U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA	NDA 204-781
Serial Number:	Application No SD 1
Drug Name:	Gadoterate Meglumine (Dotarem) - MRI diagnostic contrast agent
Indication(s):	Dotarem is a gadolinium-based contrast agent indicated for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissues in adults and pediatric patients (from neonate to 17 years of age) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity.
Applicant:	Guerbet LLC
Date(s):	NDA Submission: September 20, 2012 PDUFA Date: March 20, 2013
Review Priority:	Priority
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Keywords: Confidence Interval, t-test, Regression Analysis, Missing Values

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1. EXECUTIVE SUMMARY

The proposed indication is "Dotarem is a gadolinium-based contrast agent indicated for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissues in adults and pediatric patients (from neonate to 17 years of age) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity."

The data and analyses provided by the sponsor and additional statistical analyses conducted by this statistical reviewer provide adequate evidence to support the effectiveness and safety claims that the sponsor has made regarding the detection and visualization of lesions in brain, spine and associated tissues in adults and pediatric patients (2 to 18 years of age). However, adequate information was not provided to assess the efficacy of pediatric patients less than 2 years of age.

There were two Phase-3 trials (DGD-44- 050 and DGD-44-051) undertaken for the development in the US. The sponsor provided safety and efficacy information for these two pivotal trials. The primary efficacy objective of the phase 3 trials to demonstrate superiority of the combined non-contrast and Dotarem MRI over non-contrast MRI using lesion characteristics (assessment of border delineation, degree of contrast enhancement, and internal morphology of the lesions) in CNS lesions with a disruption of the blood brain barrier (BBB) and/or with abnormal vascularity (including tumoral, vascular, inflammatory, or infectious diseases). The sponsor met this pre-specified primary efficacy objective. Additional analyses of efficacy demonstrated that the efficacy of Dotarem is consistent across demographic subgroups and geographic regions.

One of these Phase-3 studies (DGD-44-050) compared Dotarem with Magnevist and showed, in pre-specified secondary endpoints, no difference in efficacy for both agents. Likewise, improved image quality and diagnostic confidence were consistently shown for all 3 blinded readers.

Efficacy in the pediatric population was assessed for 38 subjects ages 2 years and older enrolled in the DGD-44- 050 study with analysis for lesion visualization, number of lesions, image quality, confidence in diagnosis, signal intensity and inter and intra reader agreement. The data supported efficacy in this group also. However, for the pediatric population under 2 years of age, sufficient information was not available to conclude efficacy. There were only seven subjects properly identified in this subgroup for efficacy.

The efficacy results obtained from the supportive studies are consistent with those from the pivotal studies.

This reviewer concludes that the protocol defined analyses and additional statistical analyses provide adequate evidence to support the proposed indication for Dotarem for improved contrast-enhanced imaging in 2 years and older patients requiring contrast-enhanced MRI of the CNS.

2. INTRODUCTION

Dotarem is a macrocyclic paramagnetic gadolinium (Gd) chelate that causes shortening of relaxation times (T1 and T2) yielding contrast enhancement in magnetic resonance imaging (MRI).

Dotarem was first approved in France in 1989. In addition to approval for intracranial and spinal MRI, Dotarem is approved for contrast-enhanced MRI of the whole body as well as for contrast-enhanced magnetic resonance angiography (MRA) in pediatrics from neonates to 18 years of age (from age 2 to 18 in UK and Spain) in various countries . . The standard dose throughout the world is 0.1 mmol/kg for CNS, body, and MRA imaging with approval in some countries for an additional 0.2 mmol/kg dose (total 0.3 mmol/kg) for CNS study to increase the diagnostic accuracy of the exam. At this time, in addition to the current application for CNS MRI indication, Guerbet is performing clinical trials in US under Special Protocol Assessment (SPA) for an indication in (b) (4)

2.1 Overview

The Sponsor (Guerbet LLC) submitted an IND 65,041 for Dotarem (gadoterate meglumine) to the FDA on June 12, 2002. In early 2003, Guerbet discussed CMC issues with the FDA via three teleconferences. This resulted in additional CMC changes leading to changes in industrial strategy and subsequently, changes in planned manufacturing sites for the US market.

On September 9, 2009, Guerbet presented the pivotal CNS study DGD-44-050 to the FDA to be conducted under a Special Protocol Assessment (SPA) and proposed a reread of the images from the failed DGD-03-44 CNS study as the second study. The FDA agreed that this was acceptable following the revision of the SPA. The protocol design, statistical analysis plan, and blinded evaluation charter were rewritten and submitted to the FDA on June 11, 2010, with the SPA concurrence on July 29, 2010. The nonclinical studies and data were updated on April 22, 2010 following an FDA request for information.

The pre-NDA meeting between Guerbet and the Agency was held on June 12, 2012. The FDA agreed that Guerbet's proposed strategy for the Integrated Summary of Efficacy (ISE) and the Integrated Summary of Safety (ISS) was appropriate.

Guerbet submitted this NDA September 20, 2012. The proposed indication is for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissues in adults and pediatric patients (from neonate to 17 years of age) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity. Currently, eight GBCAs have been approved by the FDA and six of these agents are marketed with a CNS imaging indication. However, no GBCA is approved for use in pediatric patients under two years of age. Therefore, this review was granted priority review. The Dotarem application is proposed for marketing at a dose of 0.1 mmol/kg, the same dosage recommended for the other CNS imaging agents.

2.1.1 Identified Studies in the review

The Dotarem efficacy data are derived from two phase 3 studies. The main confirmatory study is known as Study DGD-44-050 (also referred as 050). Phase 3 Study DGD-44-050 is entitled : "Safety and efficacy evaluation of Dotarem® in magnetic resonance imaging (MRI) in patients with central nervous system (CNS) lesions (SENTIO Study)". The data in this study are important to assessing Dotarem efficacy. The study 050 also provided supportive efficacy data for the pediatric indication (aged 2 years and older) and comparative information of Dotarem®-enhanced MRI with Magnevist®-enhanced MRI.

Phase 3 Study DGD-44-051 (also referred as 051) is entitled: "Evaluation of MRI with Dotarem® in the diagnosis or follow up assessment of cerebral or spinal tumors. Re-reading of MRI images" This study is also known as Study DGD-3-44 and is a re-read of a previously conducted study; that is, the images had previously been interpreted for other purposes. Because of study limitations, the findings of this study are considered supportive but not the definitive determiner of efficacy.

