16.

3.2 Animal Pharmacology/Toxicology

Please see previous agency clinical review by Dr. Tong Li and pharmacology/toxicology review.

4. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The source of clinical data for the review of efficacy consisted of the re-reread of data from two phase 3 multi-center trials (MS-325-12 and MS-325-13) conducted in the United States, Canada, Columbia, Germany, United Kingdom, Argentina, and Australia. The source of clinical data for the integrated review of safety consisted of data from the entire MS-325 development program (21 trials, N=1,676) submitted to the NDA by the sponsor.

4.2 Tables of Clinical Studies

A complete table summarizing the Vasovist development program was presented in the submission as Table 3.1, pages R8 12647-50. These studies are summarized in the listing below. The program consisted of 21 phase 1, phase 2, and phase 3 studies. Four additional clinical studies were performed since the prior submission, (58 new patients and 180 new healthy volunteers).

MS-325-01A: Phase I, PK and safety study, placebo-controlled, in healthy adult volunteers

MS-325-01B: Phase I, safety and MRA imaging study, in healthy adult volunteers
MS-325-01C: Phase I, safety, PK, and dose escalation study in healthy adult volunteers
MS-325-08: Phase I methodology study assessing MRA imaging

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305608: Phase I, placebo-controlled, dose escalation study to assess safety and pharmacokinetics in healthy Japanese subjects
MS-325-06: Phase II study to evaluate safety of Angiomark in subjects with arterial vascular occlusive disease and safety and pharmacokinetics of Angiomark in patients on warfarin therapy (Angiomark changed to MS-325 in subsequent studies)
MS-325-07: Phase II study to evaluate safety and pharmacokinetics of MS-325 in subjects with renal insufficiency
MS-325-16: Phase II study to evaluate safety and pharmacokinetics using 2 doses of MS-325 in subjects with hepatic insufficiency, age-matched normals, and healthy volunteers, (0.03 mmol/kg dose and 0.05 mmol/kg)
MS-325-18: Phase II safety and PK study in patients with end-stage renal disease
MS-325-04/04a: Phase II feasibility study of safety and efficacy of coronary MRA
MS-325-05: Phase II feasibility study of safety and efficacy in identifying malignant breast lesions
MS-325-10: Phase II feasibility study of safety and efficacy for identification of myocardial perfusion
MS-325-11: Phase II feasibility study of safety and efficacy in 3D coronary MRA
MS-325-19: Phase II comparative study in healthy volunteers and patients with vascular disease
MS-325-20: Phase II study in healthy volunteers and in patients with coronary artery disease
MS-325-02: Phase II study of safety and efficacy of MRA in carotid and peripheral arteries
MS-325-09: Phase II dose-ranging placebo-controlled study for safety and efficacy of contrast-enhanced MRA for evaluation of aortoiliac occlusive disease
MS-325-12: Phase III study to determine safety and efficacy of contrast-enhanced MRA for evaluation of aortoiliac occlusive disease
MS-325-13: Phase III study to determine safety and efficacy of contrast-enhanced MRA in patients with suspected peripheral vascular disease
MS-325-14: Phase III study to determine safety and efficacy of contrast-enhanced MRA in patients with known or suspected renal disease
MS-325-15: Phase III study to determine safety and efficacy of contrast-enhanced MRA in patients with known or suspected pedal disease

4.3 Review Strategy

This reviewer addressed the efficacy data presented in the re-read of two Phase-3 trials concentrating on the primary endpoint analyses. Data from all studies submitted with the NDA were reviewed for safety.

4.4 Data Quality and Integrity

Pending the results of the DSI report, it appears that the data submitted in support of the NDA are acceptable. A detailed Blinded Reader Manual was used for interpretation of the studies and the studies were interpreted as agreed upon between the Agency and the Sponsor prior to the re-read. The Sponsor conducted an image presentation session for the FDA reviewers prior to the re-read during which the rationale for "uninterpretable" images was found to be acceptable. The readers appear to have been properly blinded and there is no evidence that the blind has not been adequately maintained. The FDA statistician verified the analyses of the primary endpoint.

4.5 Compliance with Good Clinical Practices

No major issues were identified in Dr. Tong Li's clinical review although it was noted that there were some instances of suboptimal patients' follow-up and record keeping. The Sponsor appears to have complied with the Good Clinical Practices and the acceptable ethical standards in the conduct of the trials submitted for review in support of the NDA.

4.6 Financial Disclosures

Please see previous clinical review by Dr. Tong Li regarding previously provided financial information. Financial disclosure information for the re-read was reviewed and appeared to be satisfactory. Complete information for the blinded readers is on file at

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5. CLINICAL PHARMACOLOGY

No additional clinical pharmacology review was performed for this cycle. Dr. Christy John of Clinical Pharmacology performed the FDA review of the sponsor's submission and found the pharmacological conclusions to be acceptable. A summary of the clinical pharmacology trials and findings is contained in volume 1 of the current submission, NDA 21-711 section R3, pages 127, 128, and 129.

The previous review contains a discussion of the albumin binding and clearance. In the first review cycle, the issue of stability of the investigational agent was raised due to zincuria and hypocalcemia in some subjects. Stability studies done comparing MS-325 to Optimark (another gadolinium agent) showed that Optimark had a greater degree of zincuria than MS-325 suggesting that product stability is of no greater concern than with other gadolinium products. Additionally, after review of studies in renally impaired patients, the pharmacology reviewers concluded that there is no evidence to suggest that MS-325 presents a safety issue in renally impaired patients. Gadofosveset may be removed from the body by dialysis.

Since the second cycle review, Nephrogenic Systemic Fibrosis (NSF) has been reported with other licensed gadolinium-based contrast agents. There have been no reported cases of NSF with Vasovist. However, since gadolinium agents increase the risk of NSF in patients with acute or chronic renal insufficiency or in the perioperative transplantation period, all patients should be screened for renal function, the recommended dose should not be exceeded, and a sufficient time must be allowed for elimination of the agent prior to re-administration.

6. INTEGRATED REVIEW OF EFFICACY

The sponsor evaluated the efficacy of Vasovist® (MS-325) as an imaging agent for Magnetic Resonance Angiography (MRA) evaluation of aortoiliac occlusive disease (AOID) in two independent, "open-label", Phase 3, clinical trials: Study MS-325-12 and Study MS-325-13; entitled: "Blinded Re-read of Examinations from Phase 3 Studies MS-325-12 and MS-325-13 to Confirm the Diagnostic Performance of Vasovist® in Subjects with Suspected Aortoiliac Occlusive Disease (AOID)." The objective of the current study was to re-assess the diagnostic performance of Vasovist® in the evaluation of AOID in subjects with known or suspected peripheral vascular disease (PVD). The objective was accomplished by conducting an independent, blinded re-read of Magnetic Resonance Angiography (MRA) examinations from two previously conducted studies of Vasovist® (MS-325-12 and MS-325-13). The Sponsor has designated these re-read studies as MS-325-12R and MS-325-13R. The MRA examinations were performed as both non-contrast and Vasovist®-enhanced studies. All patients received x-ray angiography (XRA) exams which served as the Standard of Reference for the efficacy analysis. The results of the XRA exams were taken from the prior submission of Vasovist® which received an "Approvable" designation.

The Blinded Re-read of the MRA exams included extensive reader training with ongoing assessments of intra-reader variability, provided guidelines for vessel segment delineation, measurement, and technical evaluation, and utilized a prospective statistical analysis plan with a clear definition of success. The enrolled population and the evaluable population were planned to be the same as the population intended to receive Vasovist® in commercial use. Since this was a re-analysis of existing data, there were no additional treatments. For Data Quality Assurance and Compliance with GCP standards, please see prior reviews by Dr. Tong Li, (1-10-05), and Dr. Melanie Blank, (10-17-05) and Section 4 of this document.

The review strategy used by this medical officer for this clinical review included assessing the two prior FDA reviews by the medical officers, team leaders, and office directors with summaries of their observations and conclusions. The following was also

reviewed independently: the Blinded Re-read protocol and Reader Training Manual, the 2008 safety update, the re-analysis of the data provided by the Sponsor, the articles cited by the Sponsor, the package insert, and the proposed labeling.

6.1 Indication

The sponsor seeks the following indication for Vasovist® (MS-325):

“Vasovist Injection is a gadolinium-based [] contrast agent indicated for use with magnetic resonance angiography (MRA) to evaluate aortoiliac occlusive disease (AIOD) in adults with known or suspected peripheral vascular disease.”

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6.1.1 Methods

For the integrated review of efficacy, the reviewer analyzed clinical data from the two aforementioned Phase 3 trials. The statistical analyses were performed and verified with the assistance of Dr. Anthony Mucci of the Division of Biometrics.

6.1.2 General Discussion of Endpoints

In accordance with FDA Guidance for Industry, Developing Medical Imaging Drug and Biologic Products, Part 2: Clinical Indications, the sponsor attempted to assess the performance characteristics of the proposed Test agent, MS-325, in detecting AIOD by measuring sensitivity and specificity of MS-325. Sensitivity and Specificity are the recommended parameters for measurement and are independent of disease prevalence in the study population, i.e. Sensitivity is determined by assessing patients with the disease, and Specificity is determined by assessing patients without the disease.

In the two Phase 3 efficacy trials of MS-325, x-ray angiography (XRA) served as a Comparator and is the accepted “gold standard” (Standard of Reference [SOR]) for the diagnosis of aortoiliac occlusive disease.

6.1.3 Study Design and Investigational Plan

6.1.3.1 Summary of Study Methodology: Studies MS-325-12 and MS-325-13

Studies MS-325-12 and MS-325-13 and were designed to test the efficacy of MS-325 (contrast-enhanced MRA) using XRA as the SOR. Prior to enrollment, patients were evaluated for peripheral vascular disease with aortoiliac disease diagnosed by physical examination and/or medical history. Patients were scheduled for x-ray angiography within 30 days including aortoiliac evaluation within 30 days of enrollment. The study population consisted of adult men and women with known or suspected PVD who were scheduled for evaluation of AIOD and who were scheduled for XRA. The specific inclusion and exclusion criteria for Studies MS-325-12 and MS-325-13 are presented in

their respective Case Study Reports (CSRs). All subjects underwent contrast-enhanced and non-contrast MRA exams and XRA exams. Full study reports of the original analyses are available and were submitted with the original NDA.

Vasovist was administered as an intravenous bolus injection, manually or by power injector, at a dose of 0.12 mL/kg body weight (0.03 mmol/kg) as a bolus injection up to 30 seconds. Patients were monitored during Vasovist administration and evaluated for up to 3-4 days following the procedure.

During MRA exams, images were acquired using both flow-based non-contrast magnetic resonance (MR) angiography (MRA) and gadolinium-based contrast MRA (Vasovist®-enhanced MRA). XRA images were acquired according to the standard of care at the institution and the read was conducted separately to establish the standard of reference (SOR). Images included the anatomic area extending from the infrarenal abdominal aorta (IRAA) through the common femoral arteries. The following seven vessel segments were evaluated both by MRA and XRA exam: infrarenal abdominal aorta (IRAA), left and/or right common iliac artery (CIA), left and/or right external iliac artery (EIA), and left and/or right common femoral artery (CFA). Since the objective of the current study was to confirm the diagnostic performance of Vasovist in the evaluation of AIOD by performance of a re-read of two previous Phase 3 studies, results of the previous XRA studies were used as the SOR for the current Vasovist re-read study. In the original studies, MRA exams were always performed prior to angiography which was always performed within 30 days of study enrollment. At the time of magnetic resonance angiography, a clinically significant stenosis was defined as $\geq 50\%$ stenosis.

6.1.3.2 Blinded Re-read: Summary of Methodology (Studies MS-325-12R and MS-325-13R)

The current submission is a Blinded Re-read (R) of Studies MS-325-12 and MS-325-13, designated by the Sponsor as MS-325-12R and MS-325-13R, involving images from 424 subjects. All examinations were sent to a core imaging facility for processing. []

[] The Blinded Re-read of MRA examinations was performed by 3 independent radiologists at []. Seven vessel segments as follows were evaluated: infrarenal abdominal aorta (IRAA), left and/or right common iliac artery (CIA), left and/or right external iliac artery (EIA), and left and/or right common femoral artery (CFA). These were compared to the results of XRA, determined at the time of the previous NDA submission by a separate, independent group of 3 radiologists, (2 Readers and 1 adjudicator per study). None of the readers performing interpretations of the MRA exams had any knowledge about the subjects or the XRA results.

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The Blinded Re-read was performed by [] utilizing their [] application. Quality Control checks were performed to ensure complete transfer of the datasets and proper translation into the Reader's workstation.

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6.1.3.3 Blinded Readers: Selection, Training, Intra-reader and Inter-reader Variability

Three independent radiologists were identified by [] and selected by EPIX Pharmaceuticals, Inc to read and interpret the MRA exams from all treated subjects in each trial. All readers were board-certified radiologists in the United States and had no affiliation with any sites participating in the clinical trials. Readers were required to sign conflict of interest statements and to agree to hold confidential all information presented to them during the Blinded Re-read process. Readers received compensation commensurate with industry standard rates for these services.

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Each of the readers attended a mock read and training session at [] which included the following: AIOD/PVD overview, overview of the enhancement properties of Vasovist, radiology aspects of contrast/non-contrast MRA with examples, tutorial on MRA evaluation describing MRA scoring and artifacts, use of the [] as would be used for image presentation, formatting, and measurement, how to identify and document findings reasons for the findings when vessels are not visualized or are unable to be interpreted, and how to complete the electronic case form. The training session included a video that was available for reference at all times. Formal testing after training required at least an 80% score. Repeat training (video) was required in the event there was a period of 14 days or longer between reading sessions. At the onset of training and when times between readings were 14 days or longer, readers had to sign a Read Rules document, (document reproduced in the Blinded Read Manual contained in the submission summarizes the processes and procedures of the read).

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Intra-reader variability was evaluated at the end of the study using the kappa statistic. This was obtained by presenting 4 subject examinations (2 non-contrast and 2 Vasovist-enhanced examinations, total of 28 vessel segments) from a prior Phase 2 study to each reader at baseline and then randomly during the Blinded Re-read at each 100-examination presentation interval. Re-training was required in case of a 5-vessel-segment mismatch (i.e. 5/28) with replacement of a reader if this mismatch occurred ≥ 3 times during the Blinded Re-read. Inter-reader variability was also calculated using the kappa statistic.

In the event of the need to replace a Reader, all exams were interpreted by the replacement Reader. The original Reader's data were listed and tabulated but not included in the primary analysis.

6.1.3.4 Conduct of the Blinded Re-read

All MRA examinations were sent to a core imaging facility for processing. The blinded re-read of MRA examinations was performed by 3 independent radiologists. All readers were blinded in relation to the clinical details of the examinations, such as the individual patient findings of the other imaging methods, the patient's medical history, and the patient's clinical diagnosis. Readers received initial training to encompass an overview of contrast MRA, a tutorial on MRA evaluation as applicable to the read, use of the workstation, and a review of the electronic case report form. Non-contrast and contrast images were interpreted by the same reader using a blocked randomization scheme to

eliminate the possibility of the same subject being seen one after another or closely spaced. The XRA studies that were used as the standard of reference (data from the prior NDA submission) were read by multiple readers with the SOR established on the basis of an adjudicated read (i.e. 3 readers with agreement by 2/3 on a vessel segment).

The Blinded Re-read took place at [] Personnel from EPIX were not permitted on site at [] during the Blinded Re-read sessions. Readers each performed independent evaluations and provided quantitative measurements, working in maximum 8 hour sessions with mandatory breaks. Each of the 3 Readers independently reviewed all MRA examinations for evaluation of the 7 vessel-segments, recording interpretations on an electronic case report form.

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The order in which examinations were presented to each reader was randomized which was accomplished by a random code according to a predetermined randomization scheme. A blocked randomization scheme of 4 groups was used with assignment of the non-contrast and contrast-enhanced exams for any one subject into different blocks. Each of 4 sub-sections used for presentation to the readers contained both non-enhanced and enhanced images from different groups of subjects.

Before the Blinded Re-read could be performed, randomization codes were checked against project tracking spreadsheets and codes assigned to files were checked against random code spreadsheets. A test of system stability was performed the day before each read session with a read system checklist completed by the [] clinical systems support staff prior to each Blinded Re-read.

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At the time of examination review, a [] Operator assisted the Reader in display of examinations, verification of code number, and confirmation of code number when the electronic case report form (eCRF) was launched. MRA data were presented on a [] which is a 510(K) approved device for the display and processing of medical examinations.

