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 Serial Number:	**201277**
Drug Name:	**Gadovist (Gadobutrol)**
Indication(s):	**MRI of the CNS**
Applicant:	**Bayer Health Care**
Date(s):	**Submitted: May 14 2010 ; PDUFA Date: March 14 2011**
Review Priority:	**Standard**
Biometrics Division:	**V**
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Keywords: Clinical Studies , Image Evaluation, Cross-Over Design , Diagnostic Accuracy Sensitivity (Specificity)

Table of Contents

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1. EXECUTIVE SUMMARY

Gadovist(Gadobutrol) is a gadolinium based contrast agent proposed by Bayer for MRI visualization of the central nervous system (CNS). There are currently five gadolinium agents approved by the FDA for this indication. The reviewer considers the two primary Phase III studies submitted by the Sponsor under NDA201277 (Study310123 and Study310124) as supportive of the proposed visualization claim.

The two Phase III studies focused on four primary endpoints: three visualization endpoints for lesions and structures, and a fourth, lesion detection, endpoint. The three visualization endpoints were: Contrast Enhancement , Border Delineation , and Internal Morphology. The Sponsor achieved the objective of Superiority in visualization of paired reads of images (Unenhanced plus Gadovist Enhanced MRI) over Unenhanced MRI for all three. The Non-Inferiority objective for the fourth endpoint for numbers of detected lesions for paired reads versus unenhanced reads was achieved in Study310123, and was borderline successful in Study310124. The reviewer considers this borderline success as adequate for non-inferiority in lesion detection. It is noted here that the visualization endpoints are somewhat soft. First, these scores represent the readers' subjective assessments of levels of clarity in visualization. Next, the individual reader assessments are scores that are smoothed over structures and lesions. Finally, the endpoint statistics are the averages across readers of these already smoothed individual reader scores. However, this smoothed assessment has been used and accepted in earlier submissions of gadolinium based MRI imagings of the CNS. Moreover, the FDA requested, and the Sponsor included, a secondary set of primary endpoint comparisons of paired Gadovist evaluations to paired ProHance evaluations in Study310123 in order to assess how well Gadovist performed relative to an already approved contrast agent for CNS imagings. The Gadovist and ProHance performances were virtually identical.

Standard Safety analyses for Gadovist MRI revealed no significant issues. However, Gadovist is a gadolinium agent, and, as such, is under scrutiny for Nephrogenic systemic fibrosis (NSF), a serious disease whose occurrence has been documented among subjects who have significant renal problems and who have undergone gadolinium based imagings. (NSF manifests in scaling of the skin, stiffness, and, in some cases, fibrosis of internal organs, which can lead to death.) The approved gadolinium products have been tracked for NSF incidence, and there is growing evidence that some of these agents put patients at greater risk than do others; the former agents now have appropriate warnings included in labeling. Thus far, and inclusive of this submission, there is little evidence that Gadovist belongs to the high risk category. An Advisory Committee meeting, convened on January 21 2011, largely for the purpose of evaluating Gadovist for NSF risk, concluded that a warning label was unnecessary at this time.

2. INTRODUCTION

2.1 Overview

Gadovist (Gadobutrol) is a gadolinium (Gd) imaging agent intended for use in MRI imaging of the central nervous system (CNS). The family of such imaging agents approved for CNS imaging includes Omniscan, Magnevist, Prohance, Multihance and Optimark. Gadovist for MRI Imaging was originally submitted as IND56410 by Berlex in July 1998 , (b) (4) The IND was reactivated in December 2003 with a focus on CNS imaging. Bayer subsequently acquired Berlex, and a Type C meeting was held with the FDA in May 2007 to discuss a Phase III program for CNS Imaging. A SPA for Phase III was submitted in October 2008 for one of the two primary studies (Study310123) and another SPA was submitted in December 2008 for the second primary study Study 310124). The pre-NDA meeting was held on February 4 2010. The NDA was received on May 14 2010 and was put on a regular ten month review timeline, with a PDUFA goal date of March 14 2011. Gadovist is currently approved in 64 countries outside the US, with a specific indication for contrast enhancement in cranial and spinal MRI in the European community and in several countries in Eastern Europe and Asia. Gadovist has not been extensively studied in the US prior to this submission. Two Phase III studies will be reviewed here.