2.1.2 Analysis Populations

There were 4 analysis populations considered in this submission:

All Included Patients population (AIP) consists of all patients who met the inclusion/exclusion criteria and signed the informed consent. This population was used for demography, medical history, concomitant medication, and patient disposition summaries, unless otherwise noted.

The **Full Analysis Set (FAS or ITT)** consists of all patients having at least one lesion seen and scored on either "pre" or "paired" images, i.e., all patients with valid co-primary endpoint assessments. The statistical analyses were performed for this population. This population is the focus of this review.

The **Per-protocol population** (**PP**) efficacy population - a sub-group of the ITT population and includes all patients who have no significant protocol deviations or violations.

The **safety population** - all patients receiving at least one injection of contrast agent, regardless of the quantity.

2.2 Data Sources

This was an electronic submission. The sponsor provided adequate definition files and the data in xpt format. During the analyses by stat team, some additional data and clarification were requested which the sponsor promptly provided.

The NDA in eCTD and SAS export files of these data are located at:
\\CDSESUB1\EVSPROD\NDA204781\204781.enx

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

In support of this submission, the sponsor provided adequate information and data. Summary data were provided in SAS xpt format. During the course of statistical review, some additional data were also requested which the sponsor promptly provided.

3.2 Evaluation of Efficacy

3.2.1 Study Design

Study DGD-44-050 is a multicenter, international, randomized, double-blind, fixed sequence (unenhanced MRI followed by either Dotarem- or Magnevist-enhanced MRI), active comparator study. Patients served as their own control for Dotarem evaluations and Magnevist served as an internal validation. This study was conducted in 11 countries with patients coming from US and Europe (France, Germany, Italy, Spain, UK and Austria), Korea and Latin America (Argentina, Brazil and Chile). Dotarem was administered at a dose of 0.1 mmol/kg.

Adult patients (364) were randomly assigned to receive Dotarem or Magnevist in a 2 (245 in Dotarem) to 1 (119 in Magnevist) ratio. Age range for the adult population was 18 to 94 years. Majority of patients were Caucasian (84.5% for Dotarem and 79.8% for Magnevist). Pediatric patients (38), aged 2-18 years were assigned to the Dotarem group only. A total of 355 adult patients (238 in Dotarem and 117 in Magnevist) completed study.

An unenhanced MRI (within 28 days of screening) was followed immediately by the contrast-enhanced MRI. MR images of all patients were read by each of the three off-site independent readers blinded to clinical information. The primary endpoint was assessed only among the subjects who received Dotarem. Secondary endpoints were assessed for the pediatric patients and the patients who received Magnevist.

Table 1: Randomized Pivotal Study -050 (Sponsor's Table)

Randomized clinical studies in CNS imaging									
Phase of study Type of study regarding the Application	Study Identifier	Location of Study report	Main Objective of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of injected subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status Report Status
Phase III/IV Efficacy and Safety	DGD-44-050	Module 5.3.5.1.	Efficacy of Dotarem®-enhanced MRI as compared to unenhanced MRI in terms of lesion visualization (border delineation, visualization of internal morphology and degree of contrast enhancement)	Multicenter, international, double-blind, randomized, comparative trial with independent expert centralized blinded reading in CNS lesions with a disruption of the BBB and/or with abnormal vascularity (including tumoral, vascular, inflammatory or infectious diseases)	Dotarem® 0.1 mmol/kg, IV Magnevist® 0.1 mmol/kg, IV	Dotarem® = 278 Magnevist® = 117	Patients with CNS lesions	Single dose Single dose	Complete Full

Study DGD-44-051 (re-read) was a multicenter, open label, Phase 3 study conducted in Europe (France and Germany) and was blinded centralized re-read of the previously conducted Phase 3 study (Protocol DGD-3-44)in 150 patients presenting or suspected of cerebral or spinal tumors, referred to contrast-enhanced MRI of the CNS. Age ranged from 18 to 79 years, and 97.4% of patients were Caucasians. Randomized images were read by three off-site independent readers blinded to clinical information. A total of 150 adult patients completed study.

Table 2: Non-randomized Pivotal Study -051 (Sponsor's Table)

Non-randomized clinical studies in CNS imaging

Phase of study Type of study regarding the Application	Study Identifier	Location of Study report	Main Objective of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of injected Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status Report Status
Phase IIIb Efficacy and Safety	DGD-03-044	Module 5.3.5.1.	Efficacy of Dotarem® enhanced-MRI compared to a non-enhanced MRI in the characterization of cerebral and spinal tumors	Multicenter, open-label, using the subject as his/her own control and histology as "standard of truth" for comparison	Dotarem® 0.1 mmol/kg, IV	150	Patients presenting or suspected of having cerebral or spinal tumor(s)	Single dose	Complete Full
Phase IIIb Efficacy and Safety	DGD-44-051 (re-read of the DGD-03-044 study)	Module 5.3.5.1.	Efficacy of Dotarem® enhanced-MRI compared to a non-enhanced MRI in the characterization of cerebral and spinal tumors using histology	Multicenter, open-label, using the subject as his/her own control and histology as "standard of truth" for comparison	Dotarem® 0.1 mmol/kg, IV	150	Patients presenting or suspected of having cerebral or spinal tumor(s)	Single dose	Complete Full

Basic features of two Phase 3 pivotal trials are given below.

Table 3: Features (Phase 3 Pivotal Trials 050, 051)

	Trial 050	Trial 051
Inclusion	Adults, known or suspected CNS lesions; peds ≥2 to < 18 years	Adults, known brain tumors, 3 lesions max to undergo surgery or biopsy
Exclusion	Grade 4/5 renal insufficiency or long QT syndrome	1 site for renal failure; no cardiac exclusions
Sites	Global	8/9 sites in France
Design	Randomized, comparator Dotarem/Magnevist comparisons	Dotarem only
Drug Admin.	Dotarem 2mL/sec	Dotarem 1-2 mL/sec
Safety	Laboratory, vital signs, AEs f/u 24 hrs.	Vital signs and AEs f/u 24 hrs.