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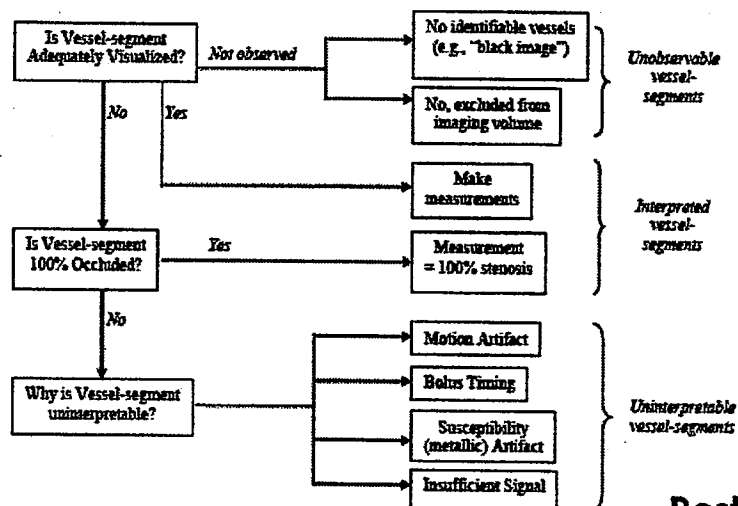
Readers interpreted examinations according to the block randomization pattern previously presented. Evaluations were performed using both dynamic and steady-state data sets. For each vessel-segment (7 segments per examination) the reader was asked, "Is the vessel-segment adequately visualized?" The reader could answer yes or no or select "no identifiable vessels" or "excluded from imaging volume." In the instance where one of the two latter choices was selected, no stenotic measurements occurred and the vessel-segment was deemed unobservable. When "yes" was selected, the Readers measured the diameter of greatest stenosis and an adjacent normal diameter within the vessel-segment. When "no" was selected, the Reader was asked whether the vessel-segment was 100% occluded and if so then calculated the percent stenosis as 100%. If the vessel-segment was not deemed to be 100% occluded, the reader selected the reason for uninterpretability from the following reasons: insufficient signal, bolus timing, susceptibility (metal) artifact, or motion artifact.

For each subject where the Readers were able to identify a stenosis ("yes" responses), the Readers identified the most severe stenosis within each of the 7 vessel-segments individually and recorded the measurements on the eCRF. Stenosis was determined by measurement of the diameter of the greatest stenosis and of the diameter for the "normal" region. Readers were asked to make their best clinical judgment as to the diameter of the "normal" region for vessel-segments with large areas of plaque and calcification and were instructed to find the nearest normal caliber proximal to the stenosis or, if not possible, to measure the nearest distal area. All vessel-segment measurements and locations were recorded with a screen capture and the Reader documented the reason for their assessment. The Reader was asked to use the opacified lumen as measurement of the lumen diameter since this is most comparable to the XRA measurement. Digital calipers were used with measurement on the eCRF recorded in millimeters. Percent stenosis was generated by the computer using calculation as follows:

Percent stenosis = $([\text{normal diameter} - \text{stenotic diameter}] / \text{normal diameter}) \times 100$.

The flowchart of blinded read assessments for each vessel-segment and the table of eCRF questions duplicated from the submission was presented to each reader as part of the Blinded Reader Training Guidelines.

Flowchart of Blinded Read Assessments for each Vessel-Segment



Best Possible Copy

Source: NDA 21-711, section R8, page 3973

Screenshots of the MRA examinations and measurement data were captured and archived for future use in the review and QC process.

All comments made by the Readers that were not entered into the eCRF were recorded by [] and documented in a report.

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Data entry onto the eCRF was locked and changes could not be made in the evaluation criteria. Each data entry screen shot was captured for archive used to QC the final database entries. These were archived to long-term storage to ensure an audit trail to the original entered data. On conclusion of each Blinded Re-read session, the Reader signed and dated at least one signature sheet. Electronic Case Report Forms were designed requiring each [] Operator and each Reader to log in prior to the start of a Blinded re-read session. Each question was required to be completed and the user could not move ahead to the next subject until each question and/or category was answered and the "Commit" button was selected.

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Table of eCRF Questions *Best Possible Copy*

Questions	Possible responses
1. Is the vessel-segment adequately visualized?	Yes No – no identifiable vessels (e.g., "black image") No – excluded from imaging volume No – other
2. Is the vessel-segment 100% occluded	Yes No
3. Please comment on the 100% occluded vessel-segment	<i>Comment on ancillary findings</i>
4. Normal vessel-segment diameter	<i>Measurement in millimeters</i>
5. Stenotic vessel-segment diameter	<i>Measurement in millimeters</i>
6. Percent Stenosis	<i>% stenosis is automatically calculated</i>
7. Reason vessel-segment is uninterpretable	Motion Artifact Susceptibility (metallic) Artifact Bolus Timing Insufficient Signal
8. Please comment on the uninterpretable vessel-segment	<i>Comment on image features</i>

Source: NDA 21-711, section R8, page 3973

6.1.3.5 Data Quality Assurance

All readers were blinded in relation to the details of the protocol, including subject identity, medical history, volume of contrast received, clinical signs/symptoms, final diagnosis, location of the clinical institution where the examinations were acquired, and XRA determination. None of the readers were affiliated with any investigational site at which the trials were conducted or from which subjects were recruited. There was no image selection or deletion by the clinical investigator, the sponsor, or the core laboratories for any of the types of images. A complete set of acquired images was directly presented to the respective core laboratories from each of the investigational sites.

Data quality assurance, including clinical site monitoring and data management, for studies MS-325-12 and MS-325-13 were described in the respective CSRs. Additional quality assurance in the Blinded Re-read included validation of the database (eCRF), QC of the Blinded Re-read data, and eCRF Reader sign-off.

A test and validation of the database was conducted and completed before initiation of the Blinded Re-read. Appropriate personnel were trained in the operation, logic, and terminology of the database. MRA examinations from 10 subjects were used for this process which included creating paper eCRFs and code numbers for the data that was used for the random responses. QC of the database exports was then accomplished by comparison of the paper eCRFs, the screenshots of the digital eCRFs, and the MS Access database containing the database export data. The entire validation process was documented in a Database Validation Report accompanied by the components of the validation process.

QC of the Blinded Re-read data was performed on 10% of examinations read, randomly chosen, by checking data export against the screenshots.

Quality assurance for the eCRF Reader sign-off was performed by the [redacted] Operator during breaks and at the end of the Blinded re-read session. This operator ensured that all sheets were reviewed and signed by the reader.

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6.1.3.6 Statistical Analysis Plan

Please see complete review by Dr. Anthony Mucci, Department of Biometrics.

As mentioned earlier, the primary endpoint was the sensitivity and specificity of Vasovist-enhanced MRA compared to non-contrast MRA in detecting clinically significant stenosis (defined as $\geq 50\%$) in each of 7 vessel segments (IRAA, left and right CIA, left and right EIA, and left and right CFA) using XRA as the SOR. The most severe diameter stenosis for each vessel segment was measured and recorded. The modified McNemar test (with a technical correction to the originally submitted and agreed upon protocol used and submitted as an amendment to the protocol) was the primary analysis method. The evaluable population was defined as those patients (424) who had non-contrast MRA, Vasovist-enhanced MRA, and XRA studies. The full dataset analysis required that the following two conditions be met simultaneously by 2 of the 3 readers. For the first condition, the following was required: 1) Vasovist sensitivity is superior to unenhanced sensitivity, and 2) Vasovist specificity is non-inferior to unenhanced specificity. It is noted that in this assessment, the presumed imputation for uninterpretables is Worst Outcome (non-agreement with XRA). For the second condition, (Condition 2 of the primary analysis), the sensitivity and specificity of uninterpretable vessel segments on non-contrast MRA which were interpretable on contrast-enhanced MRA was calculated. The hypothesis that sensitivity and specificity were greater than 50% was tested for these uninterpretable segments. The significance level was adjusted for the number of vessel segments used in this calculation. For 15

vessel segments or less, no formal testing was performed due to the small size of the sample, for vessel-segments greater than 15 but less than 30 a significance level of 1.0 was used, and for more than 30 vessel segments, a significance level of 0.05 was used.

The sponsor performed a Blinded Re-read and Statistical Analysis based on examinations obtained for subjects in Studies MS-325-12 and MS-325-13. Therefore, there was no estimation for sample size. The working hypothesis was that Vasovist enhances the diagnostic ability of MRA. The sensitivity of Vasovist greater than the sensitivity of non-contrast was tested by the null hypothesis that pre-contrast sensitivity equals Vasovist-enhanced sensitivity [Null hypothesis (H0) for sensitivity: sensitivity pre-contrast = sensitivity post Vasovist contrast; alternative hypothesis (HA) for sensitivity: pre-contrast sensitivity \neq sensitivity post Vasovist contrast]. For specificity, it was desirable to demonstrate that the specificity of Vasovist-enhanced exams was not clinically worse than non-contrast specificity. This difference between Vasovist-enhanced specificity and non-contrast specificity was estimated via 95% confidence intervals, and, if the lower confidence limit was greater than the specified limit of 5.0%, then the Vasovist specificity was considered to be not clinically worse than the non-contrast specificity.

For all vessel-segments that were deemed uninterpretable on non-contrast MRA examinations but classified as interpretable with Vasovist, the sensitivity and specificity of the Vasovist were calculated. The hypothesis that sensitivity and specificity were greater than 50% was tested. Because the number of observations was fixed but with an unknown number of uninterpretable examinations, the significance level for testing the hypothesis was adjusted for the number of vessel segments as follows: N (vessel-segments) ≤ 15 , no formal testing to be performed due to the small sample size; $15 < n$ (vessel-segments) ≤ 30 , significance level of 0.10 was used; and n (vessel-segments) > 30 , significance level of 0.05 was used.

The reasons presented for uninterpretable vessel-segments (motion artifact, susceptibility artifact, insufficient signal, and bolus timing in addition with contrast exams) were considered as not producing correct results and not agreeing with XRA for purposes of the primary analysis. An additional category of unobservable (non-visualized) vessel-segments possible with these segments was excluded from analysis of corresponding contrast and non-contrast MRA images. The SOR for the Blinded Re-read as determined by XRA was generated previously by XRA readers and reported in the clinical study reports for Studies MS-325-12 and MS-325-13. Results of the XRA were determined by 2 primary blinded readers with an adjudicator who re-interpreted all the vessel segments when there were discordant results between the two primary readers.

The determination of unobservable vessel-segments and the classification of and determination of uninterpretable vessel-segments was discussed with FDA during the pre-NDA submission meetings. The FDA agreed to accept these categories as long as they appeared clinically meaningful in view of the expected levels of performance of the diagnostic modality and as long as adequate training was provided to the Blinded Readers

in the use of these categories. The use of these categories in the statistical analysis plan was then also coordinated with the FDA. Use of the results of the previous XRA read as the SOR was also accepted by the FDA as these results had been acquired in a blinded read fashion and as XRA has long-served as the accepted "gold standard" for diagnostic evaluation of lower limb arteries.

Inter-reader variability was assessed using the kappa statistic. Intra-reader variability was also assessed using the kappa statistic with data summarized using descriptive statistics. Kappa statistic for inter-reader agreement was 0.3355. Intra-reader variability using the standard deviation of the mean ranged from 0% to 39% but was mostly less than 20%.

6.1.4 Efficacy Findings

6.1.4.1 Study Conduct

Please see prior FDA clinical reviews for major inclusion and exclusion criteria.

There were a total of 443 patients in the Intent to Treat (ITT) population, 268 in Study MS-325-12 and 175 in Study MS-325-13. All of these patients had non contrast MRA, Vasovist-enhanced, and XRA exams. A total of 424 patients were in the Evaluable population, 251 in Study MS-321-12 and 173 in Study MS-325-13. Information regarding the study subjects, including disposition, protocol deviations, compliance/exposure, and concomitant medications was reported in the respective CSRs.

In the conduct of the Blinded Re-read, the numbers of uninterpretable vessel-segments (exclusive of unobservable vessel-segments) was 3.3 to 9.1 times greater on non-contrast as compared to Vasovist-enhanced MRA and the number of patients with at least 1 uninterpretable vessel-segment was 3.5 to 5.6 times greater. In pre-NDA meetings held with the FDA, it was agreed upon that as this was a re-read of images from two prior clinical trials, any patients with unobservable (non-visualized) vessel-segments would be excluded from the efficacy analysis. A total of 424/473 patients receiving all 3 imaging exams were in the Evaluable population (i.e. did not have unobservable vessel-segments).

The following table summarizes the uninterpretable categories by blinded reader overall for segment numbers and numbers of patients.

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Summary of Uninterpretable Categories by Blinded Reader

Image Method	Uninterpretable Examinations ^a		Insufficient Signal n (%)	Bolus Timing n (%)	Motion Artifact n (%)	Susceptibility Artifact n (%)
	Patients ^b	Vessel-segments ^c				
Reader D						
Non-Contrast MRA	137	288	251 (87.2)	0 (0.0)	14 (4.9)	23 (8.0)
Vasovist-Enhanced	29	40	12 (30.0)	0 (0.0)	2 (5.0)	26 (65.0)
Reader E						
Non-Contrast MRA	112	290	122 (42.1)	0 (0.0)	140 (48.3)	28 (9.7)
Vasovist-Enhanced	20	32	8 (25.0)	0 (0.0)	2 (6.3)	22 (68.8)
Reader F						
Non-Contrast MRA	87	146	94 (64.4)	0 (0.0)	24 (16.4)	28 (19.2)
Vasovist-Enhanced	22	44	15 (34.1)	1 (2.3)	8 (18.2)	20 (45.5)

Note: The n is the number of uninterpretable vessel-segments, and the percentage is based on the denominator of total number of uninterpretable vessel-segments.

- a Patients with more than one uninterpretable vessel-segment are counted only once under patients, but all the patients uninterpretable vessel-segments are counted under number of vessel-segments.
- b Number of patients with at least 1 uninterpretable vessel-segment.
- c This column represents the number of uninterpretable vessel-segments.

Source: NDA 21-711, section R8, page 3908

6.1.4.2 Patient Demographics and Other Characteristics

Demographic and baseline data for patients included in the Blinded Re-read are presented in the table on the following page. Overall median age was 67 years with a range of 29 to 87 years. 179/424, (42.2%) were < 65 years of age. 82.8% were White. 68.4% were male. Demographic and baseline data were similar for Study MS-325-12 and MS-325-13.

Inclusion into Study MS-325-12 or MS-325-13 required that the patient have known or suspected aortoiliac occlusive disease and to have a referral for x-ray angiography of the aortoiliac region. The medical and surgical histories of patients were consistent with the population of intended use (i.e. patients with cardiovascular disease).

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Demographic and Baseline Characteristics for the Blinded Re-read

Table 10-1. Demographic and Baseline Characteristics for the Blinded Re-read

Variable Statistic	Full Data Set (N=424)	By Study	
		MS-325-12 (N=251)	MS-325-13 (N=173)
Age (yrs)			
n	424	251	173
Mean (SD)	65.5 (10.7)	65.7 (10.3)	65.2 (11.3)
Median	67	67	67
(Min,Max)	(29.0, 87.0)	(33.0, 87.0)	(29.0, 83.0)
Age Category [n (%)]			
<65 yrs	179 (42.2)	107 (42.6)	72 (41.6)
≥65 yrs	245 (57.8)	144 (57.4)	101 (58.4)
Race [n (%)]			
Caucasian	351 (82.8)	184 (73.3)	167 (96.5)
Black	33 (7.8)	30 (12.0)	3 (1.7)
Asian	0 (0.0)	0 (0.0)	0 (0.0)
Hispanic	38 (9.0)	36 (14.3)	2 (1.2)
Other	2 (0.5)	1 (0.4)	1 (0.6)
Sex [n (%)]			
Male	290 (68.4)	178 (70.9)	112 (64.7)
Female	134 (31.6)	73 (29.1)	61 (35.3)

Source: NDA 21-711, section R8, page 2045

6.1.4.3 Efficacy Analyses Based on the Primary Endpoint

Detection/Exclusion of Disease

The primary analysis was of vessel-weighted sensitivity and specificity for the 7 vessel segments identified within each patient and required that two agreed upon conditions be met. Condition (1) required that two of the three independent blinded readers had to simultaneously achieve superiority for sensitivity and non-inferiority for specificity of Vasovist MRA over Unenhanced MRA on the reads of the combined aortoiliac studies (MS-325-12 and MS-325-13) where:

(a): Superiority required that the lower limit of the 2-sided 95% CI for the Vasovist minus Unenhanced Sensitivity exceed zero.

(b): Non-Inferiority required that the lower limit of the 2-sided 95% CI for the Vasovist minus Unenhanced Specificity exceed -.05.

Condition (2) required that for each reader for whom Condition (1) was obtained, Vasovist Sensitivity and Specificity had to statistically exceed 50% (chance) on the images that reader had classified as Uninterpretable.

The Sponsor has achieved these paired criteria for the combined aortoiliac studies. The following two tables summarize the overall findings of the primary analysis as presented by the Sponsor for the blinded re-read.

As shown in the first table (see page 30), for all 3 blinded MRA readers, the Vasovist-enhanced vessel-weighted sensitivity is significantly increased when compared with the non-contrast vessel-weighted sensitivity differences (Vasovist-enhanced minus non-contrast ranging from 12.2% to 20.4%, $p < 0.001$ for all comparisons). For all readers, Vasovist-enhanced vessel-weighted specificity was non-inferior to non-enhanced vessel-weighted specificity differences (enhanced minus non-enhanced) with ranges of 0.2% to 7.9% and all 95% CIs overlapping or exceeding 0 in favor of Vasovist-enhanced specificity.

As shown in the second table (see page 30) which summarizes the analysis of sensitivity and specificity of Vasovist-enhanced MRA where the corresponding non-contrast MRA vessel segment was deemed uninterpretable, the sensitivity and specificity exceeded 50% on Vasovist-enhanced images for the subset of images classified as non-interpretable on non-contrast images.