Study310123: A multicenter, randomized, double-blind, Phase III Study to determine the Safety and Efficacy of Gadobutrol 1.0 molar (Gadovist) in patients referred for Contrast-Enhanced MRI of the Central Nervous System (CNS).

Study310124: A multicenter, open-label, Phase III Study to determine the Safety and Efficacy of Gadobutrol 1.0 molar (Gadovist) in patients referred for Contrast-Enhanced MRI of the Central Nervous System (CNS).

The two tables immediately below provide an overview of designs, objectives, and patient dispositions for the primary studies.

Table(1): ***Overview of Design/Objectives/Inclusion Criteria***

	STUDY310123	**STUDY310124**
Indication	**Contrast MRI of the CNS**	**Contrast MRI of the CNS**
Inclusion Criteria	**Subjects referred for Contrast MRI based on symptoms or previous imaging results**	**Subjects referred for Contrast MRI based on symptoms or previous imaging results**
Design	**Single Arm Crossover Image Evaluations:** **Primary: Test (Gadovist plus Baseline MRI) versus Baseline MRI** **Secondary: Test versus Active Control (ProHance plus Baseline MRI)**	**Single Arm Image Evaluations:** **Primary: Test (Gadovist plus Baseline MRI) versus Baseline MRI** **(No Active Control)**
Primary Endpoints	**(1): Quality of Visualization of CNS for both Structures and Lesions** **(2): Detection of Lesions**	**(1): Quality of Visualization of CNS for both Structures and Lesions** **(2): Detection of Lesions**
Objectives	**(1): Demonstration of Superiority of Test Visualization to Baseline Visualization for both Structures and lesions** **(2): Demonstration of Non-Inferiority of Test to Baseline in #Lesions detected**	**(1): Demonstration of Superiority of Test Visualization to Baseline Visualization for both Structures and lesions** **(2): Demonstration of Non-Inferiority of Test to Baseline in #Lesions detected**
Study Period	**June 2008 to April 2009**	**December 2009 to December 2009**
# Subjects	**Enrolled: 419** **Completers: 380** **FAS: 336** **PP: 316**	**Enrolled: 347** **Completers: 336** **FAS: 321** **PP: 314**
# Centers	**Total: 51** **US: 13** **Germany: 15** **Japan: 12** **Other: 11**	**Total: 22** **US: 7** **South America: 6** **China: 4** **South Korea: 5**

Table(2): ***Subject Disposition for the two primary Phase III studies under review***

	Study310123	Study310124
Subjects Enrolled	**419**	**347**
Completers (Dosed&Imaged)	**380**	**336**
Total Discontinued	**39**	**11**
Reasons:		
No Dosing	**17**	**4**
Withdrawal of Consent	**6**	**2**
Protocol Deviations	**7**	**4**
Adverse Event/Loss to Follow-Up	**9**	**1**
FAS (Full Analysis Set)	**336***	**321**
PPS (Per Protocol Set)	**316**	**314**

2.2 Data Sources

The primary electronic data set sources used for this review are located in:

\\CDSESUB1\EVSPROD\NDA201277

Additionally, the statistical reviewer received and utilized several requested additional data sets and statistical tables from the Sponsor on October 22 2010. These were submitted as amendments and are identified by the Sponsor as:

FDA123EF.XPT and FDA124.XPT

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

No issues with data and analysis quality.

3.2Evaluation of Efficacy

The Sponsor conducted two Primary Phase III studies. The protocols and principal results from these two studies are presented below, as follows:

Section3.2.1 will provide an overview of the Protocol and Endpoints for Study310123
Section3.2.2 will provide an overview of the Results for Study310123
Section3.2.3will provide an overview of the Protocol and Endpoints for Study310124
Section3.2.4will provide an overview of the Results for Study310124

Preliminary Note: *Study310123 differs from Study310124 only in having an Active Control (ProHance) for evaluations of Test versus Control as secondary endpoints. Thus, the Design presentation for Study310124 is identical to that of Study310123 except for the absence of a description of Test versus Active Control comparisons.*

3.2.1 Design/Endpoints

Clinical Study 310123: Design/Endpoints

Study Title: A multicenter, randomized, double-blind, Phase III Study to determine the Safety and Efficacy of Gadobutrol 1.0 molar (Gadovist) in patients referred for Contrast-Enhanced MRI of the Central Nervous System (CNS).