3.2.2 Demographic and Baseline Characteristics

Demographic data for the 2 pivotal studies, DGD-44-050 and DGD-44-051, are presented in Tables 4 below. Study DGD-44-050 enrolled a somewhat greater number of female than male patients. The age range for the entire adult population was 18 to 94 years. The majority of patients were Caucasian (84.5% for Dotarem and 79.8% for Magnevist). In study DGD-44-051 (the blinded image re-reading of DGD-3-44 MRI scans), there were numerically more male than female patients and a slightly narrower range for age, 18 to 79 years. The majority of patients were Caucasian (97.4%)

Table 4: Patient Demographics and Baseline Characteristics: Randomized Trial DGD-44-050 (Adults) & DGD-44-051 (Adults), Full Analysis Set

Study	**DGD-44-050**			**DGD-44-051**
Characteristic	**Dotarem**	**Magnevist**	**Pediatric**	**Dotarem**
Gender, N (%)				
Male	114 (46.5%)	54 (45.4%)	54 (45.4%)	84 (55.6%)
Female	131 (53.4%)	64 (54.6%)		67 (44.4%)
Age (Yr)				
N	245	119		151
Mean (SD)	53.2 (14.4)	56.0 (14.4)		53.9 (13.5)
Median	55.1	57.4		55.0
Min., Max	18.89, 85.1	19.0, 94.4		18.0, 79.0
Ethnic Origin, N (%)				
Caucasian	207 (84.5	95 (79.8 %)		147 (97.4 %)
Asian	%)	15 (12.6 %)		
Black	27 (11.0 %)	8 (6.7 %)		1 (0.7%)
Other	9 (3.7 %)	1 (0.8 %)		3 (2.0 %)
	2 (0.8 %)			
Height (cm)				
N	242	119		136
Mean (SD)	168.3 (9.9)	167.3 (10.0)		169.8 (9.1)
Median	168.0	168.0		170.0
Min., Max	138.0, 194.0	146.0, 196.0		141.0, 197.0
Weight (kg)				
N	244	118		151
Mean (SD)	76.0 (17.0)	76.7 (16.4)		73.2 (13.8)
Median	74.0	75.0		72.0
Min., Max	43.0, 139.0	44.0, 135.4		41.0, 120.0
BMI (kg/m^2)				
N	241	118		136
Mean (SD)	26.8 (5.3)	27.3 (4.9)		25.6 (4.0)
Median	26.1	26.8		25.1
Min., Max	16.7, 57.3	16.6, 47.3		16.9, 30.2

Abbreviations: BMI = body mass index; cm = centimeter; kg = kilogram; m^2 = meter squared; Max = maximum value; Min = minimum value; N = number of patients; SD = standard deviation; yr = year

3.2.3 Patient Disposition

In study DGD-44-050, 377 adult patients were screened, 364 were enrolled, and 357 patients were administered contrast agent (Dotarem 240, Magnevist 117). The Full Analysis Set (FAS) for off-site MRI readings was 345, 347, and 354 patients for Readers 1, 2, and 3, respectively. A total of 355 (97.5%) adult patients completed the trial. The most common reasons for discontinuation were adverse events (2 patients) and technical incidents (3 patients).

Table 5: Patient Disposition: Randomized Trial DGD-44-050

Category	Dotarem	Magnevist
All Included Patients, N	245	119
Safety (Treated) Population, N	240	117
Full Analysis Set, N	R1 = 345; R2 = 347; R3 = 354	
Completed the Study, N (%)	238 (97.1%)	117 (98.3%)
Number of Patients Prematurely Discontinued, N (%)		
Withdrew Consent	1 (0.4%)	0 (0.0%)
Adverse Event	2 (0.8%)	0 (0.0%)
Patient Lost to Follow-up	1 (0.4%)	0 (0.0%)
Technical Incident	2 (0.8%)	1 (0.8%)
Other*	1 (0.4%)	1 (0.8%)

Abbreviations: N = number of patients; R1 = Reader 1 (Vossoug); R2 = Reader 2 (Tsiouri); R3 = Reader 3 (Maldjia)
*Other reasons reported as psychological disorder (Dotarem), failed inclusion criteria (metal coil in brain), no drug

In DGD-44-051, 151 adult patients were in the trial, of which 2 withdrew consent to participate, leaving 149 in the FAS. A total of 149 (98.7%) completed the study.

3.2.4 Objective

The primary objective was to demonstrate the superiority of Dotarem-enhanced MRI as compared to unenhanced MRI in terms of lesion visualization (border delineation, internal morphology and degree of contrast enhancement) in CNS lesions with a disruption of the BBB and/or with abnormal vascularity (including tumoral, vascular, inflammatory or infectious diseases) (off-site assessment).

3.2.5 Statistical Method for Image Evaluation

This primary analysis was performed within the Dotarem group at the patient level using these off-site readings. Each image reader reviewed all images from “Pre”, “Post” and “Paired” MRI modalities and rated up to a limit of the 5 largest representative lesions identified, employing a 3-point scale; unevaluable (0), seen but imperfectly (1), or seen completely/perfectly (2). For each co-primary variable, a subject score was calculated by adding up all within-subject lesion scores (up to 5 lesions) and the within-subject difference between the “Pre” and “Paired” scores (primary analysis) and the “Pre” and “Post” scores (secondary analysis) was then derived for each variable.

The Full Analysis Set (FAS) was used for the analyses reported in this document. The definition of the FAS was: all patients with valid co-primary endpoint assessments.

For each co-primary endpoint, a patient score was computed by:

- summing all lesion scores within patient for each MRI modality (per patient "Paired" scores sum and "Pre" scores sum);
- calculating within patient the difference between the 2 MRI modalities ("Paired" scores sum and "Pre" scores sum).

An example below in Table 6 is given to understand the scoring system:

Table 6: Example of scoring system

Subject #	Lesion #	Score Pre	Score Paired	Subject's score Paired – Pre*
01	1	1	2	4 – 2 = 2
	2	1	1	
	3	0	1	
02	1	1	2	5 – 4 = 1
	2	2	2	
	3	1	0	
	4	-	1	
	5	0	-	
03	1	1	2	3 – 4 = -1
	2	2	1	
	3	1	-	

(*) No matching lesion needed to compute the subject's score

The primary criteria, the sum of lesions' scores instead of mean of lesions' scores within patient was used, in order to reflect the number of lesions detected.

Statistical hypotheses for each of co-primary endpoints

μ and s are respectively the expected mean and standard deviation of the patient score (within subject difference ["Paired" scores sum – "PRE" scores sum]) for each of co-primary endpoints in the Dotarem® group.

$\mu 1 = 0.5$ (average minimum patient score if there is benefit to use Dotarem®)
$\mu 0 = 0.0$ (average score in case of no benefit of Dotarem®)
$s = 2.5$

The success hypothesis (sum of lesion scores in "Paired" MRI is at least in average 0.5 higher than sum of lesion scores in "PRE" MRI) is based upon the Multihance® label results where this outcome was observed in average for the 3 readers of a phase III pivotal study MH-105 (referred as study A) which included a population of patients similar to the one targeted in the present study.