Additionally, the second table (condition for uninterpretables) reveals that the numbers of vessel-segments for sensitivity were low (22 to 36 vessel segments across the 3 readers). The vessel-weighted sensitivity ranged from 72.0% to 92.7%. The lower bounds of either 90% or 95% CIs were used, depending on the number of vessel-segments with 90% used when the number of vessel-segments was ≤ 30 . Vessel-weighted CIs ranged from 54.4% to 92.7% for sensitivity. For all 3 readers, vessel-weighted specificity ranged from 71.5% to 84.4% with the lower bounds of the CIs ranging from 66.7% to 80.7%.

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Efficacy Table 1: Primary Analysis of Blinded Re-read Results of Vasovist Sensitivity and Specificity-Overall

Reader	Number Evaluated ^a		Vessel-weighted Ratio Estimates					
	Patients	Vessel-segments	Vasovist Enhanced MRA (%)	Non-Contrast MRA (%)	Difference (%) ^b	ICC ^c	p-value ^d	95% CI ^e
Reader D								
Sensitivity	212	353	89.0	68.6	20.4	0.4777	<0.001	(14.5 to 26.3)
Specificity	411	2185	71.6	71.2	0.4	0.4079		(-3.0 to 3.8)
Reader E								
Sensitivity	215	360	82.5	70.3	12.2	0.259	<0.001	(6.5 to 17.9)
Specificity	412	2232	80.7	72.8	7.9	0.4811		(4.4 to 11.4)
Reader F								
Sensitivity	217	363	79.3	64.5	14.9	0.3777	<0.001	(9.2 to 20.6)
Specificity	410	2272	85.3	85.1	0.2	0.4096		(-2.2 to 2.6)

a Sensitivity population is the number of patients or vessel-segments determined to be abnormal by X-ray and observable by that MRA reader. Specificity population is the number determined to be normal by X-ray and observable by that MRA reader.

b Difference= (Vasovist-enhanced MRA) minus (non-contrast MRA).

c ICC = Intra-class correlation, estimated using the formula presented in Eliasziw and Donner (1991).

d p-value is from the modified McNemar test.

e 95% CI for the difference in sensitivity and specificity are constructed using asymptotic normal theory.

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Source: NDA 21-711, section 8, page 3906

Efficacy Table 2: Analysis of the Sensitivity and Specificity of Vasovist-enhanced MRA Where Corresponding Non-Contrast MRA Vessel-Segment Was Deemed Uninterpretable

Reader	Variable	Number of Patients	Number of Vessel-segments	Vessel-weighted %	Vessel-weighted CI ^a (%)
Reader D	Sensitivity	32	36	97.2	92.7 to 101.7
	Specificity	118	239	71.5	66.7 to 76.3
Reader E	Sensitivity	21	22	90.9	78.9 to 102.9
	Specificity	97	257	84.4	80.7 to 88.2
Reader F	Sensitivity	23	25	72.0	54.4 to 89.6
	Specificity	65	109	81.7	75.6 to 87.7

a If the number of vessel-segments was ≤ 15, no confidence intervals would be derived. If the number of vessel-segments was > 15 but ≤ 30, 90% CIs were derived, and if >30 vessel-segments, 95% CIs were derived. CIs were constructed using asymptotic normal theory with no adjustment made to the variance for clustered binary data. Asymptotic normal theory relies on large sample size. Due to the limitations of the normal approximation, some estimates exceed 100% (Reader D Sensitivity and Reader E Sensitivity).

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Source: NDA 21-711, section R8, page 3907

6.1.4.4 Additional Analyses

The numbers of uninterpretable vessel-segments and the reasons for their uninterpretability were summarized previously by reader (see above). The number of

uninterpretable vessel-segments was 3.3 to 9.1 times greater on non-contrast MRA as compared to Vasovist-enhanced MRA. The number of patients with at least 1 uninterpretable vessel-segment was 4.0 to 5.6 times greater. For Readers D and F, the greatest portion of uninterpretable vessel-segments on non-contrast MRA were uninterpretable due to insufficient signal. For Reader E, the greatest proportion was due to motion artifact. For all 3 Readers, the greatest portion of uninterpretable vessel-segments on Vasovist-enhanced MRA were uninterpretable because of susceptibility artifact.

6.1.4.5 Inter-Reader and Intra-Reader Agreement

The generalized kappa statistic for inter-reader agreement analysis was 0.3355 (95% CI: 0.3125 to 0.3586).

Intra-reader variability was assessed in an ongoing basis during the Blinded Re-read. Examinations were presented to the readers at the onset of the read and then randomly at 100 examination intervals. Section 8, pages 3928-31 list the seven vessel-segments that were evaluated by reader and summarize the mean, standard deviation, and range percent stenosis assessed during the 10 quality control reads for each of 4 subject quality control subjects (2 unenhanced studies with 28 segments each and 2 contrast-enhanced studies with 28 segments each). The standard deviations of the mean ranged from 0% to 39% with most less than 20%. Of 84 standard deviations presented (7 vessel segments x 3 Readers x 4 subjects), 73 (86.9%) were less than 20%, 41 (48.8%) were less than 10%, and 20 (23.8%) were 0%. Based on these standard deviations, it appears that reader training was adequate.

6.1.4.6 Statistical/Analytical Issues

No adjustments for covariates were made in the efficacy analysis.

All available data were used. No missing data were imputed for the Blinded Re-read.

A tabulation of individual response data is listed in Appendix 16.2 of the NDA submission. The listing includes all individual listings for the non-contrast MRA read, the Vasovist-enhanced re-read, and the XRA original read. It includes a listing where either individual non-contrast or Vasovist-enhanced Blinded Re-reads were not contained in the same category for all 3 readers. There is also a listing of intra-reader case assessments.

There were no secondary efficacy endpoints or exploratory analyses.

6.1.5 Clinical Microbiology

Clinical microbiology review was not performed.

6.1.6 Efficacy Conclusions

The Sponsor has achieved the paired conditions for the primary efficacy analysis of Vasovist. In the analysis of the full dataset (condition 1), the protocol-defined criteria for success were met by all 3 readers. That is, Vasovist-enhanced sensitivity was superior to non-contrast sensitivity and Vasovist-enhanced specificity was non-inferior to non-contrast specificity. For uninterpretable vessel segments on Vasovist-enhanced images, the second condition of the primary efficacy analysis was met. That is, Vasovist-enhanced sensitivity and specificity was >50%.

7. INTEGRATED REVIEW OF SAFETY

The current document submitted for review is a revised Integrated Summary of Safety (ISS). This ISS Update 2008 extends the ISS submitted with the original NDA (ISS 2003) and includes 21 clinical studies with Studies MS-325-18, MS-325-19, MS-325-20, and 305608 added since the prior update. In addition to presenting integrated data from all 21 clinical studies, ISS Update 2008 compares the safety results with ISS 2003. MS-325-12/13R is not included in ISS Update 2008 since it represented an analysis of efficacy data only with no additional subject exposure to Vasovist. A safety summary and tables for XRA safety for studies MS-325-09 and MS-325-12 are also included.

Three subject deaths (none for the 0.03mmol/kg dose) occurred during the Vasovist clinical trials, 2 in Study MS-325-09 and one in Study MS-325-18, and were reported on by Dr. Tong Li in the first cycle review. See the prior review for complete discussion of the deaths. All three deaths occurred in MS-325 treated groups during the Phase 2 development period, with no deaths reported in the Phase 3 studies. According to the Sponsor, one of the patients reported on experienced fatal arteriosclerosis and the event may have been related to Vasovist. The other two deaths were considered unlikely related to Vasovist.

Overall, the 1,379 Vasovist-treated subjects (with 297 healthy volunteers who received Vasovist in addition to this number) experienced 1,337 AEs, including 799 considered by the investigator as treatment-related AEs. The NDA summarizes these into tables both by numbers and incidence. This represents an increase of 45 AEs, including 30 treatment-related AEs, compared to ISS 2003. The proportion of mild, moderate, and severe AEs is similar for both ISS 2003 and ISS 2008. The proportion of AEs for Vasovist-treated patients (592 patients, 42.9%) was similar to the proportion of AEs for placebo-treated patients (23 patients, 46.9% and the proportion of treatment-related events was similar (31.4% of Vasovist-treated patients and 32.7% of placebo-treated patients). Of all AEs, 1,074 (80.3%) were mild, 225 (16.8%) were moderate, and 38 (2.8%) were severe. Of the treatment-related AEs, 655 (83.2%) were mild, 128 (16.0%) were moderate and 16 (2%) were severe. Chest pain, myocardial infarction, and syncope (each 0.1% of SAEs for all doses combined) were the most common serious SAEs. The

rate of severe SAEs did not appear strongly related to dose, the rate of deaths did not appear to be related to dose, and the rate of discontinuations did not appear strongly related to dose however there was a dose-related increase in the overall percentage of patients experiencing AEs.

No patients receiving placebo and 3 patients (0.2%) receiving Vasovist withdrew from the study because of AEs. No patients receiving the 0.03 mmol/kg dose withdrew due to AEs. 41 patients (3%) discontinued a study early with the most common reason cited as non-compliance with the protocol

The most frequently reported adverse events (experienced by 1% or more of patients who received Vasovist) were pruritis not otherwise specified (NOS), paresthesia, headache NOS, nausea, vasodilatation, burning sensation NOS, dysguesia, dizziness (excluding vertigo), feeling cold, injection site bruising, venipuncture site bruise, hypertension NOS, rash NOS, and diarrhea NOS, all similar to the ISS 2003 report. Their occurrence appears to be dose-dependent and not related to any immunological response. The frequency of events is tabulated in section 7.1.5 of this document. In patients who received the proposed 0.03mmol/kg bw dose, hyperglycemia NOS was also included (1.2% of patients) however dizziness (excluding vertigo), rash NOS, diarrhea NOS, and feeling cold occurred in fewer than 1% of patients.

Please refer to following sections for tabulations and further discussion of safety findings.

An increase in the QTc interval (calculated using Bazett's correction) was seen at 45 minutes post-dosing at the 0.03 mmol/kg group and the >0.05 mmol/kg dose levels, but not at 0.05mmol/kg. The 0.03 mmol/kg reached statistical significance at 2.8 msec. This was similar for the placebo group N=38 with a mean at 3.2. There was also a slightly greater frequency in upward shifts of the QTc from normal to borderline or high at 45 minutes. A similar increase in the QT interval (Bazett's correction) was noted at 45 minutes post-dosing. A low proportion of patients (18) had QTc increases >60 msec at any of the three post-dosing time points. This group of patients had no cardiac AEs, specifically arrhythmias.

12-lead ECG results showed a statistically significant decrease in heart rate for all doses at 45 minutes with a statistically significant increase in heart rate at 24 and 72 hours post dose however the magnitude of the changes was not clinically significant. In addition, there were statistically significant increases in PR and QRS intervals at 45 minutes post dose, increased QT interval at 45 minutes also statistically significant, with statistically significant decrease in QT at 24 and 72 hours post dose. There were also changes in QTc which were statistically significant at 45 minutes but not at 24 and 72 hours.

Additional Holter monitor 12-lead ECG PK studies (no MRA assessment) also showed early post dose decreases in heart rate, QRS, and QT interval compatible with findings for placebo and not clinically meaningful. No QTc changes in these studies were noted

for up to 30 minutes. Overall, 12-lead ECG and Holter monitor findings were essentially unchanged from ISS 2003.

Overall, the reported adverse events in Vasovist clinical trials were mostly of mild to moderate intensity and were similar for both the ISS 2003 Update and the ISS 2008 update. The rate of severe AEs was low and was not dose dependent and there were no strong dose dependent effects on SAEs, death, or discontinuation because of AE. With an increase in dose, an increase in AE reporting rate was noted.

7.1 Methods and Findings

The original NDA included 18 studies. Since that time 3 additional trials (one Phase I trial and 2 Phase II trials) have been completed for a total of 1676 subjects who received Vasovist and 87 who received placebo. The assessment of Vasovist as an imaging agent to be used for detection of aortoiliac occlusive disease included an updated Integrated Summary of Safety (ISS 2008) and a comparison of ISS 2008 to ISS 2003. The ISS Update also includes information from foreign marketing experience and experience with other gadolinium-containing contrast agents. The overall conclusions of ISS 2008 are unchanged from ISS 2003.

In addition to no change overall, the percentages of placebo-treated healthy volunteers who experienced AEs and who experienced treatment related AEs were as high or higher than the respective percentages among healthy volunteers receiving Vasovist.

A summary of all trials included in the safety analysis of this NDA is listed in the following table on the next page with bolded entries reflecting studies and subjects new to the ISS Update 2008.

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Summary of Exposure to Vasovist or Placebo in MS-325 Clinical Trials

Table 3.8.8.2-1 Summary of Exposure to Vasovist or Placebo in MSA-325 Clinical Trials

Group Number	Group Description	Number of Subjects	Studies Included	Subjects Included (N)
1*	All patients who received Vasovist	1,379	MS-325-02 MS-325-04/04A MS-325-05 MS-325-06 MS-325-07 MS-325-09 MS-325-10 MS-325-11 MS-325-12 MS-325-13 MS-325-14 MS-325-15 MS-325-16 MS-325-18 MS-325-19 MS-325-20	All (81) All (106) All (46) Active-treatment arm (31) All (52) Active-treatment arm (200) All (2) One patient (1) All (274) All (178) All (145) All (185) 0.05 mmol/kg arm (20) All (7) Part 2 (35) Step C (16)
2*	All healthy volunteers who received Vasovist	297	MS-325-01A MS-325-01B MS-325-01C MS-325-08 MS-325-11 MS-325-16 MS-325-19 MS-325-20 305608	Active-treatment arm (18) All (17) Active-treatment arm (42) Active-treatment arm (25) 5 healthy subjects (5) 0.03 mmol/kg arm (10) Part 1 (80) Steps A&B (76) Active-treatment arms (24)
3	All patients with vascular disease who received Vasovist	1,254	MS-325-02 MS-325-04/04A MS-325-06 MS-325-09 MS-325-10 MS-325-11 MS-325-12 MS-325-13 MS-325-14 MS-325-15 MS-325-19 MS-325-20	All (81) All (106) Active-treatment arm (31) Active-treatment arm (200) All (2) 1 patient (1) All (274) All (178) All (145) All (185) Part 2 (35) Step C (16)
4	All placebo-treated subjects	49 patients, 38 healthy volunteers	MS-325-01A MS-325-01C MS-325-06 MS-325-09 305608	Placebo arm -healthy subjects (9) Placebo arm -healthy subjects (21) Placebo arm -patients (11) Placebo arm -patients disease (38) Placebo arm -healthy subjects (8)
5	All patients who received the proposed clinical dose of Vasovist (0.03 mmol/kg)	802	MS-325-02 MS-325-04/04A MS-325-09 MS-325-12 MS-325-13 MS-325-14 MS-325-15 MS-325-19	0.03 mmol/kg arm (33) 0.03 mmol/kg arm (2) 0.03 mmol/kg arm (39) All (274) All (178) All (145) 0.03 mmol/kg arm (96) Part 2 (35)

Bolded entries reflect studies and subjects new to the ISS Update 2008.

* Groups 1 and 2 comprise all 1,676 subjects who received Vasovist in all studies.

Source: NDA 21-711, section R3, page 145

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7.1.1 Deaths

Three subject deaths occurred during the Vasovist clinical trials, 2 in Study MS-325-09 and one in Study MS-325-18. Please see the previous first cycle clinical review by Dr. Tong Li for discussion of the three deaths and introduction to this section for further discussion. The conclusion of the Sponsor (ISS 2003 and ISS 2008) was that one of the patients in the first study experienced fatal arteriosclerosis and that the event may have been related to Vasovist. However, my conclusion and the conclusion of Dr. Melanie Blank, the second cycle reviewer, is that none of the deaths were clearly related to MS-325. The other two deaths were considered unlikely related to Vasovist.

7.1.2 Other Serious Adverse Events

For complete discussion of SAEs, please see first cycle review by Dr. Tong Li. Since ISS 2003, there have been no additional reports of SAEs that are probably related to the agent. All patients experiencing SAEs recovered. There have been two serious cases of anaphylactoid reaction and two cases of syncope with the latter cases occurring within 72 hours of administration of MS-235 and associated with non-sustained VT. In the previous second cycle clinical review, Dr. Melanie Blank recommended continuing cardiac monitoring during future clinical development as this could signal a relationship between MS-325 and cardiac arrhythmia. Since there have been no additional reported events of this nature, a causal relationship to the drug is unlikely. A QTc study has also been performed in the interim and did not suggest any cardiac signals in the Vasovist-treated group when compared to healthy volunteers.

No SAEs were reported in normal volunteers.

Narrative summaries of the deaths and SAEs are provided in the current NDA as Appendix 20.1 of ISS 2008.

7.1.3 Dropouts and Other Significant Adverse Events

Please see previous clinical review by Dr. Tong Li for complete details. Three patients discontinued a study because of AEs, one of whom died for whom there was no definite causal relationship to MS-325.

7.1.3.1 Overall Profile of Dropouts

Please see previous clinical review by Dr. Tong Li for complete details. There were no dropouts for the blinded re-read of Studies MS-325-12 and MS-325-13 as the full dataset was defined by all patients having undergone non-contrast MRA exam, Vasovist-enhanced MRA exam, and x-ray angiography, all of the aortoiliac region.

7.1.3.2 Adverse Events Associated With Dropouts

Please see section 7.1.3. above.

7.1.3.3 Other Significant Adverse Events

All SAEs are summarized by dose group, patient, and narrative in the above table presented in section 7.1.2. There was no evidence of dose dependency either in the frequency of SAEs in general or for any particular SAE. Three patients in Study MS-325-12 and one patient in Study MS-325-13 experienced SAEs. Apart from the four cases already discussed, the SAEs demonstrate no definite causal relationship to the study drug but appear related to the underlying medical conditions of the patients.