Study Efficacy Endpoints/Objectives
The primary Efficacy objectives focused on comparisons of paired Unenhanced plus Gadovist Contrast Enhanced MRI (hereafter: Paired) to Unenhanced MRI (hereafter: Unenhanced) with respect to visualization endpoints. There were four such endpoints, and evaluations of Paired images were required to be superior to evaluations of Unenhanced images for three of these endpoints. For the fourth endpoint- number of detected lesions- evaluations under Paired reads had to be non-inferior to evaluations under Unenhanced reads.

Several secondary endpoints addressed Efficacy in diagnostics (rather than visualization). Evaluation of the Paired versus Unenhanced reads proper to these secondary objectives, (such as efficacy for Sensitivity/Specificity), required a Standard of Reference (SOR), while the primary objectives did not.

Important secondary comparisons in this study were evaluations of Gadovist paired reads to ProHance paired reads for all efficacy endpoints. ProHance is an approved agent for MRI imagings, and the Agency considered it important that Gadovist Paired reads be evaluated not only to the baseline Unenhanced reads, but also to Paired reads conducted with a similar and approved agent in at least one of the two primary trials. However, hypothesis testing of Paired Gadovist versus Paired ProHance, though important, was not considered primary.

Study Inclusion Criteria
Subjects were referred for a Contrast Enhanced MRI of the CNS based on current symptoms or on results from a previous imaging procedure. Subjects were referred either for MRI imaging of the brain and/or MRI imaging of the spine. It is noted here that, even if subjects were imaged for both brain and spine, the efficacy analyses were limited to one of these areas, presumably determined by the investigator.

Imaging Protocol
Subjects underwent two imaging sessions, each of which consisted of Unenhanced MRI followed by Contrast Enhanced MRI. The Contrast Enhanced MRI sequence was randomized as First Gadovist/ Next ProHance , or First Prohance /Next Gadovist.

Image Reads
There were several types of reads in the study, each determined by intended endpoint evaluations. Three (expert radiologist) blinded readers independently read all Unenhanced and Paired Gadovist images , and all Unenhanced and paired ProHance images. These reads were dedicated to both primary and secondary endpoint objectives.
However, there were also separate reads confined to Gadovist Paired MRI and ProHance Paired MRI by two other blinded readers (along with a possible third adjudicator.) These reads addressed additional secondary endpoint objectives (detailed later below.)
Finally, there were the unblinded investigator reads.

Standard of Reference (SOR) Evaluations
The final Truth diagnosis was determined by (several) region specific independent Truth committees, each consisting of two experienced physicians in the neuroscience field. The diagnoses were achieved by consensus, and were based on all information collected on the subjects within three months post study imagings, but exclusive of the study specific image read results. Typical information included referral diagnoses, medical histories, histopathology, therapies, and alternative imagings.

Primary Objectives for Visualization (Superiority in Visualization):

The Paired Gadovist read had to demonstrate Superiority to the Unenhanced read simultaneously for three Visualization endpoints:

(a): Degree of Contrast Enhancement
(b): Border Delineation
(c): Internal Morphology

Thus, for each Visualization Endpoint the hypotheses were:

Null: Mean Paired Score ≤ Mean Unenhanced Score
Alternative: Mean Paired Score > Mean Unenhanced Score

Statistical Test: ***T-Test for Paired Observations***

Decision Criterion*:* The mean score was calculated as an average smoothed across readers. The Null was rejected if the 2-sided 95% CI for the difference – Paired Score minus Unenhanced Score - had its lower limit above zero.

Primary Objective for Detection: (Non-Inferiority in Lesion Detection):

The Paired read had to demonstrate Non-Inferiority to Unenhanced MRI in total number of lesions detected.

Null: Mean # Paired Read minus Unenhanced Read Lesion Detections ≤ -.35
Alternative: Mean # Paired Read minus Unenhanced Read Lesion Detections > -.35

Statistical Test: ***T-Test for Paired Observations***

The mean # lesion detections was calculated as an average across readers. The Null was rejected if:
The 2-sided 95% CI for Paired minus Unenhanced # detections > -.35

Note: The rationale for the Non-Inferiority limit is not completely convincing, but it was accepted by the Agency.