Null hypothesis: $H_0 : \mu_1 = \mu_0$; one-sided $\alpha = 0.025$

Alternative hypothesis: $H_1 : \mu_1 > \mu_0 ; 1-\beta = 0.80$

The efficacy goal was to show that the paired patient scores for each primary endpoint component were superior for the paired images compared to the uncontrasted images. In both DGD-44-050 and DGD-44-051, each co-primary criterion was analyzed using a multiple regression model, modeling the patient's score as a function of the MRI modality ("Pre", "Post" and "Paired") with adjustment for centers and repeated measures for each patient.

To be successful, 2 out of 3 off-site blinded readers had to meet the alternative hypothesis for the 3 co-primary variables in the Dotarem group: a statistically significant (with 1-sided $p \leq 0.025$) positive difference in score means in border delineation, morphology and degree of contrast enhancement.

In study DGD-44-050, a similar statistical approach was employed to compare Dotarem and Magnevist for these same co-primary variables. (In DGD-44-051, there was only a Dotarem group.)

In addition to the co-primary variables, the secondary criteria for the evaluation of efficacy were also assessed in both DGD-44-050 and DGD-44-051, such as sum of scores of lesion visualization on "Post only" and "Pre" at patient level.

Handling of Missing Data

Two situations of missing data could occur in the study for the primary endpoints: a patient with no lesion and a patient with non-assessable images. In these situations, rules for handling missing data on primary endpoints for a given off-site reading are described in the following table 7.

Table 7: Rules for handling missing data

Missing Situation	Status	Score Pre	Score Paired	Score (Paired-Pre)	Included in Analysis
No lesion	No lesion on Pre and Paired	-	-	-	No
	No lesion on Paired but lesions on Pre	2	0	-2	Yes
	No lesion on Pre but lesions on Paired	0	2	2	Yes
Not assessable	Subject with Pre or Contrast agent MRI not performed	-	-	-	No
	Non assessable on Pre and Paired	-	-	-	No
	Non assessable on Pre but assessable on Paired	0	2	2	Yes
	Assessable on Pre but non assessable on Paired	2	0	-2	Yes

3.3 Results and Conclusions

There were different sets of readers for two studies -050 and -051.

3.3.1 Primary Efficacy Analysis

The primary analysis consisted of a within-group comparison of the "Paired" (U + C) versus the Pre-Dotarem (U) images for the 3 co-primary variables. The Study DGD-44-050 achieved all components of its primary endpoint as summarized in Table 8. The statistical assessments demonstrated the superiority of the "Paired" image evaluations over the "Pre" (unenhanced) images for CNS lesion visualization for all 3 co-primary variables for all 3 readers favoring the "Paired" over the "Pre" Dotarem administration images with a statistically significant difference ($p < 0.001$) for all within-group comparisons for each of the 3 co-primary variables for each of the 3 readers.

Table 8: Trial 050 Primary Endpoints Results – Pre vs. Paired (FAS): Patients Score (Sum) for Lesion Visualization, by Reader (mean, SD)

Readers	Reader 1		Reader 2		Reader 3	
Modality	Pre	Paired	Pre	Paired	Pre	Paired
N Patients	224	230	224	230	222	235
Border Delineation Score						
Mean (SD)	1.06 (1.23)	3.30 (2.64)	1.62 (1.43)	4.49 (2.94)	1.43 (1.29)	2.54 (2.30)
Estimate*	1.09	3.35	1.65	4.57	1.43	2.58
Prob > T*	< 0.001		< 0.001		< 0.001	
Internal Morphology Score						
Mean (SD)	0.97 (1.05)	3.70 (2.63)	1.76 (1.24)	4.49 (2.93)	1.45 (1.13)	2.93 (2.30)
Estimate*	0.97	3.72	1.80	4.57	1.42	2.96
Prob > T*	< 0.001		< 0.001		< 0.001	
Contrast Enhancement Score						
Mean (SD)	0.01 (0.20)	3.11 (2.52)	0.01 (0.15)	3.73 (2.67)	0.01 (0.13)	2.95 (2.44)
Estimate*	0.05	3.18	0.05	3.81	0.02	3.01
Prob > T*	< 0.001		< 0.001		< 0.001	

*Estimate and p-values based on Regression Model: Lesion border delineation score = Treatment group + Session + Treatment group x Session + Region, Repeated Session within subject / type=CS

For Study DGD-44-051 the blinded image reviews and the subsequent statistical assessments demonstrated the superiority of the "Paired" (Dotarem-enhanced) image evaluations over the "Pre" (unenhanced) images for lesion visualization for all 3 co-primary variables for all 3 readers favoring the "Paired" readings with a statistically significant difference ($p < 0.001$) for each of the 3 co-primary variables for each of the 3 readers (Table 9).

Table 9: Trial 051 Primary Endpoints Results – Pre vs. Paired: Patients Score (Sum) for Lesion Visualization, by Reader (mean, SE)

Readers	Reader 1		Reader 2		Reader 3	
Modality	Pre	Paired	Pre	Paired	Pre	Paired
N Patients	149	149	149	149	149	149
Border Delineation Score						
Mean (SE)	0.94 (0.07)	1.98 (0.07)	1.41 (0.08)	2.18 (0.08)	0.34 (0.08)	1.62 (0.08)
Difference* (SE)	1.05 (0.08)		0.77 (0.08)		1.28 (0.10)	
95% CI 0f difference	(0.88, 1.21)		(0.62, 0.92)		(1.07, 1.48)	
Internal Morphology Score						
Mean (SE)	1.09 (0.07)	2.23 (0.07)	1.34 (0.08)	2.28 (0.08)	0.67 (0.08)	2.41 (0.08)
Difference* (SE)	1.14 (0.07)		0.94 (0.07)		1.74 (0.09)	
95% CI 0f difference	(1.00, 1.29)		(0.80, 1.08)		(1.56, 1.92)	
Contrast Enhancement Score						
Mean (SE)	0.00 (0.06)	2.06 (0.08)	0.00 (0.07)	2.11 (0.07)	0.00 (0.07)	2.21 (0.07)
Difference* (SE)	2.06 (0.08)		2.10 (0.10)		2.21 (0.10)	
95% CI 0f difference	(1.90, 2.22)		(1.91, 2.29)		(2.02, 2.40)	

*p-value , all analyses, < 0.001

Abbreviations: CI = confidence interval; Paired = side-by-side comparison of MRI scans obtained before and after Dotarem administration; Pre = MRI obtained before Dotarem administration; SE = standard error

3.3.2 Secondary Efficacy Analysis for Study 050

Among the pediatric patients within Study 050, the average visualization scores also showed a generally consistent pattern of improvement following Dotarem administration (Table 10). This pattern was also found in multiple other subsets such as patients grouped by gender and ethnicity.