7.1.4 Other Search Strategies

No other search strategies were applied.

7.1.5 Common Adverse Events

The overall adverse event profile is unchanged from the original NDA. ISS 2003 coded AEs by Medra terminology 4.0. ISS 2008 coded by Medra terminology 8.0. Of 1,337 AEs reported, 80.3% were mild, 16.8% were moderate, and 2.8% were severe. The most common AEs experienced by 1% or more of patients who received Vasovist were pruritis (not otherwise specified) (NOS), paresthesia, headache NOS, nausea, vasodilatation, burning sensation NOS, dysguesia, dizziness (excluding vertigo), feeling cold, injection site bruising, venipuncture site bruising, hypertension NOS, rash NOS, and diarrhea NOS.

The incidence of the most common AEs for those considered by the study investigator to be related to the drug is discussed in section 7.1.5.1.

The additional table presented on the following page summarizes adverse events by number and percent for patients treated with the 0.03 mmol/kg dose.

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**Number and Percent of Patients Experiencing the Most Frequently Occurring AEs
with 0.03 mmol/kg dose of Vasovist (802 patients)**

Preferred Term	N (%)
Pruritis	42 (5.2)
Paresthesia	25 (3.1)
Headache	33 (4.1)
Nausea	33 (4.1)
Vasodilatation	26 (3.2)
Burning sensation	17 (2.1)
Dysgeusia	18 (2.2)
Dizziness (excluding vertigo)	8 (1.0)
Feeling cold	7 (0.9)
Injection site bruising	19 (2.4)
Venipuncture site bruise	17 (2.1)
Hypertension	11 (1.4)
Rash	3 (0.4)
Diarrhea	4 (0.5)

In summary, data presented demonstrate that the incidence of adverse events is dose dependent and was similar for all clinical trials where the 0.03 mmol/kg dose was used. Most of these AEs were mild to moderate in intensity.

7.1.5.1 Eliciting Adverse Events Data in The Development Program

Overall, 433 patients (31.4%) of the 1,379 patients who received Vasovist experienced treatment-related AEs (those considered by the investigator as possibly or probably related to the treatment) with a dose-related increase in the overall percentage of patients experiencing treatment-related AEs (14.7, 23.6, 41.8, and 67.6% patients reporting at least one treat-related AE in the <0.03, 0.03, 0.05, and >0.05mmol/kg groups, respectively). The most common events included all the most common events overall with the addition of nausea, vasodilatation, burning sensation NOS, and dysgeusia with treatment-related AEs generally similar to AEs overall. In general, the incidence of events appears to be dose-related. All of these were considered to be related to treatment except headache, considered to be related in 34 patients and not related for 45 patients. See the following table for treatment-related events.

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Number and Percent of Patients who Experienced the Most Common Treatment-Related Adverse Events (Events Reported by > 1% of All Patients) by Dose group and Preferred term for All Patients who received Vasovist

Preferred Term	Placebo (N = 49)	Dose Group (mmol/kg)				All Doses Combined (N = 1,379)
		< 0.03 (N = 95)	0.03 (N = 302)	0.05 (N = 371)	> 0.05 (N = 111)	
Any treatment-related AE	16 (32.7)	14 (14.7)	189 (23.6)	155 (41.8)	75 (67.6)	433 (31.4)
Pruritus NOS	1 (2.0)	1 (1.1)	38 (4.7)	42 (11.3)	20 (18.0)	101 (7.3)
Paresthesia	1 (2.0)	0 (0.0)	23 (2.9)	40 (10.8)	19 (17.1)	82 (5.9)
Headache NOS	2 (4.1)	1 (1.1)	17 (2.1)	13 (3.5)	3 (2.7)	34 (2.5)
Nausea	0 (0.0)	1 (1.1)	30 (3.7)	27 (7.3)	5 (4.5)	63 (4.6)
Vasodilatation	0 (0.0)	1 (1.1)	23 (2.9)	19 (5.1)	22 (19.8)	65 (4.7)
Burning sensation NOS ..	0 (0.0)	0 (0.0)	17 (2.1)	28 (7.5)	17 (15.3)	62 (4.5)
Dysgeusia	6 (12.2)	2 (2.1)	18 (2.2)	20 (5.4)	5 (4.5)	45 (3.3)
Feeling cold	0 (0.0)	2 (2.1)	6 (0.7)	10 (2.7)	0 (0.0)	18 (1.3)

N is the total number of patients in the dose group; % is based on N.

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Source: NDA 21-711, section R3, page 152

7.1.5.2 Appropriateness of Adverse Event Categorization and Preferred Terms

The MedDRA dictionary (version 8.0 for ISS 2008), was used for coding the collected verbatim terms. Examination of the events leading to dropouts (see above) shows that the sponsor's categorization of the events, as assessed in comparison to the preferred terms, appears acceptable.

7.1.5.3 Incidence of Common Adverse Events

The table on page 38 section 7.1.5 presents the overall incidence of AEs for all patients by terminology. The table on the following page summarizes the number of these adverse events by dose and severity to include placebo.

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Overall summary of the Number of Adverse Events by Dose for All Patients

Variable Category	Placebo (N=49)	Vasovist Dose Group (mmol/kg)				All Vasovist (N=1,379)
		< 0.03 (N=95)	0.03 (N=882)	0.05 (N=371)	> 0.05 (N=111)	
Number of AEs						
All AEs	44	40	528	574	195	1,337
Related AEs ^a	25	18	299	347	135	799
Number of AEs by Severity						
All AEs	44	40	528	574	195	1,337
Mild	34	32	423	451	168	1,074
Moderate	10	3	88	111	23	225
Severe	0	5	17	12	4	38
Not Specified	0	0	0	0	0	0
Related AEs ^a	25	18	299	347	135	799
Mild	23	18	248	275	114	655
Moderate	2	0	45	65	18	128
Severe	0	0	6	7	3	16
Not Specified	0	0	0	0	0	0
Number of SAEs	0	4	5	5	2	16

Note: N is the number of patients in each group; data represent the number of events experienced by those patients.
^a Related AEs were those considered by the investigator to be possibly or probably related to study drug.

Source: NDA 21-711, section R3, page 149

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As shown in these tables, 42.9% of all patients receiving Vasovist reported at least one AE with 36.0% who received the 0.03mmol/kg dose reporting AEs according to ISS 2008. This same table notes this later number to be unchanged from the 35.9% reported in ISS 2003, (1,379 patients overall, 800 receiving treatment with 0.03 mmol/kg dose).

The most frequently reported adverse event in all patients receiving Vasovist (1,379) was pruritis NOS with the group receiving the 0.03 mmol/kg dose reporting this also (4.7% of patients). Following pruritis, the next most frequently reported adverse events were paresthesia (5.9% all groups, and nausea, burning sensation, and vasodilatation all about 4.5% for all groups. For the group receiving the 0.03 mmol/kg dose, nausea was reported for 3.7% of patients with vasodilatation listed as the third most frequent AE (2.9%) As shown in the above tables, 31.4% overall and 23.6% for the 0.03 mmol/kg dose experienced AEs of any adverse events that were considered by the investigator to be related to or possibly related to Vasovist. In general, AEs were mild, of rapid onset, and of short duration.

7.1.5.4 Common Adverse Event Tables

Please see tables and discussion in above sections.

7.1.5.5 Identifying Common and Drug-related Adverse Events

The events of both reported AEs and treatment-related AEs were noted at a lower rate in the group dosed with 0.03 mmol/kg versus placebo (36.0% vs 46.9% for all reported AEs and 23.6% versus 32.7% for all treatment-related AEs for the 0.03 mmol/kg group and placebo group, respectively).

7.1.5.6 Additional Analyses and Explorations

Please see the first-cycle clinical review by Dr. Tong Li for comparative analysis between MS-325 and other gadolinium contrast agent for adverse events. In that review, there is also a table of the time of onset of AEs noting that this varied considerably with 14.6% of AEs occurring after 72 hours. Adverse event subgroup analyses did not reveal any clinically significant differences in the safety profile when adverse event rates were examined based on age, gender, race, baseline creatinine, baseline albumin, renal or hepatic impairment, or injection method. Concomitant medication usage was also not a factor in AEs with 95% of enrolled patients having cardiovascular disease and 33% with a history of diabetes, all receiving concomitant medications for their disease. Concomitant medications included common albumin binding drugs, blood pressure medications, warfarin, digitalis, glycosides, and salicylates among others.

7.1.6 Less Common Adverse Events

The adverse events of $\leq 1\%$ frequency have been presented with the overall adverse event analysis.

7.1.7 Laboratory Findings

Please see first cycle clinical review by Dr. Tong Li for complete discussion. No clinically significant treatment-related effects were noted. One patient with significantly increased liver enzymes died of multi-organ failure (not treatment-related).

7.1.8 Vital Signs

Please see previous clinical review by Dr. Tong Li for complete discussion. There was no evidence of a clinically significant systematic change from baseline in any post-dosing vital signs measure for all patients who received Vasovist. Hypertension changes noted as an AE in 1.3% of patients were not unexpected given that 60% of the baseline population had hypertension.

7.1.9 Electrocardiograms (ECGs)

Based on the review of data submitted by the Sponsor, there was no evidence of cardiotoxicity.

At the proposed 0.03mmol/kg dose (731 subjects studied), a statistically significant mean change from baseline QTc (2.8 msec) was observed at 45 minutes post dosing however this mean change was similar in magnitude to the QTc for placebo dosed patients at the same time point and similar in magnitude to the degree of change observed between two pre-dose QTc measurements. Twelve-lead Holter ECG results showed no clinically or statistically significant changes in QTc at 1 to 30 minutes post-dosing in a group of 103 patients that received the 0.05mmol/kg dosing however it was noted that patients dosed at the higher dose of $>0.05\text{mmol/kg}$ had QTc increases at 45 minutes post-dose. No arrhythmias were reported with these changes. No substantive differences were noted between subgroups. Clinically significant ECG abnormalities were noted in 36 patients

(2.7%) who received Vasovist and 2 patients (4.1%) who received placebo but with no dose relationship noted.

Although there was a statistically significant decrease in heart rate at 45 minutes post-dose and a statistically significant increase at 24 and 72 hours post-dose, none of the changes were clinically significant, (-1.2, 1.2, and 1.2 bpm respectively). At the highest doses tested, there was a slightly higher frequency of change however sample size was small and many subjects had underlying coronary artery disease. Statistically significant increases in PR interval and QRS interval were noted at 45 minutes post-dose, however were also not significant.

7.1.10 Immunogenicity

See previous review by Dr. Tong Li. No immunogenicity concerns were noted based on immunological assays performed for acute changes and no evidence for delayed hypersensitivity (greater than 96 hours post dose) up to a period of 21 days post-administration.

7.1.11 Human Carcinogenicity

Carcinogenicity studies were not performed in the development program of this single-dose imaging agent.

7.1.12 Special Safety Studies

In addition to the subgroup analyses mentioned earlier, patients with renal and hepatic impairment were studied. There was no evidence that these groups were at increased risk for experiencing AEs, clinical laboratory abnormalities, or ECG abnormalities following Vasovist administration however because gadolinium-based contrast agents increase the risk for NSF in patients with acute or chronic renal insufficiency and in patients with acute renal insufficiency of any severity due to hepato-renal syndrome in the perioperative liver transplantation period, gadolinium-based contrast agents should be avoided unless the diagnostic information is essential and not available with non-enhanced MRA.

In patients receiving a stable dose of warfarin, there was no effect of a single dose of Vasovist Injection (0.05 mmol/kg) on the anticoagulant activity of warfarin as measured by INR.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There is no pharmacologic basis for dependency, withdrawal, or rebound.

7.1.14 Human Reproduction and Pregnancy Data

Vasovist has not been administered to pregnant or lactating women, who were systematically excluded from clinical trials with Vasovist.

7.1.15 Assessment of Effect on Growth

Vasovist has not been administered to pediatric patients.

7.1.16 Overdose Experience

No overdoses have occurred, and the clinical consequences of overdosing with Vasovist are not known. Single administrations of up to 5 times the recommended dose have been used in clinical trials (MS-325-01C).

7.1.17 Postmarketing Experience

Vasovist has been approved for marketing in 33 countries outside the US. The initial ex-US approval was on October 3, 2005 in the European Union. Vasovist was first launched for marketing in the Netherlands on April 3, 2006. Total post-marketing exposure to date in Europe is [] in other countries, []

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7.2 Adequacy of Patient Exposure and Safety Assessments

The clinical development program for Vasovist consisted of 21 clinical trials which have been previously listed in section 4 of this document. There were 297 healthy volunteers, 1,254 patients with known or suspected vascular disease, and 125 other patients who received Vasovist and 87 subjects (38 healthy volunteers and 49 patients) who received placebo (saline). Of the 1,379 patients who received Vasovist injection, 903 (65.5%) were men and 476 (34.5%) were women. Mean age was 62.7 years with a range of 18-91 years. 1,100 (79.8%) were Caucasian, 107 (7.8%) Black, 159 (11.5%) Hispanic, and 0.9% of other races. There were 32 healthy Japanese volunteers who took part in a bridging study. The program included five Phase-1 studies, 12 Phase 2 studies, and 4 Phase 3 studies. This provided a safety database of 1,676 patients who received MS-325 and 87 subjects who received placebo which was evaluated for the incidence of death, serious adverse events, and discontinuations. 802 of the patients received the proposed clinical dose of 0.03 mmol/kg. Laboratory abnormalities, ECG and rhythm changes, and physical findings were assessed in the Phase-3 population.

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The demographic and other baseline characteristics in the overall safety database presented in ISS 2008 were similar to ISS 2003. Similarly, the review of the concomitant medications revealed a pattern consistent with what would be expected for the patients with the suspected or diagnosed peripheral vascular disease.

In summary, the overall safety database appears to be adequate for the safety assessment of a drug given as a single dose in a monitored environment.

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

There are no currently identified adverse events with risk-related issues.

Overall, the reported adverse events in Vasovist clinical trials were mild, acute in onset, and of short duration. Many were consistent with those expected in patients with cardiovascular disease.

7.4 General Methodology

The issues of general methodology are discussed in the Integrated Safety Review section above and involve the pooling of the safety data across the available studies. The analyses of the common predictive factors such as age, race, sex, and concomitant medications have not revealed additional factor-specific safety signals.

8. ADDITIONAL CLINICAL ISSUES

A request for a full waiver from the requirement to conduct pediatric studies with Vasovist (gadofosveset trisodium) has been made in accordance with the "Food and Drug Administration Amendments Act of 2007," Title IV-Pediatric Research Equity Act of 2007: Section 505B(a)(4). Granting the waiver appears to be reasonable.

The Sponsor has noted the proposed indication as follows and cites the indication in requesting a waiver: Vasovist Injection is a [] agent for use with magnetic resonance angiography (MRA) to evaluate aortoiliac occlusive disease (AIOD) in adults with known or suspected peripheral vascular disease (PVD). The Sponsor notes that Arteriosclerosis is included as an adult-related condition that may qualify for a waiver. In requesting this waiver, the Sponsor cited the following two reasons:

1. Necessary studies are impossible or highly impractical (because, for example, the number of pediatric patients is so small or geographically dispersed).

The first reason involves the extent of the patient population. The most common disorder associated with compromised blood flow to the limbs is atherosclerosis. PVD is a disease of middle and old-age with data from the 26-year longitudinal surveillance of the Framingham Heart Study cited in support of this with further note that May 2002 report

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of the National Heart, Lung, and Blood Institute (NHLBI) Task Force on Research in Pediatric Cardiovascular disease did not mention peripheral vascular disease. Arteriosclerosis in infants, children, or young adults could be encountered but only in rare hereditary disorders such as homozygous familial hypercholesterolemia. A review of data generated by [] Inc., shows that in 2007, there were [] magnetic resonance angiographic procedures of the extremities in pediatric patients less than 18 years of age. According to the Sponsor, given the extreme rarity of atherosclerosis in this population, it is likely that these procedures were carried out in pediatric patients with diseases such as vascular tumors for which the product would not be labeled. b(4)

In addition, the Sponsor requested full pediatric waiver based on number 2 below.

2. The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

"Meaningful therapeutic benefit" is defined under Section 505B(c)(1) of FDAAA, Title IV-Pediatric Research Equity Act (PREA) of 2007 as: "If approved, the drug or biological product could represent an improvement in the treatment, diagnosis, or prevention of a disease, compared with marketed products adequately labeled for that use in the relevant pediatric population."

The Sponsor notes that in addition to no additional marketed products, the NDA has been resubmitted with an indication restricted to "adults with known or suspected PVD" as was specifically directed by the re-read of the imaging data.

9. OVERALL ASSESSMENT

9.1 Conclusions

This reviewer finds the efficacy results from the Blinded Re-read met the two conditions pre-specified to achieve the primary efficacy endpoint. The re-read demonstrated that the sensitivity for disease using Vasovist-enhanced MRA is greater than non-contrast MRA and that the specificity for disease using Vasovist-enhanced MRA is non-inferior to non-contrast MRA. In addition, for vessel segments deemed uninterpretable on non-contrast MRA but interpretable with Vasovist, the sensitivity and specificity of Vasovist MRA was greater than 50%.

There were no major safety signals related to Vasovist clearly identified in the review of the application, however a safety concerns remains as related to possible NSF even though this has not been reported with this product to date.