Protocol/Algorithm for Primary Visualization Scores
The scoring for visualizations is very complex. The scoring protocol for each of the three visualization parameters involves a sequence of steps, addressed in detail in the appendix, but broadly described here as follows:

Each reader scores lesions and Normal Structures separately, using a graded scale that reflects increased clarity of visualization.

An overall reader score is then determined as an average of the separate Normal Structure and lesion scores.

The final overall score for the endpoint is the average of these scores across readers. It is this score that constitute the endpoint value.

The four Principal Secondary Endpoints/Objectives

(Secondary Objective#1): Identifications of presence/absence of abnormal brain tissue:
Subject level evaluations for Presence/Absence of abnormal brain tissue was recorded for all three reads - Paired Gadovist/Paired ProHance/Unenhanced. Success levels – Sensitivity, Specificity , Accuracy - were determined with respect to a diagnostic SOR , and the differences in these levels (Paired Gadovist versus Unenhanced , Paired ProHance versus Unenhanced , Paired Gadovist versus Paired ProHance) were evaluated.

(Secondary#2): Subject Level identification of a malignant lesion:
Paired Gadovist MRI was compared to Unenhanced MRI for the detection of malignant lesions. Likewise, Paired ProHance MRI was compared to Unenhanced MRI for the detection of malignant brain lesions. Finally, direct comparisons of Gadovist Enhanced MRI to ProHance Enhanced MRI for the detection of malignant lesions was made. One malignant lesion per subject was implicated – typically a malignancy confirmatory for subject inclusion in the study. All these comparisons involve Sensitivity/Specificity evaluations with respect to the SOR.

(Secondary#3): Subject Level Diagnoses
Paired Gadovist MRI was compared to Unenhanced MRI for *exact* patient level diagnoses . Likewise, Paired ProHance MRI was compared to Unenhanced MRI for exact patient level diagnoses. (Paired Gadovist was also be compared to Paired ProHance.) The Reviewer's inference here is that the Secondary#2 binary classification endpoint of malignant, not malignant is derived from this exact diagnosis endpoint.

(Secondary#4):
Gadovist Enhanced MRI was compared to Gadoteridol (ProHance)
Enhanced MRI for the determination of differences in the numbers of Contrast Enhanced lesions detected. Note that, unlike the previous secondary endpoint comparisons, these comparisons do not utilize Unenhanced images. Moreover, the reads were performed by a set of (two) new independent readers. (If the independent reads here yield different numbers of contrast enhanced lesions for any particular subject, an adjudicator reader was brought in to determine if the difference was real and what the "true" number of lesions was.

3.2.2: Clinical Study 310123 Results

Table(3): Demographics for Study310123

		Gadovist-ProHance (N = 228)	ProHance-Gadovist (N = 174)
Age		**50 +/- 16 yrs**	**51 +/-16 yrs**
Age Group	**< 45 yrs**	**86 (38%)**	**58 (33%)**
	45 to 64 yrs	**89 (39%)**	**75 (43%)**
	>= 65 yrs	**53 (23%)**	**41 (24%)**
Gender	**Male**	**96 (42%)**	**79 (45%)**
	Female	**132 (58%)**	**95 (55%)**
Race	**Caucasian**	**128 (56%)**	**107 (62%)**
	Hispanic	**20 (9%)**	**11 (6%)**
	Asian	**66 (29%)**	**46 (26%)**
	Black	**13 (6%)**	**10 (6%)**
Country	**Germany**	**56 (25%)**	**51 (29%)**
	Japan	**64 (28%)**	**45 (26%)**
	USA	**71 (31%)**	**52 (30%)**
	Columbia	**16 (7%)**	**14 (8%)**
	Other	**21 (9%)**	**12 (7%)**

Table(4): Patient Disposition for Study310123:

	Study310123
Subjects Enrolled	**419**
Completers	**380**
Total Discontinued	**39**
Reasons:	
No Dosing	**17**
Withdrawal of Consent	**6**
Protocol Deviations	**7**
Adverse Event/Loss to Follow-Up	**9**
FAS (Full Analysis Set)*	**336**
PPS (Per Protocol Set)	**316**

**There is a considerable drop in sample size from Completers to FAS. The Sponsor reports that some of this difference is due to removal of "training" subjects from the Completer population, and some of the difference is due to absence of reads. However, the reviewer couldn't find the hard numbers that would confirm these explanations..*

PRIMARY ENDPOINT RESULTS

Table(5) below presents the Paired Gadovist versus Unenhanced results for the three visualization endpoints, both by individual reader and by reader average. The reader average was used to test the primary hypotheses. The success criterion was that the 95% 2-sided confidence intervals for Paired versus Unenhanced reads for the average read have their lower limits above zero. The table shows that all confidence intervals for these differences, both for the average read and for the individual readers, have lower limits well above zero. Thus, the criteria for efficacy for visualization endpoints was met.