Table 10: Trial 050 Secondary Endpoints (Pediatric 2 Years & Older)
Results – Pre vs. Paired:
Patients Score (Sum) for Lesion Visualization, by Reader (mean, SD)

Readers	Reader 1		Reader 2		Reader 3	
Modality	Pre	Paired	Pre	Paired	Pre	Paired
N Patients*	31	32	34	35	33	36
Border Delineation Score						
Mean (SD)	1.42 (1.09)	2.47 (1.52)	1.18 (1.03)	3.51 (2.50)	1.06 (0.66)	1.36 (1.10)
Difference	1.05		2.33		0.30	
95% CI on Diff	(0.40, 1.70)		(1.43, 3.23)		(-0.12, 0.72)	
Internal Morphology Score						
Mean (SD)	1.13 (0.88)	2.75 (1.50)	1.41 (0.78)	3.51 (2.48)	1.06 (0.56)	1.81 (1.09)
Difference	1.62		2.1		0.75	
95% CI on Diff	(1.01, 2.23)		(1.24, 2.96)		(0.35, 1.15)	
Contrast Enhancement Score						
Mean (SD)	0	1.81 (1.09)	0	2.69 (2.03)	0	1.64 (1.25)
Difference	1.81		2.69		1.64	
95% CI on Diff	(1.43, 2.19)		(1.99, 3.39)		(0.21, 2.05)	

* FAS – Full Analysis Set or Efficacy Evaluable

Dotarem, compared to Magnevist, demonstrated similar diagnostic performance in terms of lesion visualization endpoints (Table 11). No significant difference between the performance of Dotarem and Magnevist for all 3 co-primary variables for the 3 off-site readers was noted (Table 12).

Table 11: Results (Secondary Endpoint)
Lesion Visualization Scores with Magnevist
Paired vs. Pre (Patient Level)
FAS Adults: Randomized Trial DGD-44-050

Readers	Reader 1		Reader 2		Reader 3	
Modality	Pre	Paired	Pre	Paired	Pre	Paired
N Patients	111	114	113	114	113	116
Border Delineation Score						
Estimate	1.30	3.67	1.65	4.57	1.70	2.94
Difference	2.38		2.91		1.24	
p-value	<0.001		<0.001		<0.001	
Internal Morphology Score						
Estimate	1.14	4.00	1.82	4.58	1.51	3.13
Difference	2.86		2.76		1.62	
p-value	<0.001		<0.001		<0.001	
Contrast Enhancement Score						
Estimate	0.09	3.47	0.10	3.81	0.04	3.19
Difference	3.38		3.71		3.15	
p-value	<0.001		<0.001		<0.001	

Table 12: Results (Secondary Endpoint)
Dotarem vs. Magnevist (Patient Level)
FAS Adults: Randomized Trial DGD-44-050

Readers	Reader 1	Reader 2	Reader 3
Border Delineation Score			
Dot-Mag	-0.30	-0.05	-0.29
95% CI (Dot-Mag)	(-0.75, 0.16)	(-0.53, 0.44)	(-0.71, 0.13)
Internal Morphology Score			
Dot-Mag	-0.19	-0.11	-0.11
95% CI (Dot-Mag)	(-0.59, 0.20)	(-0.53, 0.32)	(-0.44, 0.22)
Contrast Enhancement Score			
Dot-Mag	-0.26	-0.10	-0.15
95% CI (Dot-Mag)	(-0.65, 0.12)	(-0.50, 0.30)	(-0.51, 0.21)

Conclusion – No significant difference between the performance of Dotarem and Magnevist for all 3 co-primary variables for the 3 off-site readers.

3.3.3 Patient-level Lesion Visualization for Study 050

Table 13 displays the proportion of patients with paired read as better, or not better as the pre-contrast MRI images. Table 13 shows improvement for the three visualization parameters for all three readers; more lesions were seen in the paired images than in the pre-contrast images alone; and the percentage of patients with improved lesion visualization for Paired images compared to Pre images ranged from 56% to 94%.

Table 13: Results (Secondary Endpoint)
Patient-level Lesion Visualization Results with Dotarem
FAS Adults: Randomized Trial DGD-44-050

	Reader 1	Reader 2	Reader 3
	N = 231	N = 232	N = 237
Border Delineation :			
Not Better*	28 (12%)	7 (3%)	88 (37%)
Better	195 (84%)	215 (93%)	132 (56%)
Missing	8 (4%)	10 (4%)	17 (7%)
Internal Morphology :			
Not Better*	5 (2%)	8 (3%)	33 (14%)
Better	218 (94%)	214 (93%)	187 (79%)
Missing	8 (4%)	10 (4%)	17 (7%)
Contrast Enhancement :			
Not Better*	15 (6%)	6 (3%)	12 (5%)
Better	208 (90%)	216 (93%)	208 (88%)
Missing	8 (4%)	10 (4%)	17 (7%)

* Not better = # of patient with paired score is the same as or worse than the pre score
Better = # of patients paired score is greater than the pre score.
Missing = # of patients with missing images

3.3.4 Pre versus Post Analysis for Study 050

The Study 050 also achieved all components of secondary endpoint of comparing pre versus post (U versus C) as summarized in Table 14. The Table shows that the average patient scores for the post (C) image results were higher than the pre or uncontrasted (U) image results. All comparisons are consistent with success upon the primary endpoint.

Table 14: Trial 050 Secondary Endpoints Results – Pre vs. Paired: Patients Score for Lesion Visualization, by Reader

Readers	Reader 1		Reader 2		Reader 3	
Modality	Pre	Post	Pre	Post	Pre	Post
N Patients*	224	228	224	230	222	226
Border Delineation Score						
Mean SD	1.06 (1.23)	2.95 (2.56)	1.62 (1.43)	3.85 (2.74)	1.43 (1.29)	2.35 (2.18)
Difference	1.89		2.23		0.92	
p-value**	<0.001		<0.001		<0.001	
Internal Morphology Score						
Mean SD	0.97 (1.05)	2.40 (2.09)	1.76 (1.24)	2.53 (1.93)	1.45 (1.13)	1.63 (1.37)
Difference	1.43		0.77		0.18	
p-value**	<0.001		<0.001		0.04	
Contrast Enhancement Score						
Mean SD	0.01 (0.20)	3.15 (2.51)	0.01 (0.15)	3.70 (2.68)	0.01 (0.13)	3.04 (2.41)
Difference	3.14		3.69		3.03	
p-value**	<0.001		<0.001		<0.001	

*** FAS – Full Analysis Set or Efficacy Evaluable**
**** p-value (t-test), all analyses**

3.3.5 Lesion Level Exploratory Analysis

The scale of 0, 1, and 2 used to rate visualization in studies - 050 and – 051 may be difficult to interpret and have little clinical relevance. This becomes especially challenging when these scores are added for up to five largest lesions to arrive at a total score on a patient level and then nominal or ordinal level scores converted to continuous level and averaged. These averages may have little of no clinical relevance. The total score may be biased as some patients, especially severely ill patients may contribute more to total. Per recommendation of the clinical review team additional lesion level analyses were performed.