Clinical Review
Barbara Stinson DO
NDA 21-711
Vasovist (Gadofosveset Trisodium)

9.2 Recommendation on Regulatory Action

At this time, the reviewer recommends approving NDA # 21711 for Vasovist as an imaging agent for use in Magnetic Resonance Angiography to evaluate the aorto-iliac occlusive disease.

9.3 Recommendation on Postmarketing Actions

Recommendations on a post-marketing action are to continue periodic safety update reports and annual reports with interval reporting for adverse events as required.

9.4 Labeling Review

Review of Labeling Due to the potential for NSF with administration of gadolinium products, a Black box Warning Label is mandatory.

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/s/

Barbara Stinson
12/11/2008 01:37:55 PM
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CLINICAL REVIEW

Application Type NDA
Submission Number 21-711

Letter Date May 23, 2005
PDUFA Goal Date November 23, 2005

Reviewer Name Melanie J. Blank, M.D.
Review Completion Date October 17, 2005

Established Name Gadofosveset Trisodium
(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 IV
Indication Contrast MRA Agent [

Intended Population Adults with suspected or known vascular disease

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This document is a second-cycle FDA clinical review of the product Vasovist™, generic name: Gadofosveset Trisodium, also known as MS-325, a gadolinium containing contrast agent that is intended for use in magnetic resonance arteriography (MRA). In this document, reference is made to the first cycle FDA review which was completed with the action letter decision of "Approvable" on January 12, 2005. The second review cycle was initiated on May 23, 2005 with the submission of the "complete response" by the Sponsor, EPIX Pharmaceuticals.

The reviewer recommends that the decision of approvable status should not be changed.

The basis of this recommendation is the following:

1. There were no new efficacy data in the Sponsor's complete response.
2. Our reassessment of the original NDA review revealed that the original clinical review team rendered an appropriate set of conclusions based on a fair analysis of the data.
3. Neither sensitivity nor specificity of MS-325 were shown to be superior to the comparator in two adequate and well controlled trials in the same vascular region.
4. The central review issue that made this NDA problematic was the Sponsor's use of an imputation method that assigned a "wrong" answer to uninterpretable scans. The reason that this was problematic was that there was a striking imbalance between the two study arms in the number of uninterpretable scans (1-3% for MS-325 and 10-34% for the comparator). Therefore, assigning so many "wrong" answers to the comparator arm resulted in a statistical advantage for the investigational arm. In the developmental stages of the Phase 3 studies the Agency was not informed that there would be this asymmetry between the two arms of the study. Therefore, it was not at all clear during the pre-NDA phase that the Sponsor's primary imputation method for uninterpretable scans would be problematic.
5. The ten-fold imbalance in rates of uninterpretable scans between the two study arms raised concerns about the standardization and validation of the

procedures that were in place for determining appropriate scanner settings, for verification of scan interpretability, and for training the blinded readers to be able to classify a scan as interpretable or uninterpretable with a reasonable degree of inter-reader agreement.

There was a safety issue raised in the first cycle regarding the *in vivo* stability of the agent; that issue has been resolved by new stability data. A few safety concerns remain, in particular transient abnormalities in clinical laboratory data, serious adverse events including immediate hypersensitivity reactions and cardiac arrhythmia that will likely require further evaluation. However, there are no serious issues in this area that should affect the Agency's pending action.

The reviewer agrees with the previous FDA recommendations to the Sponsor:

1. Perform a reread of the scans from the two aorto-iliac studies after sufficient training of new blinded readers with the primary intention of significantly reducing the number of uninterpretable scans. Part of the Division's reasoning behind this recommendation is that we observed that uninterpretable scans were not uniformly considered uninterpretable by all readers. In fact, most scans were thought to be uninterpretable by only one or two of the readers, rarely by all three. Additionally, the readers did just as well statistically on sensitivity and specificity in their readings of scans that other readers considered uninterpretable. This is evidence that reader training (focused on variation in image quality from different clinical sites, artifact identification, anatomic variation, and application of contextual diagnosis using clues from adjacent vessel segments) might reduce the number of uninterpretable scans.
2. For future studies, standardization and validation of scanning and reading of scans needs to be done which would include the evaluation of the adequacy of baseline images prior to contrast administration, a provision for repeating baseline images if found to be suboptimal, rigorous blinded reader training, and quality assurance protocols.
3. Separate evaluations of dynamic and steady-state images may be a useful strategy for the Sponsor as there is evidence that the dynamic images may perform much better than the steady-state images.

The reviewer recommends that the Sponsor redefine the potential clinical utility of MS-325 (and potential claims) based on the trial experience to date. The reviewer recommends that the sponsor consider the following.

1. Should the sponsor determine that that their product is unlikely to be superior to MRA both in sensitivity and specificity it might be reasonable to assess the utility of the product based on the improvement

Agency's concerns about lack of standardization of the methods used in the protocol. This analysis reflected the Sponsor's misunderstanding of what the Agency means by standardization of imaging procedures and did not provide useful information regarding the performance of MS-325 as compared to baseline MRA.

2. A reanalysis of the efficacy data wherein a variety of imputation methods were applied to uninterpretable images. Right, wrong or neutral values were assigned depending on the imputation method as opposed to "wrong" as had been done in the original submission. These post-hoc analyses did not address the central review problem of the imbalance between the comparator and investigational arms in percentages of uninterpretable scans and therefore, do not assist in evaluating the efficacy of MS-325.
3. A request for FDA to apply to MS-325 efficacy criteria used for FDA approvals of certain other imaging agents. The application of win criteria in post-hoc fashion is clearly inappropriate. In addition the agents referenced by the Sponsor are not considered by the reviewer to be relevant examples for the following reasons. The agents cited are either intended as add-ons (not as replacement for their comparator as is the case for MS-325), or are intended for use in the case of the baseline study being uninterpretable, or contain specific information for use based on the demonstrated sensitivity or specificity findings of the clinical trials.
4. A request for FDA to consider secondary efficacy endpoints such as increased rate of scan interpretability, and decreased scanning time as rationales for approval. The FDA might consider approving MS-325 on this limited basis if the studies had been designed to test these hypotheses.

The following is a recapitulation of the main findings of the FDA clinical review performed in the first review cycle.

The protocol-specified analyses for these studies imputed an incorrect diagnosis for baseline images that contain uninterpretable vessels. This is a problem for the reason that there were relatively high baseline uninterpretable rates compared to post-contrast scans (14% vs. 2% in the aorto-iliac studies, 34 % vs. 3% in the renal studies, and 10% vs. 1% in the pedal studies). This imbalance made it so that imputing a "wrong" diagnosis to the uninterpretable scans put the baseline images at a distinct statistical disadvantage.

When the uninterpretable scans were eliminated from the statistical analysis, MS-325 was not shown to be either more sensitive or more specific in two adequate and well

controlled trials than the baseline scans in any single vascular region. DMIHP requires that for any imaging trial, sensitivity and specificity be co-primary endpoints. The minimum win criteria are that at least 2 of 3 blinded readers demonstrate superiority in either sensitivity or specificity and noninferiority in sensitivity or specificity for the other endpoint.

The two aorto-iliac studies were the main focus of attention of the review as the aorto-iliac region is the only vascular region in which two adequate and well controlled trials were conducted. In one of these aorto-iliac studies (MS-325-12) MS-325 MRA was statistically more specific than the baseline MRA. In the other similarly designed aorto-iliac study (MS-325-13) MS-325 MRA was statistically more sensitive than the baseline MRA. These are two different endpoints and therefore, do not meet the regulatory requirements for approval (there must be two adequate and controlled clinical trials proving the same endpoint).

From a clinical perspective, it must be emphasized that a diagnostic modality might be used in one of two different ways depending on whether it is proven to be a more sensitive modality, i.e. it will have few false negatives at the expense of potentially having a relatively high degree of false positives or a more specific modality, i.e. it will have few false positives at the expense of potentially having a relatively high degree of false negatives. The former is likely to be used as a screening test, the latter more as a confirmatory test when the diagnosis is highly suspected. Therefore, in order to use a diagnostic modality effectively, the clinician needs to know if the modality is proven to be more specific and/or more sensitive than the comparator. In the case of MS-325, the two aorto-iliac studies provided conflicting results. Therefore, it is not clear from the outcome of these studies how MS-325 might be used.

Although this was not the hypothesis tested, these studies provide evidence that MS-325 might reduce the amount of uninterpretable baseline MRA images. However, the studies provide no *consistent* evidence in any vascular region that blinded readers will read an MS-325 scan with improved sensitivity or specificity over an interpretable baseline MRA.

There is evidence that separate evaluation of dynamic and steady-state images may be helpful for providing proof of efficacy for MS-325 as the onsite readers appeared to perform better in sensitivity and specificity when they read the MS-325 dynamic as compared to the steady-state images. Separate reads of dynamic and steady-state images were not done by the blinded readers so there is no assurance that the same pattern would hold.

The Safety of MS-325 seems acceptable. Clinical laboratory abnormalities were identified in the clinical trials at the time of the first review cycle and included hypoglycemia, hypocalcemia, zincuria, and drop in hemoglobin; transient changes in vital signs were also observed. DMIHP was concerned about the stability of the agent

in vivo as a potential mechanism for these changes. This concern was addressed by the sponsor in a stability study.

The Division's conclusion from the data from that study is that the *in vivo* stability of MS-325 is adequate and that the laboratory abnormalities observed are not attributable to the dissociation of gadolinium and do not suggest a more insidious underlying health concern such as heavy metal toxicity. The safety database also showed evidence of serious adverse events including immediate hypersensitivity reaction and cardiac arrhythmia. The safety update provided by the Sponsor in the complete response showed no new trends or concerns. In summary, the laboratory abnormalities (hemoglobin decline, hypocalcemia and mild and transient vital sign changes) and serious uncommon adverse reactions need to be balanced by convincing evidence of efficacy and will require continued assessment as clinical development proceeds.

1.3.1 Brief Overview of Clinical Program

There have been 18 clinical trials with MS-325. A total of 2087 subjects have been exposed to the agent and 767 patients have been exposed to the proposed clinical dose of 0.03 mmol/Kg. A total of 672 patients were studied in the four Phase 3 studies that were presented in the original NDA - two for pelvic region, one for renal region, and one for pedal (foot) region. The efficacy population consisted of 631 patients and 3408 vessels were studied.

These studies were designed to demonstrate that MS-325 enhanced MRA can improve the detection of a > 50% stenotic lesion in terms of sensitivity and specificity, by using X-ray angiogram as the gold standard. While the studies were powered to detect 10%-15% MS-325 associated performance improvement, no minimal performance level of MS-325 MRA was specified as a win criterion. Below is a table that summarizes the design of the four phase 3 clinical trials.

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Table 1.3.1: Phase 3 Studies in the NDA for MS-325

Trial Identifier Numbers of Patients and Vessels	Vascular Region	Design	Imaging Protocol	Endpoint	Original Statistical Analysis Plan
MS-325-12 268 Patients 1754 Vessels	Aorto- Iliac (see footnote)	Baseline MRA comparator against MS- 325 MRA using X-Ray contrast arteriography (intraoperative or DSA) as the gold standard Dose: 0.03 mmol/kg	No specifications for standards in MRA, MS-325 MRA, or X- ray arteriography were provided. There were on-site readers and 3 blinded readers. No rescanning criteria were provided for in the case of poor scan quality.	Vessel level stenosis $\geq 50\%$. The margin of superiority over baseline MRA, the level of performance compared to X-Ray angiography, and the number of blinded readers needed to show improvement were not pre-specified	Demonstrate improved vessel level sensitivity* and vessel level specificity** for MS-325 MRA over baseline MRA by rejection of the null hypothesis
MS-325-13 175 Patients 1206 Vessels	Aorto- Iliac				
MS-325-14 136 Patients 297 vessels	Renal				
MS-325-15 93 Patients with .03 mm/kg dose 336 vessels	Pedal				

Aorto-iliac vessels: Intra-renal abdominal aorta, Common iliac artery Intra-renal abdominal aorta, Common iliac artery (left and right), External iliac artery, (left and right), Common femoral artery (left and right), External iliac artery (left and right), Common femoral artery (left and right).

Renal vessels: proximal and distal renal arteries

Pedal vessels: posterior tibial, dorsalis pedis, medial plantar, and lateral plantar arteries

*Sensitivity: proportion of vessels identified as stenosed by XRA and correctly identified as stenosed by MRA

** Specificity: proportion of vessels identified as non-stenosed by XRA and correctly identified as non-stenosed by MRA

1.3.2 Efficacy

A. Please refer to the clinical FDA review of the original application for details of the assessment of the adequacy of the efficacy data.

The following table (Table 1.3.2 A) reflects the results that the Sponsors supplied to the Agency in the original submission and also includes two columns which display the rate of uninterpretable scans in the investigational and the comparator arms.


**Table 1.3.2A Sponsor's Analysis of Outcomes Based on Imputation of
"Incorrect" for Uninterpretable Scans**

Study	Sensitivity Improvement	Specificity Improvement	Baseline MRA Uninterpretable Rate	MS-325 MRA Uninterpretable Rate
MS-325-12 aorto-iliac	6 - 19 % for 2/3 readers (p<.001)	8 - 20% for 3/3 readers (p<.001)	13%	1%
MS-325-13 aorto-iliac	22 - 31% for 3/3 readers (p<.001)	9 - 12% for 3/3 readers (p<.001)	16%	2%



b(4)

Key:

	at least 2/3 readers win
---	--------------------------

This table (1.3.2A) shows the striking imbalance in rate of uninterpretable scans between the two study arms.

To assess the robustness of the efficacy data, DMIHP performed the following exploratory analyses. All the uninterpretable scans from both arms of the studies were eliminated from analysis so that the rate of uninterpretable scans in the comparator arm would not drive the results of the trial. Once the uninterpretable scans were eliminated from analysis, however, none of the studies were able to show superiority of MS-325 on the coprimary endpoints of sensitivity and specificity. As an additional post-hoc analysis, DMIHP redefined the studies' primary efficacy endpoint such that a win could be obtained by achieving superiority on just one endpoint (either sensitivity or specificity) in both the aorto-iliac studies with a trend for efficacy in the other vascular regions studied. For these analyses, the Division used the following definition for a win for sensitivity or specificity. It was that 2/3 of the blinded readers must win on the endpoint of sensitivity or specificity without losing on the other.

The Division's reason for specifying that a reader must not only be superior to baseline in sensitivity or specificity without being inferior in the other in order for the reader to be counted as a win for that particular study and endpoint was that a reader can too easily win on just one of the two endpoints if they are just a more sensitive or conversely, a more specific reader.

Please refer to table 1.3.2B below. It is important to note that Reader A in study MS-325-12 cannot count for a "win" on sensitivity because he demonstrated inferiority for MS-325 in specificity. The same thing holds for Reader A in study MS-325-13. (Reader A is in study MS-325-12 is not the same as reader A in study MS-325-13.)

b(4)

Table 1.3.2B shows that each of the aorto-iliac studies wins on a different endpoint. MS-325-12 won on specificity and MS-325-13 won on sensitivity. Therefore, DMIHP concludes that these analyses do not provide supportive evidence of the utility of MS-325.

Table (1.3.2B) Agency Analysis Based on Interpretable Scans by Reader

	READER A				READER B				READER C			
	PRE ^a	POST ^b	DIFF ^c	95% CI ^d	PRE	POST	DIFF	95% CI	PRE	POST	DIFF	95% CI
Study MS-325-12 (win for specificity)												
Sens.	.69	.82	.12	(.06, .19)	.68	.74	.05	(-.01, .11)	.51	.61	.10	(.05, .15)
Spec.	.88	.85	-.04	(-.07, -.01)	.88	.94	.05	(.03, .07)	.93	.96	.03	(.01, .05)
Study MS-325-13 (win for sensitivity)												
Sens.	.61	.85	.24	(.16, .32)	.66	.84	.18	(.10, .26)	.56	.71	.15	(.06, .24)
Spec.	.89	.81	-.08	(-.11, -.05)	.85	.84	-.02	(-.05, .01)	.94	.93	-.01	(-.03, .01)

Source Document: FDA's statistical review

^aPre-dose image (baseline); ^bPost-dose image (MS-325); ^cDifference between pre-dose and post-dose; ^d 95% Confidence Interval for the difference

Key:

	Superior
	Not Inferior
	Inferior

Exploratory Efficacy Analyses Provided by the Sponsor in the Present Review Cycle

The Sponsor was informed in the Action letter that the suboptimal performance of baseline MRA might have been due to inadequate standardization and validation of the imaging procedures (See Section 1.3). In addition there was no provision in the study protocol for repeating scans with adjusted settings if appropriate if a scan was identified to be uninterpretable. Because of the open-label design of the study, the quality of the images obtained might have been influenced by the experience or the opinion on the part of the on-site technicians, on-site readers as to the value of the baseline MRA. If this were true, it could have affected the quality or interpretation of the images in a non-random manner.

The Sponsor responded to this suggestion by carrying out two reanalyses of the data in which they eliminated from the analysis subjects whose scanner settings did not meet certain criteria. One analysis had a strict definition and excluded approximately 16% of the scans; the other had a looser definition and excluded 4% of the scans. Excluding those scans that did not conform to manufacturers' settings made no meaningful difference in uninterpretable rates or in the primary endpoints of sensitivity, and specificity.