Table(5): Primary Endpoint Visualization Parameter Results for Gadovist

Contrast Enhancement (Scores: From 1 = No Enhancement through 4 = Clear and Bright Enhancement)				
	Reader#1 (N=314)	**Reader#2 (N=314)**	**Reader#3 (N=312)**	**Reader Average (N=316)**
Paired Read	**2.21**	**2.60**	**2.02**	**2.26**
Unenhanced Read	**.94**	**1.01**	**.96**	**.97**
Difference	**1.26**	**1.59**	**1.06**	**1.29**
95% CI	**(1.20 , 1.33)**	**(1.50 , 1.67)**	**(1.00 , 1.18)**	**(1.23 , 1.35)**
Border Delineation (Scores: From 1 = No Delineation through 4 = Clear and Complete Delineation)				
	Reader#1 (N=314)	**Reader#2 (N=314)**	**Reader#3 (N=312)**	**Reader Average (N=316)**
Paired Read	**2.70**	**2.91**	**2.16**	**2.58**
Unenhanced Read	**2.03**	**2.19**	**1.73**	**1.98**
Difference	**.67**	**.72**	**.43**	**.60**
95% CI	**(.60 , .75)**	**(.63 , .81)**	**(.37 , .49)**	**(.54 , .65)**
Internal Morphology (Scores: From 1 = Poor Visibility through 3 = Sufficient Visibility)				
	Reader#1 (N=314)	**Reader#2 (N=314)**	**Reader#3 (N=312)**	**Reader Average (N=316)**
Paired Read	**1.78**	**2.28**	**1.76**	**1.93**
Unenhanced Read	**1.16**	**1.46**	**1.34**	**1.32**
Difference	**.62**	**.82**	**.41**	**.61**
95% CI	**(.57 , .68)**	**(.76 , .89)**	**(.36 , .47)**	**(.56 , .66)**

Comment: *The Sponsor reports that the FAS population had N = 336. The table above presents statistics on N ≈316. This discrepancy is due to the fact that 20 subjects not imaged for the brain had no detected lesions, and therefore were not included in the computation of averages.*

Table(6) refines the presentation of visualization results for the average read by partitioning performances into visualization on lesions and visualization on normal structures. Again, all lower limits of CI's for Paired reads versus Unenhanced reads are above zero, but there is a pattern that reveals that visualization by paired reads is better on normal structures than it is on lesions.

Table(6): Gadovist Average Read Visualization Statistics by Lesion/Structure
(N = Number of Subjects)

Contrast Enhancement			
	Average Paired	**Average Unenhanced**	**Difference (95% CI)**
Lesions (N = 293)	**1.62**	**.85**	**.78 (.66 , .90)**
Normal Structures (N = 310)	**2.76**	**1.06**	**1.70 (1.67 , 1.73)**
All (N = 316)	**2.26**	**.97**	**1.29 (1.23 , 1.35)**
Border Delineation			
	Average Paired	**Average Unenhanced**	**Difference**
Lesions (N = 293)	**2.26**	**1.82**	**.44 (.32 , .56)**
Normal Structures (N = 310)	**2.81**	**2.09**	**.72 (.70 , .75)**
All (N = 316)	**2.58**	**1.98**	**.60 (.54 , .65)**
Internal Morphology			
	Average Paired	**Average Unenhanced**	**Difference**
Lesions (N = 293)	**1.65**	**1.23**	**.42 (.32 , .51)**
Normal Structures (N = 310)	**2.14**	**1.38**	**.76 (.74 , .79)**
All (N = 316)	**1.93**	**1.32**	**.61 (.56 , .66)**

Table(7) presents lesion detection results by individual reader and by average read.
Here the results are not as positive as with the visualization parameters. In particular, the success criterion – lower limit of the 95% 2-sided CI for Paired versus Unenhanced average read – does not exceed the pre-specified value of -.35. However, the reviewer considers this threshold value to be somewhat mysterious in any event, and the achieved value, -.44, is close enough to be considered borderline. Moreover, when these results are integrated with the Study310124 results and the ProHance results from Study310123, and in light of the results presented in Table(8) below, this mild failure to meet the threshold is not considered decisive.