The exploratory analytical examination of the distribution of visualization outcomes have consistently shown improved visualization with gadoterate. The following table 15 shows the distribution of patients by the lesions visualized by Readers (a patient could have up to five lesions scored) for Border Delineation using the FAS patient population. A similar distribution pattern was found for other co-primary endpoints. Highlighted is the distribution of patients with “seen completely” lesions, the highest visualization score.

Table 15: Study 44-050 – Dotarem Adult Population
Number of Patients by Five Largest Lesions Visualized & Lesion Score

Lesion Score*	Study 44-050 - **Border Delineation** - Adult, Reader 1										Total Number of Lesions (All)	
	First Largest Lesion		Second Largest Lesion		Third Largest Lesion		Fourth Largest Lesion		Fifth Largest Lesion			
	Pre	Pair	Pre	Pair	Pre	Pair	Pre	Pair	Pre	Pair	Pre	Pair
0 (%)	95 (42)	1 (1)	24	0	11	1	9	0	5	0	144 (41)	2 (1)
1 (%)	107 (48)	67 (29)	27	20	22	9	11	0	9	1	176 (50)	97 (22)
2 (%)	22 (10)	162 (70)	7	74	2	43	0	29	0	23	31 (9)	331 (77)
Total	224	230	58	94	35	53	20	29	14	24	351	430
	Study 44-050 - **Border Delineation** - Adult, Reader 2											
0	34	0	6	0	1	0	1	0	0	0	42	0
1	187	1	74	0	43	0	22	0	17	0	343	1
2	3	229	3	119	1	85	2	52	1	31	10	516
Total	224	230	83	119	45	85	25	52	18	31	395	517
	Study 44-050 - **Border Delineation** - Adult, Reader 3											
0	39	2	7	0	6	0	5	0	2	0	59	2
1	164	128	45	38	28	17	16	10	11	11	264	204
2	19	105	4	38	2	24	2	17	0	12	27	196
Total	222	235	56	76	36	41	23	27	13	23	350	402

* 0= Unevaluable 1= Seen, but imperfectly, 2=Seen completely/perfectly

Note – First refers to first lesion seen and provides number of patients with a lesion score of 0, 1, or 2 seen first by the readers. Second refers to second largest lesion seen in patients who also had first lesion seen by the same reader. And so on. Fifth means four largest lesions were already seen by the same reader in a patient and also had a visible fifth lesion. By design, only 5 largest lesions seen by a reader were documented. Lesion size was not documented. First lesion seen appears to be representative of performance of Dotarem in visualizing CNS lesions. It is also a per-patient analysis.

The exploratory analyses are consistent with success upon the primary endpoint. These analyses also indicate improved visualization of the paired images compared to the pre-contrast images. The following table 16 summarizes the imaging efficacy outcomes for adults based upon a distribution of the number of patients with various scores for the "first" lesion listed within the dataset tabulations.

Table 16: Study 050 – Dotarem Adult Population
Number of Patients Categorized by "First Lesion" Visualization Score*

	Readers					
Lesion Score*	Reader 1		Reader 2		Reader 3	
	Border Delineation - Adult					
	Pre	Paired	Pre	Paired	Pre	Paired
0 (%)	95 (42)	1 (1)	34 (15)	0 (0)	39 (18)	2 (1)
1 (%)	107 (48)	67 (29)	187 (84)	1 (1)	164 (74)	128 (54)
2 (%)	22 (10)	162 (70)	3 (1)	229 (99)	19 (8)	105 (45)
Total # of Patients	224	230	224	230	222	235
	Internal Morphology- Adult					
	Pre	Paired	Pre	Paired	Pre	Paired
0 (%)	77	1	2	0	14	5
1 (%)	144	5	222	1	202	50
2 (%)	3	224	0	229	6	180
Total # of Patients	224	230	224	230	222	235
	Contrast Enhancement - Adult					
	Pre	Paired	Pre	Paired	Pre	Paired
0 (%)	224	26	223	13	221	13
1 (%)	0	18	0	29	0	34
2 (%)	0	186	1	188	1	188
Total # of Patients	224	230	224	230	222	235

* 0= Unevaluable 1= Seen, but imperfectly, 2=Seen completely/perfectly

Pediatric Population for Study 44-050

Pediatric Population for Study 44-050 analyses also indicate improved visualization of the paired images compared to the pre-contrast images. The following table summarizes the pediatric imaging efficacy outcomes based upon a distribution of the number of patients with various scores for the "first" lesion listed within the dataset tabulations.

Table 17: Study 44-050 Treatment – Dotarem Pediatric Population (2 years & Older) # of Patients by Lesion Score for first detected/visualized lesion - FAS Population

	Readers					
Lesion Score*	Reader 1		Reader 2		Reader 3	
	Border Delineation - Pediatric					
	Pre	Paired	Pre	Paired	Pre	Paired
0 (%)	3 (10)	0 (0)	7 (21)	0 (0)	5 (15)	3 (8)
1 (%)	23 (74)	7 (22)	26 (76)	1 (3)	27 (82)	26 (72)
2 (%)	5 (16)	25 (78)	1 (3)	34 (97)	1 (3)	7 (20)
Total # of Patients	31	32	34	35	33	36
	Internal Morphology - Pediatric					
	Pre	Paired	Pre	Paired	Pre	Paired
0	7	0	0	0	4	2
1	24	0	34	0	28	14
2	0	32	0	35	1	20
Total # of Patients	31	32	34	35	33	36
	Contrast Enhancement - Pediatric					
	Pre	Paired	Pre	Paired	Pre	Paired
0	31	8	34	6	33	7
1	0	2	0	3	0	7
2	0	22	0	26	0	22
Total # of Patients	31	32	34	35	33	36

* 0= Unevaluable 1= Seen, but imperfectly, 2=Seen completely/perfectly

All these exploratory analyses are consistent with success upon the primary endpoint.