Reviewer's Comments:

- 1. The Sponsor's conclusion from these analyses was that the Agency's suggestion that the large number of uninterpretable scans was due to the lack of standardization was false. The Sponsor did not understand that the Agency was making the point that the reason for the asymmetry between the two arms in the numbers of uninterpretable scans was likely due to the absence of standardization and validation of imaging protocols which is a concept separate and apart from following manufacturer's specifications.*
- 2. Standardization and validation of imaging protocols in clinical trials means much more than merely following manufacturer's specifications. It entails a comprehensive process which requires that the imaging protocol be designed in such a way that it ensures the production of interpretable images over the entire range of body habitus and medical conditions of the subjects enrolled in the particular clinical trials. Repetition of suboptimal scans needs to be part of this process of standardizing and validating the scanning procedures as well as extensive training of the on-site and blinded readers. The readers have to be able to recognize the different artifacts that are common for the different platforms, settings, vascular regions, and medical context. This process of standardization and validation is a process that should be done for each trial due to the complexities involved with the choice of specifications since ideally, they should be individualized for each particular platform, for each particular type of imaging study to be performed, and potentially, for each subject's body habitus and/or particular medical condition.*
- 3. The Sponsor's exploratory did not address the Agency's concerns regarding the quality of the images.*

It was communicated to the Sponsor in the Action letter that the data imputation method used by the Sponsor in the original submission was not appropriate as it assigned an incorrect result to all uninterpretable scans. This was problematic because of the imbalance between the study arm and the comparator in percentages of uninterpretable vessels. In the complete response, the Sponsor also reanalyzed their

data eliminating the uninterpretable scans from evaluation. With this more acceptable way of dealing with the problem of having such a marked imbalance in the uninterpretable data between the two arms, the Sponsor was also unable to show that the MS-325 MRA is consistently and significantly superior to baseline MRA in any particular vascular region in sensitivity and/or specificity.

The Sponsor also conducted a series of post-hoc analysis in which different imputation methods were used. The results of these analyses are displayed in Table 1.3.2C,D,E and F.

Table 1.3.2 C: Imputation Scheme 1 [uninterpretable is wrong (0)]

	READER A				READER B				READER C			
	PRE	POST	DIFF	p < .05	PRE	POST	DIFF	p < .05	PRE	POST	DIFF	p < .05
Study MS-325-12 (win for sensitivity and specificity)												
Sens. (n = 237)	.62	.80	.12		.67	.73	.06		.42	.61	.19	
Spec. (n = 1409)	.75	.84	.07		.85	.93	.08		.75	.95	.20	
Study MS-325-13 (win for sensitivity and specificity)												
Sens. (n = 146)	.52	.83	.31		.60	.84	.24		.49	.71	.22	
Spec. (n = 1018)	.71	.80	.09		.74	.83	.11		.78	.90	.12	

Key for tables C-F:

	Superior
	Not Inferior
	Inferior

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Table 1.3.2D: Imputation Scheme 2 [uninterpretable is 1/2 wrong (1/2)]

	READER A				READER B				READER C			
	PRE	POST	DIFF	p < .05	PRE	POST	DIFF	p < .05	PRE	POST	DIFF	p < .05
Study MS-325-12 (win for sensitivity and specificity)												
Sens. (n = 237)	.68	.81	.13		.68	.73	.05		.5	.61	.11	
Spec. (n = 1409)	.83	.85	.02		.87	.93	.06		.85	.96	.11	
Study MS-325-13 (win for sensitivity)												
Sens. (n = 146)	.59	.84	.25		.65	.85	.2		.57	.72	.15	
Spec. (n = 1018)	.81	.81	0		.81	.84	.03		.86	.91	.05	

b(4)

Table 1.3.2E: Imputation Scheme 3 [uninterpretable by 2/3 readers is wrong (0)] and [uninterpretable by 1/3 readers takes the average reading of the others]

	READER A				READER B				READER C			
	PRE	POST	DIFF	p < .05	PRE	POST	DIFF	p < .05	PRE	POST	DIFF	p < .05
Study MS-325-12 (win for sensitivity and specificity)												
Sens. (n = 237)	.66	.81	.15		.67	.73	.06		.52	.61	.09	
Spec. (n = 1409)	.79	.85	.06		.82	.90	.08		.83	.95	.12	
Study MS-325-13 (win for sensitivity and specificity)												
Sens. (n = 146)	.55	.83	.28		.6	.84	.24		.53	.72	.19	
Spec. (n = 1018)	.77	.81	.04		.76	.83	.06		.82	.91	.09	

b(4)

Table 1.3.2F: Imputation Scheme 4: [uninterpretable by 3/3 readers is wrong (0)] and [uninterpretable by 2/3 readers takes the reading of the other reader] and [uninterpretable by 1/3 readers takes the average of the other readers]

	READER A				READER B				READER C			
	PRE	POST	DIFF	p < .05	PRE	POST	DIFF	p < .05	PRE	POST	DIFF	p < .05
Study MS-325-12 (win for sensitivity and specificity)												
Sens. (n = 237)	.68	.81	.13		.67	.73	.06		.54	.61	.07	
Spec. (n = 1409)	.84	.85	.1		.85	.93	.08		.87	.96	.09	
Study MS-325-13 (win for sensitivity and specificity)												
Sens (n = 146)	.57	.84	.27		.61	.85	.24		.54	.73	.19	
Spec (n = 1018)	.80	.81	.01		.78	.84	.06		.84	.91	.07	

b(4)

The imputation methods used by the Sponsor suggest that a reduction in the number of uninterpretable scans is likely to result in a successful study outcome. Therefore, the Sponsor should be encouraged to conduct a blinded reread of the images.

Exploratory Analyses Performed by the Agency

DMIHP performed a number of analyses to explore the possibility that the uninterpretable images obtained by the baseline scans were attributable to causes intrinsic to the scans. The analyses showed that there was a low rate of concordance between the blinded readers in terms of which scans they would call uninterpretable.

For a detailed description of these analyses, please see the statistical review by Anthony Mucci Ph.D.

The table below provides the estimate of the likelihood that a baseline MRA scan would be read as uninterpretable given that at least one reader read it as uninterpretable.

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Table 1.3.2 G Conditional Probabilities for Uninterpretable MRA Scans

STUDY	Reader			Number of Readers		
	A	B	C	One	Two	Three
#12	.61	.16	.77	.60	.26	.14
#13	.75	.48	.63	.48	.18	.34

b(4)

Source: FDA Statistical Review

Table 1.3.2 G lists statistics conditioned on the sample of all those images for which at least one of the three readers classified the image as uninterpretable. A, B, C list the probabilities that respective readers A, B, C classified an image as uninterpretable, given that at least one of them did. The number of readers (one, two, or three) who classified the same image as uninterpretable are also shown.


This post-hoc analysis is consistent with the hypothesis that reader-specific factors (e.g. different levels of experience with artifacts associated with various imaging platforms and/or insufficient “training” for the purpose of the blinded read) might have contributed to the assessment of certain images as uninterpretable. This analysis supports the potential value of a reread of the images by a new set of trained blinded readers.

The table below shows the results of a post-hoc subgroup analysis to explore the factors that might have contributed to the uninterpretability of the MRA scans. It is reasonable to expect that the performance of the readers might decline for the subset of images that at least one of the readers considered uninterpretable. For this analysis the subgroup of interest is R defined as the set of images for which the reader classified the image as interpretable while at least one other reader classified the image as uninterpretable. The notations NR, SR, AR are respectively the number, and the sensitivity, specificity, and accuracy of the reads for this image subgroup. The diagnostic performance in this subgroup was compared to the performance in the larger subgroup of interpretable images.

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Table 1.3.2H: Sensitivity and Specificity Endpoints by reader for those scans that were considered to be uninterpretable by at least one of the other blinded readers

STUDY#12														
	Sensitivity					Specificity					Accuracy			
	NR	SR	N	S		NR	SPR	N	SP		NR	AR	N	A
RDR A	29	.62	211	.70		126	.90	1196	.88		155	.85	1407	.86
RDR B	48	.81	230	.69		283	.78	1353	.88		331	.78	1583	.85
RDR C	14	.64	196	.51		72	.88	1142	.93		86	.84	1338	.87
STUDY#13														
	Sensitivity					Specificity					Accuracy			
	NR	SR	N	S		NR	SPR	N	SP		NR	AR	N	A
RDR A	9	.78	126	.60		66	.80	811	.89		75	.80	937	.85
RDR B	16	.75	133	.66		144	.81	889	.85		160	.80	1022	.83
RDR C	6	.83	123	.58		107	.86	852	.93		113	.86	975	.90

 Numerically higher reading in subgroup

Source: FDA statistical review

NR = Sample size for the subsample R for which the reader classified the image as interpretable while at least one other reader classified the Image as uninterpretable.

N = Total sample size of uninterpretable sample for the reader

SR; SPR; AR = Sensitivity; Specificity; Accuracy over the subsample R

S; SP; A = Sensitivity; Specificity; Accuracy over the larger sample of interpretables

The table provides no evidence of deterioration of performance when a reader reads scans that other readers found uninterpretable. Highlighted are cells with numerically higher success rates for the subgroup of "uninterpretable" images compared to the subgroups of interpretable images.

Diagnostic Performance of Dynamic vs. Static Imaging

The first review cycle also raised the issue of the value of the static imaging obtained with MS-325 scans. MS-325 is an agent designed to achieve slower clearance than the marketed gadolinium agents by virtue of its albumin binding ability.

Static imaging is obtained by scanning during the "steady-state" phase of the contrast which occurs following the initial ("first-pass") dynamic scan and prior to physiologic clearance of the contrast from the vascular compartment. This "steady-state" is very short-lived for marketed gadolinium contrast agents, and does not allow static imaging.

A dynamic scan is the "first-pass" imaging of an area of the body prior to, during, and immediately following the initial ("first-pass") passage of a contrast agent into/through the arterial vascular bed, the arteriolar vascular bed, the capillary bed, the venule vascular bed, and the venous vascular bed. Dynamic imaging is very short in duration (usually less than 30 seconds).

The efficacy studies were not designed to demonstrate the value of steady-state images, bringing into question the added clinical value of an albumin-bound, long acting contrast agent. Analyses performed by DMIHP suggested that the agent might perform better in the dynamic imaging phase.

The table below (1.3.2I) shows that there was a disparity in performance between the onsite readers when they read the static as compared to the dynamic scans. Dynamic scans appeared to be read by the on-site readers with greater sensitivity and specificity than static scans.

Table 1.3.2I On-site reader differences in sensitivity and specificity when reading the dynamic vs. the steady state scans

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

Other Secondary Efficacy Outcomes

The Sponsor has requested consideration of patient and physician convenience (shorter scanning time and fewer uninterpretable images) as a rationale for approval of MS-325. These outcomes were not prespecified in the original protocols.

Reviewer's Comments:

- 1. Shorter Acquisition time for MS-325 MRA than for 2-D or 3-D TOF MRA might be an advantage, however it cannot be considered in the absence of convincing evidence of the efficacy of the diagnostic agent.*
- 2. Greater chance of acquiring an interpretable image is an advantage although this finding could be secondary to the lack of incentive to produce interpretable baseline images, nothing in the protocol to change settings and/or repeat baseline scans, and/or insufficient blinded reader training.*
- 3. Theoretically, MS-325 MRA might reduce the need to perform X-ray arteriography, an invasive, higher risk procedure. This is still a theoretical consideration.*
- 4. Finally the studies were not designed to assess the above endpoints.*

Additional Considerations

The Sponsor's complete response also questioned the efficacy standards applied to MS-325. The Sponsor believes that previous FDA approvals of certain imaging agents were based on a less stringent set of standards than that which they are being held. The reviewer does not agree with the Sponsor's contention. Below is a summary of the issues. Please refer to Appendix A for a detailed review.

Reviewer's Comments:

- 1. Most of the agents cited by the Sponsor were approved as diagnostic adjuncts to their comparators, not as replacements. Therefore, the standards for their approval did not have to necessarily show superiority over their comparators.*
- 2. Most of these agents have indications that limit their indicated use to a particular population, e.g. patients with suboptimal baseline imaging studies.*
- 3. These agents have specific instructions written in the Package Insert on how to interpret the information derived from them in relation to their proven sensitivity and/or specificity.*
- 4. Most of the information on these drugs submitted by the Sponsor was taken out of context and was thus misinterpreted and some information was wrong (e.g. Neurolite).*

1.3.3 Safety

B. The following is a summary of the safety signals that were observed in the original review, the Agency's requests for information and the Sponsor's responses.

Safety Signals Observed in the Original Review

1. 2.5% of patients and 0.7% of healthy volunteers exposed to MS-325 had a ≤ 2.0 gm drop in Hb.
2. Hypocalcemia
3. Increased Zinc in the Urine
4. Mean 10 msec prolongation of QTc interval
5. Decrease in systolic and diastolic blood pressures and increase heart rate
6. Decrease in pulse oximetry
7. Hypoglycemia

Please see the FDA review (Dr. Tong Li) for greater detail.

Agency Requests

1. The Agency requested stability data on the in vivo product to assure that the chelate does not exchange Gd in vivo for other ions such as Calcium and Zn.
2. The Agency requested a safety update in all ongoing studies.

Sponsor Responses

1. The Sponsor provided the stability data in January, 2005 in which MS-325 is compared for stability with other gadolinium based agents. It compared favorably and therefore, despite some safety signals that need to be observed further in future clinical development, the stability of the product is acceptable and there are no active serious safety concerns at this time.
2. The safety update summarized safety data on 156 subjects in 3 ongoing trials with MS-325. The types of adverse events experienced, their severity, and the relationship to drug do not indicate there are significant changes in the findings in comparison to what was reported in the NDA.

Table 1.3.3 Numbers of subjects administered MS-325 in ongoing trials through February 1, 2005, subjects with adverse events, and approximate adverse event rates

Protocol	Number of Subjects	Dose (mmol/kg)	Subjects with AE's (%)	Number of AE's
MS-325-19	53	0.03	11 (20.7)	18
MS-325-20	71	0.05	23 (32.3)	31
Study 305608	6	0.01	2 (33.3)	2
	6	0.03	2 (33.3)	4
	6	0.05	5 (83.3)	10
	6	0.10	5 (83.3)	13
	8	placebo	3 (37.5)	6
Total	156		51 (32.7)	84

1.3.4 Dosing Regimen and Administration

Please see previous Agency review.

1.3.5 Drug-Drug Interactions

Please see previous Agency review.

1.3.6 Special Populations

Please see previous Agency review.

In the complete response data was submitted on hemodialysis patients and it was concluded that clearance of MS-325 was much more efficient with high flux as opposed to low flux treatment and should be recommended in hemodialysis patients. See pharmacology review for more details.

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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 agents, MS-325 binds to albumin which lengthens its in vivo half life considerably.

2.2 Currently Available Treatment for Indications

Please see previous Agency review.

2.3 Availability of Proposed Active Ingredient in the United States

MS-325 had not been approved or marketed in any countries at the time of the original review. It was approved for use in MRA in the E.U. in October 2005.

2.4 Important Issues With Pharmacologically Related Products

Please see Previous Agency review

2.5 Presubmission Regulatory Activity

The following is a summary from the initial FDA medical review:

The timeline for the regulatory activities related to MS-325 is 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 28, 2001 - End of Phase 2 Meeting. The imputation method that the Sponsor used was known by the Agency at this time. However, since the sponsor did not

address the issue of the imbalance between the investigational and comparator arm, therefore the problems posed by the proposed imputation method were not recognized.

- March, 2003 - Pre-NDA Meeting for MS-325
- December 2003 - Submission of NDA 21711
- January 12, 2005 – Approvable Letter finalized.
- May 23, 2005—Complete Response from the Sponsor Received by the Agency
- November 23, 2005 – 6 month PDUFA date

2.6 Other Relevant Background Information

None

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Please see previous agency clinical review and CMC review.

3.2 Animal Pharmacology/Toxicology

Please see previous agency clinical review and pharmacology/toxicology review.

4 Data Sources, Review Strategy, and Data Integrity

4.1 Sources of Clinical Data

The sponsor requested 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 \bar{L}

¹ In addition, two Phase 2 dose ranging studies (MS-325-02 & MS-325-09) were 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.

b(4)

4.2 Tables of Clinical Studies

See Table 1.3.1 in section 1.3.1.

4.3 Review Strategy

This clinical reviewer assessed the original FDA review by the medical officer, team leader and office director and summarized their observations and conclusions. In this review cycle, the following was reviewed independently: the safety update, the reanalysis of the data provided by the Sponsor, the articles cited by the Sponsor, the Package Inserts of the products cited by the Sponsor.

4.4 Data Quality and Integrity

Please see previous Agency clinical review.

4.5 Compliance with Good Clinical Practices

No major issues were identified in Dr. Tong Li's clinical review.

4.6 Financial Disclosures

Please see previous Agency review.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

For a discussion of the albumin binding and clearance of MS-325 please see the FDA clinical pharmacology review by Dr. Christy John.

In the first review cycle, the issue of the stability of the investigational agent was raised due to excess Zn found in the urine of subjects and hypocalcemia in some subjects. Studies were done comparing MS-325 to Optimark and it was found that Optimark had a greater degree of zincuria than MS-325. This suggest that product instability is of no greater concern for this product than with other gadolinium products and was reassuring. Additionally, the pharmacology reviewers also concluded that there is no evidence to suggest that MS-325 presents a safety issue in renally impaired patients.

5.2 Pharmacodynamics

N/A

5.3 Exposure-Response Relationships

Please see previous clinical review.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The sponsor proposed the following statement: [

b(4)

]

Reviewer's Comments:

[

b(4)

]

6.1.1 Methods

Please see previous agency review.

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:

- Subjects with known or suspected peripheral vascular disease diagnosed by physical examination and/or medical history who are scheduled for a X-ray angiogram within 30 days prior or post-study enrollment.
- Subjects may not have undergone surgery or angioplasty of the target vessels within 30 days prior to study enrollment.
- Subject must not have had any major cardiovascular events (e.g., myocardial infarct or stroke) within 30 days prior to enrollment.
- Subjects must have a serum creatinine level within the normal range for the site laboratory on the day of 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.

Se

lection 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

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 table below shows that after excluding uninterpretable images from the analysis, the phase 3 studies failed to meet their endpoint of superior specificity and sensitivity of MS-325 MRA relative to MRA.

Table (1.2)
Statistics on Interpretables by Reader

	READER A				READER B				READER C			
	PRE	POST	DIFF	95% CI	PRE	POST	DIFF	95% CI	PRE	POST	DIFF	95% CI
Study MS-325-12 (win for specificity)												
Sens.	.69	.82	.12	(.05, .18)	.68	.74	.05	(-.01, .11)	.51	.61	.10	(.05, .15)
Spec.	.88	.85	-.04	(-.07, -.01)	.88	.94	.05	(.03, .07)	.93	.96	.03	(.01, .05)
Study MS-325-13 (win for sensitivity)												
Sens.	.61	.85	.24	(.16, .32)	.66	.84	.18	(.10, .26)	.56	.71	.15	(.06, .24)
Spec.	.89	.81	-.08	(-.11, -.05)	.85	.84	-.02	(-.05, .01)	.94	.93	-.01	(-.03, .01)

Source Document: FDA statistical review

	Superior
	Not Inferior
	Inferior

Key:

Please see previous clinical review for tables of efficacy analyses provided by the sponsor in which the uninterpretable MRAs were considered inaccurate for the purposes of analysis.

Please see Table 6.1.4.6 for Dr. Tong Li's table of results of sensitivity analysis by vessel studied. There was wide variation between different vessels in sensitivity analysis results.

Table 6.1.4.6 Sensitivity by type of selected vessels

Trials	Vessel	Patient Numbers	Vessel Numbers	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
MS-325-14	Accessory Renal Artery	40	8	
MS-325-14	Renal Artery	40	45	

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

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6.1.5 Clinical Microbiology

N/A

6.1.6 Efficacy Conclusions

The FDA clinical review of the original submission listed the following conclusions.

- There is no adequate evidence to demonstrate improved sensitivity and specificity of MS-325 MRA relative to MRA.
- MS-325 MRA did not 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 was no clear dose-response from the phase 2 data
- Lack of standardized baseline MRA imaging protocol to ensure the optimal performance of MRA at baseline.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Please see previous clinical review for assessment of safety from data received before the first review cycle.

7.1.1 Deaths

Please see previous clinical review for discussion of the three death cases.

Reviewer's Comment: As there were no post mortem exams done, it is difficult to determine if there was a causal relationship between MS-325 and the deaths. None of the deaths were clearly related to MS-325.

7.1.2 Other Serious Adverse Events

Please see previous clinical review.

Reviewer's Comments: The only cases of SAEs that are probably related to the agent were anaphylactoid reactions. Neither of the two serious anaphylactoid reactions was fatal. There were two cases of syncope, one within 24 hours and one within 72 hours of MS-325 administration. The latter was associated with non-sustained VT after hospitalization and raises the possibility of a relationship between MS-325 and cardiac arrhythmia. The cardiac signals are significant enough to continue cardiac monitoring during future clinical development.

7.1.3 Dropouts and Other Significant Adverse Events

Please see previous clinical review.

7.1.4 Other Search Strategies

Please see previous clinical review.

7.1.5 Common Adverse Events

Please see previous clinical review.

Medical Reviewer (Tong Li, MD) Comments: 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 were pruritus, paresthesia, headache, nausea and vasodilatation. The Sponsor's main conclusion included with which the Agency agrees:

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

7.1.5.6 Additional analyses and explorations

Please see previous clinical review for comparative analysis between MS-325 and other gadolinium based contrast agents in terms of adverse events. There is also a table that emphasizes that the time of onset of adverse events varied considerably. 14.6% of adverse events occurred after 72 hours. There is also a table in this section that shows that 76% of AEs were mild, 20% were moderate and 4% were severe.

7.1.6 Less Common Adverse Events

Please see previous clinical review.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Please see previous clinical review.

7.1.7.5 Special assessments

Medical Reviewer, Dr. Tong Li's Comments: Among all patients treated with MS-325, 5 (0.4%) had hypocalcemia reported as an AE, including 2 at the proposed clinical dose. One SAE (chest pain) was reported by a patient concomitantly experiencing hypocalcemia. There is also an apparent increase in zinc excreted in urine post dosing, and only 89% of MS-325 was recovered from urine and feces.

In the original review cycle the concerns of review staff centered around the possibility that MS-325 was unstable in vivo and the thinking was that if this were the case, hypocalcemia could be a clinical issue, as well as heavy metal toxicity. This issue was resolved (see section 5.1 and therefore, the AEs, while still concerning, do not reflect a more serious clinical issue.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Please see previous clinical review.

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

Please see previous clinical review.

Medical Reviewer, Tong Li's comments: The patient blood pressure and pulse were not monitored for the first 30 minutes post dosing. If patients had developed mild hypoxia post-dosing, this phenomenon could, conceivably, have been missed. The safety monitoring procedure was suboptimal.

7.1.8.3 Standard analyses and explorations of vital signs data

Please see previous clinical review.

There was a general trend of decreases in systolic and diastolic blood pressures and increases in heart rates within 72 hours post dosing among 764 subjects receiving the proposed clinical dose of MS-325.

Medical Reviewer, Tong Li's Comments: [

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7.1.9 Electrocardiograms (ECGs)

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

Please see previous clinical review.

7.1.10 Immunogenicity

Please see previous clinical review.

7.1.11 Human Carcinogenicity

Please see previous clinical review.

7.1.12 Special Safety Studies

Please see previous clinical review.

Reviewer's Comments: Dr. Tong Li was of the opinion that the safety of MS-325 is far from well characterized. There safety signals were transient and mild hypocalcemia, hypoglycemia, decrease in Hb, lowered blood pressure, increased pulse, and a mean QTc prolongation of 10 msec. Further data supplied by the Sponsor showed the QTc prolongation was comparable to what occurred in a Phase 1 study control group. The rare cardiac problems that arose in the Phase 3 trials were not at all clearly related to the drug but this cannot be ruled out and must be subject to further study and observation as the clinical development program proceeds.

After the NDA was submitted and prior to the action letter, stability information was provided by the Sponsor. Compared to a similar gadolinium compound, Optimark, the Sponsor showed that there was less Zn excretion with their product revealing that the stability of their product is probably superior.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Please see previous clinical review.

7.1.14 Human Reproduction and Pregnancy Data

Please see previous clinical review.

7.1.15 Assessment of Effect on Growth

Please see previous clinical review.

7.1.16 Overdose Experience

Please see previous clinical review.

7.1.17 Postmarketing Experience

N/A

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

Please see previous clinical review.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Please see previous clinical review.

7.2.3 Adequacy of Overall Clinical Experience

Please see previous clinical review.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Please see previous clinical review.

7.2.5 Adequacy of Routine Clinical Testing

Please see previous clinical review.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Please see previous clinical review.

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

Please see previous clinical review.

7.2.8 Assessment of Quality and Completeness of Data

Please see previous clinical review.

7.2.9 Additional Submissions, Including Safety Update

Please see previous clinical review for data in the first review cycle before the Action letter.

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

Please see previous clinical review.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Please see previous clinical review.

7.4.2 Explorations for Predictive Factors

Please see previous clinical review.

7.4.2.1 Explorations for dose dependency for adverse findings

Please see previous clinical review.

Explorations for time dependency for adverse findings

The table below shows the time course of adverse reactions.

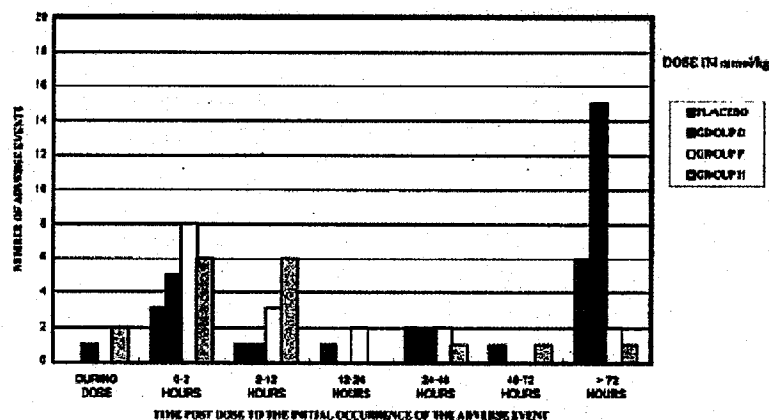


FIGURE C-59 NUMBER OF ADVERSE EVENTS OVER TIME BY DOSE
 (20 SECOND IV BOLUS DOSE)

Best Possible Copy

7.4.2.3 Explorations for drug-demographic interactions

No information was available.

7.4.2.4 Explorations for drug-disease interactions

There were theoretical concerns based on known reduced renal clearance in patients with renal insufficiency and the possibility of reduced biliary excretion in patients with hepatic insufficiency.

7.4.3 Causality Determination

Please see previous clinical review.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Please see previous clinical review.

8.2 Drug-Drug Interactions

Please see previous clinical review.

8.3 Special Populations

Please see previous clinical review.

8.4 Pediatrics

Please see previous clinical review.

8.5 Advisory Committee Meeting

The issues presented in this submission did not warrant discussion at an advisory committee meeting.

8.6 Literature Review

Package Inserts for all products listed in Appendix A
Thurnher et al, *Radiology*. 2001;219:137-146.
Kroencke et al, *AJR* 2002; 179:1573-1582.
Wikstrom et al, *Invest Rad*; Vol. 38, Num 8, August 2003:504-515.

8.7 Postmarketing Risk Management Plan

N/A

8.8 Other Relevant Materials

N/A

9 OVERALL ASSESSMENT

9.1 Conclusions

9.2 Recommendation on Regulatory Action

Recommendation for action remains as Approvable.

9.3 Recommendation on Postmarketing Actions

N/A

9.4 Labeling Review

Deferred.

9.5 Comments to Applicant

Reviewer's Comments:

1. New data and new studies will be necessary for any consideration for future change in regulatory status. MS-325 appears to have promise mostly as an adjunct to baseline MRA when suboptimal or uninterpretable scans are obtained.
2. Although it is possible that a reread of the scans after extensive reader training may reveal a small consistent increase in sensitivity or specificity for the agent in the aorto-iliac vascular bed, particularly if dynamic images are considered alone, it is this reviewer's opinion that MS-325 is probably of true clinical utility only when the baseline 2D-TOF image is uninterpretable.
3. It would benefit the sponsor to design clinical trials that would test the hypothesis that when a suboptimal baseline 2D-TOF MRA is obtained, there is a better chance of achieving an interpretable image with the agent compared to repeating the baseline study.

4. There are no current pressing safety concerns although safety monitoring should be continued to be performed in future trials, particularly the monitoring of vital sign, glucose, calcium, hemoglobin, oximetry and EKGs.
5. Future studies should be designed with extensive standardization and validation procedures with the intention of improving the rate of interpretable scans which will likely lead to an increase in inter-reader agreement and diagnostic sensitivity and specificity.

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10 APPENDICES

APPENDIX A

Table 10.0: FDA Decisions that the Sponsor feels were less Stringent

Drug Sponsor's Objection	Reviewer's Comments
<p>"Myoview is indicated as useful in delineation of myocardial ischemia despite studies suggesting it may have lower diagnostic value than its comparator, thallium-201."</p>	<p>Myoview was not meant to replace thallium-201. It was approved through a non-inferiority trial done during exercise with Myoview and was compared to exercise with Thallium. The two agents were shown to be comparable within the 95% confidence intervals for sensitivity, specificity, and both positive and negative predictive values in patients with >75% stenosis as seen on cardiac catheterization. It is true that there was another study that showed that in non-exercise stress tests, Myoview did not perform as well as Thallium.</p>
<p>"Verluma is indicated for detection of extensive stage disease in biopsy-confirmed, previously untreated small cell lung cancer patients, despite the fact that studies comparing Verluma to the standard battery of tests suggest it may have a slightly lower positive predictive value of extensive stage disease and a lower sensitivity for detecting extensive disease."</p>	<p>Verluma is indicated an adjunct to other diagnostic tests when the diagnosis of lung cancer is already confirmed and is not intended for assessment of response to therapy. It was approved with the following statement in the indications and usage category: "Where (Verluma) imaging is interpreted as limited stage disease....additional diagnostic tests should be performed to exclude extensive stage disease. Bone scan, CT examinations of head, chest, abdomen, CXR, and/or bone marrow aspirate/biopsy have been shown to demonstrate additional sites of involvement in some patients."</p>
<p>"CEA-Scan is indicated for use in conjunction with other diagnostics such as CT, even though studies suggested the combination of CEA-Scan with CT would improve sensitivity at the cost of decreased specificity relative to CT alone."</p>	<p>First, CEA-scan was not designed to replace its comparator. Secondly, In general, CEA-Scan® was more sensitive and less specific in the abdomen and pelvis than CT. However, it was shown that when the CT and CEA-scan results were discordant for the presence of a lesion and when both were negative in a region, the frequency with</p>

	<p>which tumor was found on biopsy was lower. Thus, negative CEA-scan results combined with negative CT scan results give increased confidence to a negative diagnosis.</p>
<p>“NeutroSpec was shown to improve specificity versus the comparator but appeared less sensitive than the comparator.”</p>	<p>Neutrospec is an adjunct for diagnosis in patients with suspected appendicitis. This agent was compared to a truth standard (final clinical diagnosis). Neutrospec carries a narrow indication, namely: scintigraphic imaging of patients with equivocal signs and symptoms of appendicitis.</p>
<p>“For Combidx, FDA was willing to allow an improvement in specificity without an improvement in sensitivity.”</p>	<p>While public information is available about an application to market this product, the product is not approved and FDA cannot provide further comment.</p>
<p>“Neurolite was approved despite having more false positives and false negatives than CT or MRI (suggesting possible decreases in specificity and sensitivity) because it picked up some strokes that CT or MRI alone missed.”</p>	<p>Neurolite has a very narrow indication: it is used with single photon emission computerized tomography (SPECT) as an adjunct to conventional CT or MRI in the localization of stroke in patients in whom stroke has already been diagnosed. It is not intended to replace its comparators. The Neurolite and CT/MRI imaging results versus the short standardized neurologic examination and final diagnosis (the gold standard) were comparable. Neurolite had 11 false positives and 24 false negatives whereas CT/MRI had 0 false positives and 31 false negatives. Both Neurolite and CT/MRI missed true positives (strokes) that were identified by the other modality. This was convincing enough evidence that there was clinical utility for this test as an adjunct to its comparators.</p>
<p>Definity “Not all readers in all studies saw statistically significant differences in all endpoints.”</p>	<p>This product is used solely as an adjunct in patients who have suboptimal baseline studies because the Sponsor understood that the agent’s only advantage is improved enhancement. In the PI, it is boldly written: “In these studies, although there was a statistically significant increase in ventricular chamber enhancement, activated DEFINITY® did not</p>

	<p>significantly improve the assessment of ejection fraction compared to the baseline images.”</p> <p>Activated DEFINITY® (Perflutren Lipid Microsphere) Injectable Suspension is indicated for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border. There is no claim of superiority or non-inferiority over an optimally performed echocardiogram.</p>
<p>AcuTect “Only one of the two clinical trials prospectively met the primary endpoint.”</p>	<p>AcuTect is only indicated for symptomatic patients and that only positive tests are helpful diagnostically. AcuTect is clearly an adjunct with a limited indication. It was not apparent from the label that only one of the studies produced statistically significant results so this reviewer does not know if the Sponsor’s claim is correct. The labeling also states, “How negative (AcuTect) images should be used in the diagnostic evaluation or therapeutic management of patients with suspected acute venous thrombosis has not been studied.”</p>
<p>Imagent “Clinical utility of the drug was assessed by performing a subset analysis of 26 patients which tended to show (without power for statistical significance) that improved imaging quality provided by the drug may allow for correct assessment of segmental wall motion as normal or abnormal.”</p>	<p>Similar to the case of Definity, it is important to note that the indication for Imagent is restricted to patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border. The data that led to approval was collected after a prospectively designed trial in which the criterion for eligibility was a suboptimal baseline echocardiogram. The subgroup analysis was in the P.I. but did not influence the indication.</p>

Clinical Review
Melanie Blank M.D.
NDA 21-711
Vasovist (Gadofosveset Trisodium)

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/s/

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11/16/2005 12:08:30 PM
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11/16/2005 05:31:51 PM
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11/21/2005 11:26:42 AM
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Division of Medical Imaging and Hematology Products

Secondary Team Leader Review

Date: November 7, 2005

NDA: 21-711

Product: Vasovist (gadofosveset trisodium, MS-325)

Drug Class: Gadolinium contrast agent for magnetic resonance imaging

Sponsor: Epix Medical

Proposed Use: Adjunct to Magnetic Resonance Arteriography (MRA)

RECOMMENDATION

The Team Leader concurs with the Clinical Reviewer's (Dr. Melanie Blank) assessment and recommends that the status of the New Drug Application for Vasovist remain as approvable.