3.3.6 Evaluation of Safety

For the safety evaluation report, readers are referred to the clinical review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region for Study 050

For the DGD 44-050 study, findings by gender, race, age, ethnicity, and geographic region were assessed. The results indicated a general consistency across each stratification for each of the 3 variables for each reader. The details are provided in Tables 15, 16, 17 and 18.

Table 18: Trial 050 Primary Endpoints Results – Pre vs. Paired: Patients Score (Sum) for Lesion Visualization, by Sex & Reader (mean, SD)

Readers	Reader 1		Reader 2		Reader 3	
Subgroup	Pre	Paired	Pre	Paired	Pre	Paired
Border Delineation Score						
Male (Means) (N, SD)	0.91 106, 1.17	3.44 107, 2.82	1.68 107, 1.40	4.82 110, 2.99	1.41 108, 1.30	2.73 109, 2.59
Female (Means) (N, SD)	1.19 118, 1.27	3.18 123, 2.48	1.56 117, 1.46	4.18 120, 2.86	1.46 114, 1.28	2.36 126, 2.02
Internal Morphology Score						
Male (Means) (N, SD)	0.92 106, 1,03	3.91 107, 2.78	1.85 107, 1.28	4.82 110, 2.98	1.44 108, 1.09	3.18 109, 2.578
Female (Means) (N, SD)	1.02 118, 1.08	3.51 123, 2.50	1.67 117, 1.21	4.18 120, 2.86	1.46 114, 1.17	2.71 126, 2.02
Contrast Enhancement Score						
Male (Means) (N, SD)	0 106, 0	3.44 107, 2.62	0 107, 0	4.05 110, 2.83	0.02 108, 0.19	3.25 109, 2.61
Female (Means) (N, SD)	0.03 118, 0.28	2.83 123, 2.40	0.03 117, 0.21	4.44 120, 2.49	0 114, 0	2.70 126, 2.25

Abbreviations: Paired = side-by-side comparison of MRI scans obtained before and after Dotarem administration; Pre = MRI obtained before Dotarem administration; SD = standard deviation

Table 19: Trial 050 Primary Endpoints Results – Pre vs. Paired: Patients Score (Sum) for Lesion Visualization, by Race & Reader (mean, SE)

Readers	Reader 1		Reader 2		Reader 3	
Subgroup	Pre	Paired	Pre	Paired	Pre	Paired
Border Delineation Score						
Caucasian (Means) (N, SD)	0.98 190, 1.15	3.13 195, 2.43	1.51 190, 1.38	4.37 195, 2.85	1.35 188, 1.21	2.38 199, 2.08
Non-Caucasian (Means) (N, SD)	1.53 34, 1.56	4.26 35, 3.48	2.23 34, 1.62	5.14 35, 3.37	1.88 34, 1.59	3.36 36, 3.17
Internal Morphology Score						
Caucasian (Means) (N, SD)	0.89 190, 0.95	3.55 195, 2.47	1.67 190, 1.14	4.37 195, 2.84	1.39 188, 1.08	2.79 199, 2.10
Non-Caucasian (Means) (N, SD)	1.44 34, 1.44	4.51 35, 3.34	2.24 34, 1.67	5.14 35, 3.37	1.82 34, 1.34	3.69 36, 3.09
Contrast Enhancement Score						
Caucasian (Means) (N, SD)	0 190, 0	2.93 195, 2.35	0.01 190, 0.15	3.66 195, 2.54	0 188, 0	2.80 199, 2.28
Non-Caucasian (Means) (N, SD)	0.09 34, 0.51	4.11 35, 3.15	0.03 34, 0.17	4.46 35, 3.24	0.06 34, 0.34	3.78 36, 3.09

Abbreviations: Paired = side-by-side comparison of MRI scans obtained before and after. Non-Caucasian include Black, Asian and Other.. Pre = MRI obtained before Dotarem administration; SD = standard deviation

Table 20: Trial 050 Primary Endpoints Results – Pre vs. Paired: Patients Score (Sum) for Lesion Visualization, by Age & Reader (mean, SE)

Readers	Reader 1		Reader 2		Reader 3	
Subgroup	Pre	Paired	Pre	Paired	Pre	Paired
Border Delineation Score						
< 65 (Means) (N, SD)	1.03 165, 1,20	3.38 170. 2.81	1.58 167, 1.35	4.65 171, 3.06	1.48 165, 1.40	2.58 175, 2.46
≥ 65 (Means) (N, SD)	1.15 59, 1.32	3.07 60, 2.11	1.74 57, 1.65	4.03 59, 2,53	1.30 57, 0.91	2.40 60. 1.77
Internal Morphology Score						
< 65 (Means) (N, SD)	0.99 165, 1.10	3.77 170, 2.80	1.76 167, 1.25	4.65 171, 3.05	1.52 165, 1.20	2.94 175, 2.41
≥ 65 (Means) (N, SD)	0.93 59, 0.92	3.48 60, 2.09	1.74 57, 1.23	4.00 59, 2.52	1.28 57, 0.88	2.87 60, 1.97
Contrast Enhancement Score						
< 65 (Means) (N, SD)	0.02 165, 0.23	3.21 170, 2.72	0.01 167, 0.08	3.86 171, 2.84	0.01 165, 0.16	2.98 175, 2.58
≥ 65 (Means) (N, SD)	0 59. 0	2.83 60, 1.83	0.04 57, 0.26	3.37 59, 2.07	0 57, 0	2.87 60, 1.97

Abbreviations: Paired = side-by-side comparison of MRI scans obtained before and after Dotarem administration; Pre = MRI obtained before Dotarem administration; SD = standard deviation

Table 21: Trial 050 Primary Endpoints Results – Pre vs. Paired: Patients Score (Sum) for Lesion Visualization, by Geographic Region & Reader (mean, SD)

Readers	Reader 1		Reader 2		Reader 3	
Subgroup	Pre	Paired	Pre	Paired	Pre	Paired
Border Delineation Score						
Europe (Means) (N, SD)	0.92 113, 1.06	3.07 115, 2.47	1.49 112, 1.27	4.28 114, 2.93	1.37 111, 1.10	2.48 115, 2.19
USA (Means) (N, SD)	1.33 54, 1.47	3.81 58, 2.69	1.80 55, 1.77	4.70 61, 2.89	1.57 54, 1.57	2.63 62, 2.35
South America (Means) (N, SD)	0.71 31, 0.64	2.29 31, 1.27	1.10 31, 0.60	4.00 29, 2.33	0.94 31, 0.57	1.69 32, 0.86
Korea (Means) (N, SD)	1.54 26, 1.65	4.38 26, 3.77	2.42 26, 1.70	5.46 26, 3.56	2.00 26, 1.72	3.62 26, 3.35
Internal Morphology Score						
Europe (Means) (N, SD)	0.81 113, 0.88	3.50 115, 2.52	1.67 112, 1.15	4.28 114, 2.93	1.41 111, 1.05	2.96 115, 2.17
USA (Means) (N, SD)	1.13 54, 1.18	4.21 58, 2.69	1.87 55, 1.32	4.69 61, 2.87	1.65 54, 1.33	2.74 62, 2.30
South America (Means) (N, SD)	0.74 31, 0.51	2.61 31, 1.23	1.32 31, 0.47	4.00 29, 2.33	0.97 31, 0.31	2.13 32, 0.87
Korea (Means) (N, SD)	1.62 26, 1.58	4.69 26, 3.58	2.42 26, 1.77	5.46 26, 3.56	1.85 26, 1.41	4.23 26, 3.37
	Contrast Enhancement Score					
Europe (Means) (N, SD)	0 113, 0	3.03 115, 2.37	0.02 112, 0.19	3.70 114, 2.66	0 111, 0	2.96 115, 2.32
USA (Means) (N, SD)	0 54, 0	3.22 58, 2.76	0 55, 0	3.70 61, 2.60	0 54, 0	2.97 62, 2.60
South America (Means) (N, SD)	0 31, 0	2.19 31, 1.17	0 31, 0	3.00 29, 1.85	0 31, 0	2.00 32, 1.01
Korea (Means) (N, SD)	0.12 26, 0.59	4.30 26, 3.30	0.04 26, 0.20	4.77 26, 3.39	0.08 26, 0.39	4.08 26, 3.26

Abbreviations: Paired = side-by-side comparison of MRI scans obtained before and after Dotarem administration; Pre = MRI obtained before Dotarem administration; SD = standard deviation

4.2 Other Special/Subgroup Populations

There were no special subgroups or populations identified by the clinical team for analyses in this review.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Currently, eight GBCAs have been approved by the FDA and six of these agents are marketed with a CNS imaging indication. However, no GBCA is approved for use in pediatric patients under two years of age. This resulted in the designation for a priority review for Dotarem application. The Dotarem is proposed for marketing at a dose of 0.1 mmol/kg, the same dosage recommended for the other CNS imaging agents.

During the review of this submission, it was noted that all three primary visualization endpoints are soft endpoints and may be subjective. Also, the scale of 0, 1, and 2 used to rate visualization in studies - 050 and – 051 may be difficult to interpret and have little clinical relevance.

GBCAs with a CNS imaging indication have all followed the same phase 3 drug development paradigm in which studies generally assessed improved anatomical visualization of CNS lesions. FDA has long accepted improved visualization as indicative of efficacy and the precedent aligns with the guidance published in 2004.

Our guidance states that, "Ordinarily the ability to locate and outline normal structures or distinguish between normal and abnormal anatomy can speak for itself with respect to the clinical value of the information." The ability to provide clinically useful information is the main determiner of efficacy for medical imaging drugs and the Dotarem phase 3 studies followed the FDA-accepted visualization paradigm.

The Dotarem efficacy data were derived from two phase 3 studies. The main confirmatory study is Study DGD-44-050. This study enrolled adults as well as pediatric subjects aged two years or more. These data are important to assessing Dotarem efficacy. The other study DGD-44-051 (also was known as Study DGD-3-44) and was a re-read of a previously conducted study; that is, the images had previously been interpreted for other purposes. Because of study limitations, the findings of this study are considered as supportive but not the definitive determiner of efficacy from statistical point of view.

In the study 050, adults were randomized, with a two to one ratio randomizing the subjects to either Dotarem or Magnevist. Magnevist is an approved drug and is indicated for use with MRI in adults and pediatric patients (2 years of age and older) to visualize lesions with abnormal vascularity in the brain, spine and associated tissues as well as visualization of lesions with abnormal vascularity of the head and neck and the body (excluding the heart). This was a valid comparison. The results found that Dotarem and the Magnevist performance were similar.

Among the pediatric patients within Study 050, the average visualization scores also showed a generally consistent pattern of improvement following Dotarem administration. This pattern was also found in multiple other subsets such as patients grouped by gender and ethnicity.

The major supportive study, Study 051, also produced results indicating improved lesion visualization with Dotarem.

Adequate data pertinent to patients aged < 2 years to evaluate safety and effectiveness were not provided. The applicant has supplied no PK data for pediatric patients, and pilot clinical trial data are limited to only 7 patients aged less than 2 years. These patients may be at greatest safety risks due to immature drug metabolism and excretion processes.

The meeting of the Medical Imaging Drug Advisory Committee was held on 2/14/2013 to address, among other things, the consideration of approval of Dotarem for use in pediatric patients less than two years of age.

The committee voted unanimously (17 to 0) for the finding of favorable "risk-to-benefit" assessment for use of Dotarem in CNS MRI among adults and pediatric patients aged two years and older. The committee voted against approving the drug for children younger than two years of age (10 to 6, with 1 abstention). Those who did vote for approval found the cited by the applicant historical data obtained outside US to be sufficient. The majority voted against approving Dotarem in infants and neonates for the lack of clinical and pharmacokinetic data in this age group as well as for the lack of supportive juvenile animal data.

5.2 Conclusions and Recommendations

This statistical reviewer's conclusion is that adequate evidence is provided to approve the following indication for Dotarem:

DOTAREM is a gadolinium-based contrast agent indicated for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissues in adults and pediatric patients (from 2 years of age and older) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity.

Adequate data pertinent to patients aged < 2 years to evaluate safety and effectiveness were not provided. The applicant has supplied no PK data for pediatric patients, and pilot clinical trial data are limited to only 7 patients aged less than 2 years. The safety and efficacy for this group is inconclusive based on the information submitted in this application.

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/s/

SATISH C MISRA
03/05/2013

JYOTI ZALKIKAR
03/05/2013

I concur with overall conclusion of the primary reviewer. I find that the primary reviewer's lesion-level exploratory analyses (section 3.3.5) are redundant and don't add any meaning to the scoring system.

THOMAS E GWISE
03/05/2013

I concur with the overall conclusion that the data submitted provide support for approving the drug under conditions stated in the reviews, but some analysis methods chosen by the sponsor are difficult to interpret with respect to clinical meaning.