SUMMARY

On May 23, 2005, the Sponsor submitted an NDA supplement as a complete response to the Agency's "approvable" letter of January 12, 2005.

Efficacy

The supplement did not contain new efficacy data nor did it contain the blinded re-read of the images that the Agency had recommended. Therefore this submission fails to address the key issue that neither sensitivity nor specificity of MS-325 were shown to be superior to the comparator in two adequate and well controlled trials in the same vascular region. The team leader concurs with the recapitulation of the original submission by the clinical reviewer.

The Sponsor provided instead the following.

1. A post-hoc analysis of the primary efficacy outcome in patient subgroups defined by whether or not specific setting on the imaging platforms had been used. This analysis was an attempt to assess the impact of lack of adherence to standard imaging methods on the efficacy.
2. A reanalysis of the primary efficacy outcome using a variety of imputation methods for uninterpretable images.
3. A request to consider secondary efficacy endpoints such as decreased scanning time and increased rate of scan interpretability as supportive of the clinical utility.

4. Cross-product comparison of primary efficacy outcomes for certain marketed imaging agents.

The team leader agrees with the reviewer's assessment that the sponsor's subgroup analyses of the efficacy data do not address the deficiency in the acquisition of the images (lack of validation of image quality at baseline before administration of contrast, provision for repeating scans found to be suboptimal).

The team leader also agrees that the additional sensitivity analyses of the primary efficacy outcome do not address the key issue. As noted in the clinical review of the original NDA, the analysis using the imputation of incorrect diagnosis for baseline images containing uninterpretable vessels is not supported by other sensitivity analyses. As Dr. Blank's review notes, the proportion of uninterpretable images is 10-fold higher in the MRA images compared to the MS-325 MRA images. In the subgroup of patients with interpretable baseline images the sensitivity and specificity of MS-325 MRA is not superior to that of MRA. This suggests that MS-325 might increase the likelihood of obtaining an interpretable scan and that MS-325 might be useful for patients who fail to image on standard MRA.

The team leader concurs that the contribution of secondary efficacy endpoints to the evidence of efficacy cannot be considered in the absence of demonstrated efficacy using the primary efficacy endpoint.

Finally with regard to the argument that the basis for approval for certain other imaging agents was different than the basis applied to MS-325, the Sponsor needs to define prospectively the potential clinical utility of MS-325 and demonstrate it in two adequate and well controlled trials. Levels of performance lower than those specified previously and manner of use or populations different from those studied to date might be acceptable.

Safety

The team leader concurs with the clinical reviewer's assessment of the product's safety profile. The following transient abnormalities in clinical laboratory data, serious adverse events including immediate hypersensitivity reactions and cardiac arrhythmia that will likely require further evaluation. However, there are no serious issues in this area that should affect the Agency's pending action.

The sponsor provided a safety update. As stated in the clinical review, no new safety findings were observed.

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/s/

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Division Director's Tertiary Review Memo

Application Type	NDA
Submission Number	21-711
Tertiary Review Completion Date	November 9, 2005
Letter Date	May 23, 2005
PDUFA Goal Date	November 23, 2005
Established Name	Gadofosveset Trisodium
(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, IV

Related Drugs:

- | | |
|---------------|-------------------|
| 1. Magnevist | (approved – 1989) |
| 2. Prohance | (approved – 1992) |
| 3. Omniscan | (approved – 1993) |
| 4. Optimark | (approved – 1999) |
| 5. Multihance | (approved – 2004) |

Review Team

Clinical

Melanie Blank, MD, Medical Officer
Louis Marzella, MD, Team Leader

Statistics

Anthony Mucci, PhD, Statistical Reviewer
Mike Welch, PhD, Team Leader

Pharmacology Toxicology

Siham Biade, PhD, Pharm/Tox Reviewer
Adebayo Laniyonu, PhD, Supervisory
Pharmacologist

Project Manager

James Moore, Pharm. D.

NDA 21-711, product Vasovist™, generic name: Gadofosveset Trisodium (MS-325)

Sponsor's Proposed indication

[]

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Intended Population

Adults with suspected or known vascular disease

Tertiary Review Recommendation for Second Cycle Review Regulatory Action

The first cycle decision of the "approvable" regulatory action should not be revised for the NDA 21-711 for the product Vasovist™, generic name: Gadofosveset Trisodium, also known as MS-325.

This Division Director's tertiary review memo incorporates written sections and comments from the excellent primary review of Dr. Blank and the excellent secondary review of Dr. Marzella, as well as sections from the Division Director's first cycle review memo.

Overall Assessment with Proposed Comments to the Sponsor

The Sponsor should consider performing a reread of the MS-325 enhanced MRA and the 2D-TOF MRA from the two aorto-iliac studies with new blinded independent readers. The reread should be performed with the intention of reducing the number of uninterpretable scans. As such, the reread should follow sufficient training of the readers in the interpretation of MS-325 enhanced MRA and the 2D-TOF MRA, as performed at the multiple clinical sites of the two aorto-iliac studies. As there is evidence that the interpretation of the dynamic images alone may demonstrate improve interpretation performance, the Sponsor should consider in the design of a reread, the separate interpretations of the dynamic and steady-state images for MS-325 enhanced MRA. If the Sponsor elects to perform a reread, the Sponsor should meet with the Agency prior to the performance of the reread to discuss the design and performance of the reread, as well as the utility of the reread results for their drug development program for MS-325 enhanced MRA.

To conduct new clinical trial(s) with MS-325 enhanced MRA, the sponsor must demonstrate the efficacy and safety, with the number of clinical trials to be consistent with the sponsor's drug development plan seeking []

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The following efficacy issues must be addressed and incorporated in the efficacy design, as well as the statistical analysis design of the sponsor's new clinical trial(s):

1. The baseline, unenhanced MRA comparator study must be prospectively designed, specifically described in the clinical trial protocol, and consistent with current standards of clinical imaging practice for unenhanced MRA. The protocol must require prospective assessment of the initial baseline, unenhanced MRA for adequacy of performance, and require repeat performance of inadequate/non-interpretable baseline, unenhanced MRA.
2. The sponsor must establish a clinical site monitoring and quality assurance program to maintain compliance with the performance of all protocol defined imaging studies.
3. Training of the independent reviewers must be documented and must incorporate training for the interpretation of the protocol defined baseline, unenhanced MRA as well as the MS-325 enhanced MRA.
4. If an imputation scheme is to be incorporated in the statistical analytical plan, the imputation scheme must be prospectively designed, and neutral in its imputation, such that the imputation scheme will not establish a bias in favor of the investigational imaging product, Vasovist.

Review of the safety database notes that there are serious adverse events which include immediate hypersensitivity reactions, cardiac arrhythmias and transient abnormalities in clinical laboratory data. The safety design of new clinical trials must be designed to include monitoring and assess for these reported serious adverse events.

The Sponsor's requested pediatric waiver is denied. Pending the approval of Vasovist in the adult population, Phase 4 commitments for pediatric efficacy and safety clinical trials with Vasovist must be established. However, at this time, further consideration of pediatric efficacy and safety studies should be deferred, given the unresolved efficacy and safety issues for the adult population.

The labeling issues, as recommended by the various review disciplines, are deferred as this time.

The final decision for the proposed Trade Name, Vasovist, is deferred at this time.

Review and Concurrence with the Primary and Secondary Reviews

The primary, second cycle, clinical review has been performed by Melanie Blank, MD. Dr. Blank has recommended an "approvable" regulatory action for the NDA 21-711 for the product Vasovist™, generic name: Gadofosveset Trisodium. I have reviewed and concur with the primary clinical review of Melanie Blank, MD.

The secondary, second cycle, clinical review has been performed by Louis Marzella, MD. Dr. Marzella has recommended an "approvable" regulatory action for the NDA 21-711 for the product Vasovist™, generic name: Gadofosveset Trisodium. I have reviewed and concur with the secondary clinical review of Louis Marzella, MD.

The primary, second cycle, statistical review for the NDA 21-711 for the product Vasovist™, generic name: Gadofosveset Trisodium has been performed by Anthony Mucci, PhD with secondary concurrence by Mike Welch, PhD. I have reviewed and concur with the primary statistical review of Anthony Mucci, PhD.

The primary, second cycle, pharmacology and toxicology review for the NDA 21-711 for the product Vasovist™, generic name: Gadofosveset Trisodium has been performed by Siham Biade, PhD. Dr. Biade has recommended approval of the NDA and suggested changes in the proposed label. I have reviewed and concur with the primary pharmacology and toxicology review of Dr. Biade.

The secondary second cycle pharmacology and toxicology review for the NDA 21-711 for the product Vasovist™, generic name: Gadofosveset Trisodium has been performed by Adebayo Laniyonu, PhD. Dr. Laniyonu has concurred with Dr. Biade and recommended approval of the NDA and suggested changes in the proposed label. I have reviewed and concur with the secondary pharmacology and toxicology review of Dr. Laniyonu.

Summary Basis of Second Cycle Review of the Complete Response

This is the second-cycle Agency review of the NDA 21-711 for the product Vasovist™, generic name: Gadofosveset Trisodium, also known as MS-325, a gadolinium containing contrast agent that is intended for use in magnetic resonance arteriography (MRA).

A total of 672 patients were studied in four Phase 3 studies presented in the original NDA - two for pelvic region, one for renal region, and one for pedal region. The efficacy population consisted of 631 patients and 3408 vessels were studied. These studies were designed to demonstrate that MS-325 MRA can improve the detection of a > 50% stenotic lesion in terms of sensitivity and specificity compared to MRA. X-ray angiography was the designated gold standard.

For detailed review discussion of the first review cycle, please see Division Director's tertiary review for the original, first cycle review and the primary and secondary reviews for the first review cycle. For detailed review elements, please see the clinical and statistical primary and secondary reviews for the second review cycle.

The first cycle review of the NDA 21-711 for the product Vasovist™, generic name: Gadofosveset Trisodium, was completed with the action letter decision of "Approvable" on January 12, 2005.

This second review cycle was initiated on May 23, 2005 with the submission of the "complete response" by the Sponsor, EPIX Pharmaceuticals.

The basis for the second cycle "Approvable" recommendation is based on following second cycle review findings and comments:

1. The Sponsor has submitted no new efficacy data or blinded rereads of the imaging dataset in the Sponsor's complete response.
2. Neither sensitivity nor specificity of MS-325 enhanced MRA has been shown to be superior to the comparator 2D-TOF MRA in two adequate and well controlled trials in the same vascular region.
3. The second cycle clinical and statistics review teams have completed a reassessment of the original, first cycle NDA review and have concurred that the original clinical review team rendered appropriate review conclusions based on an appropriate analysis of the data.
4. The second cycle clinical and statistical review teams have completed the review of the Sponsor's complete response to the first cycle review and have concurred to not change the first cycle "Approvable" regulatory action.
5. A review issue for this NDA is the Sponsor's use of an imputation method in the statistical analysis that assigns a "wrong" answer (opposite finding to the truth standard) to "uninterpretable" scans. This imputation method is problematic since there is a significant imbalance between the two study arms in the number of "uninterpretable" scans (1-3% for the investigational arm MS-325, and 10-34% for the comparator arm, MRA). As such, due to the higher rate of uninterpretable scans on the comparator arm, a remarkably higher number of "wrong" answers are assigned to the comparator arm as compared to the investigational arm. This imputation method has resulted in a significant statistical advantage/bias in favor of the investigational arm. Without the benefit of the imputation method, statistical significance was not demonstrated for sensitivity and specificity for MS-325 enhanced MRA as compared to 2D-TOF MRA. In the development of the Phase 3 studies, the Agency was not informed by the Sponsor that there would be a significant imbalance in the percentage of uninterpretable scans between the two arms of the study. Therefore, it was not apparent during the pre-NDA development that the Sponsor's primary imputation method for uninterpretable scans would be problematic.
6. The Sponsor incorporated into the Phase 3 clinical trials protocols specific imaging parameters in the investigational arm with MS-325 enhanced MRA. The sponsor did not establish specific imaging parameters within the protocol for the control arm

- The additional sensitivity analyses of the primary efficacy outcome do not address the key issue. As noted in the clinical review of the original NDA, the analysis using the imputation of incorrect diagnosis for baseline images containing uninterpretable vessels is not supported by other sensitivity analyses.
- The proportion of uninterpretable images is 10-fold higher in the MRA images compared to the MS-325 MRA images. In the subgroup of patients with interpretable baseline images the sensitivity and specificity of MS-325 MRA is not superior to that of MRA. This suggests that MS-325 might increase the likelihood of obtaining an interpretable scan and that MS-325 might be useful for patients who fail to image on standard MRA.
- The contribution of secondary efficacy endpoints to the evidence of efficacy cannot be considered in the absence of demonstrated efficacy of the diagnostic agent.
- Finally with regard to the argument that the basis for approval for certain other imaging agents was different than the basis applied to MS-325, the Sponsor needs to define prospectively the potential clinical utility of MS-325 and demonstrate it in two adequate and well controlled trials. Levels of performance of MS-325 lower than those specified previously and manner of use or populations different from those studied to date might be acceptable.

Agency's Exploratory Analyses

In the course of the second cycle review, post-hoc analyses were performed to explore the possibility that the uninterpretable images obtained by the baseline scans were attributable to causes intrinsic to the scans.

These post-hoc analyses showed that there was a low rate of concordance between the blinded readers in terms of which scans they would call uninterpretable.

A subgroup analysis sought to explore the factors that might have contributed to the uninterpretability of the MRA scans. The diagnostic performance of blinded readers on images that at least one of the readers considered uninterpretable was compared to the performance on images judged to be interpretable. It might be expected that the performance of the blinded readers might decline for the subset of images that at least one of the readers considered uninterpretable. However, as discussed in the clinical review, this analysis provided no evidence of deterioration of performance when a reader reads scans that other readers found uninterpretable.

These post-hoc analyses are consistent with the hypothesis that reader-specific factors (e.g. different levels of experience with artifacts associated with various imaging platform or insufficient "training" for the purpose of the blinded read) might have contributed to the

assessment of certain images as uninterpretable. These analyses support the potential value of a reread of the images by a new set of trained blinded readers.

Imaging Assessment Issues

MS-325 is an agent designed to achieve slower clearance than the marketed gadolinium agents by virtue of its albumin binding ability. The first review cycle raised the issue of the potential interpretation performance of the dynamic imaging, the static imaging, and the combined dynamic and static imaging obtained with MS-325 enhanced MRA.

The Phase 3 efficacy studies have been performed based on a combined dynamic and steady-state imaging interpretation. These trials are not designed to demonstrate the value of independent dynamic or independent steady-state images. The Sponsor should consider the interpretation of the MS-325 enhanced MRA with dynamic imaging only, steady-state imaging only as well as combined dynamic and steady-state imaging.

Safety

The sponsor provided a safety update in the complete response submission. No new safety findings were observed.

The most important findings of the safety database are serious adverse events including immediate hypersensitivity reactions and cardiac arrhythmia and transient abnormalities in clinical laboratory data. These findings will require collection of additional safety data in future clinical trials.

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George Mills
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MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 12, 2005
FROM: Julie Beitz, MD
SUBJECT: Deputy Office Director Memo
TO: NDA 21-711 Vasovist (gadofosveset trisodium injection); Epix Medical, Inc.

This memo documents my concurrence with the Division of Medical Imaging and Radiopharmaceutical Drug Product's recommendation for an approvable action for Vasovist, indicated for use with magnetic resonance angiography [

] The studies submitted under NDA 21-711 do not provide substantial evidence for safety and effectiveness to support approval for use of Vasovist 0.03 mmol/kg administered intravenously for magnetic resonance angiography (MRA).

Vasovist is a derivative of the first approved MRI contrast agent, Magnevist (gadopentate dimeglumine, NDA 19-596, Berlex). Vasovist is more lipophilic than Magnevist and binds reversibly to serum albumin. This slows renal elimination and enables imaging of the vasculature for up to an hour post-injection. Currently, angiography involves intra-arterial administration of iodinated contrast agents. Vasovist would have the advantage of (1) reduced anaphylactic reactions and nephrotoxicity due to use of iodinated agents, and (2) intravenous administration which is less invasive than intra-arterial administration. In addition, albumin binding slows the tumbling rate of the gadolinium chelate and increases its relaxation efficiency, so that the molar dose required is only a third of that of approved gadolinium agents.

Effectiveness: Lack of Standardization of Baseline Imaging Procedures

The original NDA, submitted December 15, 2003, contained two phase 3 studies evaluating aortoiliac vasculature (Study MS-325-12 and MS-325-13), and one study each of renal and pedal vasculature (Study MS-325-14 and MS-325-15). Sensitivity and specificity were defined with respect to the presence or absence of significant stenosis (>50%) at the vessel level. The sponsor's null hypothesis was that the sensitivity and specificity of the baseline image equaled that of the enhanced image. Thus, a win would occur if the null hypothesis was rejected. The sponsor did not specify the amount of improvement that was needed to win, but did consider a 10-15% improvement over baseline when determining the sample size for these studies.

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Julie Beitz, MD
Deputy Director,
Office of Drug Evaluation III
CDER, FDA

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/s/

Julie Beitz
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DIRECTOR