Table(7): Mean# Lesions and Differences in Mean #Lesions for Gadovist

Statistics on Total # Detected Lesions				
	Reader#1 (N=336)	**Reader#2 (N=336)**	**Reader#3 (N=336)**	**Reader Average (N=336)**
Mean #Lesions Unenhanced	**7.41 (SD=13.0)**	**10.07 (SD=16.6)**	**6.75 (SD=9.0)**	**8.08 (SD=12.4)**
Mean #Lesions Paired	**7.80 (SD=12.9)**	**9.63 (SD=15.0)**	**7.31 (SD=9.1)**	**8.25 (SD=11.4)**
Mean Difference in # Lesions	**.39 (SD=5.5)**	**-.44 (SD=12.4)**	**.56 (SD=4.1)**	**.17 (SD=5.7)**
95% CI on Mean Difference	**(-.20 , .98)**	**(-1.77 , .89)***	**(.12 , 1.00)**	**(- .44 , .78)***

Table(8) below is intended to provide a better insight into the lesion detection performances of Paired versus Unenhanced reads. The categories are to be understood as follows:

"Unenhanced > Paired" means the Unenhanced Read detected more lesions than did the Paired Read
"Paired > Unenhanced" means the Paired Read detected more lesions than did the Unenhanced Read

"Unenhanced = Paired" means both reads detected the same number of lesions

Table(8): Combined Reader/ Subject Comparisons of # Detected Lesions
(Number of Subjects = 336; Number of Reader Subjects = 1008)

	Unenhanced > Paired	**Unenhanced = Paired**	**Paired > Unenhanced**	**Difference (Paired – Unenhanced)**
	29%	**35%**	**36%**	**7%** **(-2% , 16%)**

SECONDARY ENDPOINT RESULTS: Gadovist versus ProHance Visualizations

Tables(9) through(12) below address the secondary comparisons of Gadovist to ProHance in the same manner as the earlier tables addressed the primary comparisons of Paired Gadovist to Unenhanced reads. The addition of a Gadovist to ProHance comparison was undertaken at Agency recommendation to provide a possible "corrective" for bias in visualization scores for Paired to Unenhanced reads. The opportunity for bias existed in that readers can clearly distinguish Paired from Unenhanced image sets, and can therefore score the former higher than the latter. Although this possibility is unavoidable, the addition of ProHance pairs at least provided a check that Gadovist Paired reads are consistently scored just like ProHance reads, although the readers cannot distinguish between these image types.
The results reveal parity in Gadovist versus ProHance performances.

Table(9): Secondary Endpoint Visualization Results Gadovist versus ProHance

Contrast Enhancement (Scores: From 1 = No Enhancement through 4 = Clear and Bright Enhancement)				
	Reader#1 (N=314)	**Reader#2 (N=313)**	**Reader#3 (N=312)**	**Reader Average (N=315)**
Paired Gadovist	**2.21**	**2.60**	**2.02**	**2.26**
Paired Prohance	**2.16**	**2.55**	**1.97**	**2.22**
Difference	**.05**	**.05**	**.05**	**.04**
95% CI **	**(0, .10)**	**(0 , .12)**	**(-.02 , .08)**	**(0 , .08)**
Border Delineation (Scores: From 1 = No Delineation through 4 = Clear and Complete Delineation)				
	Reader#1 (N=314)	**Reader#2 (N=313)**	**Reader#3 (N=312)**	**Reader Average (N=315)**
Paired Gadovist	**2.70**	**2.91**	**2.16**	**2.58**
Paired Prohance	**2.66**	**2.86**	**2.14**	**2.55**
Difference	**.04**	**.05**	**.02**	**.03**
95% CI	**(- .02, .10)**	**(-.01 , .15)**	**(- .04 , .06)**	**(-.01 , .08)**
Internal Morphology (Scores: From 1 = Poor Visibility through 3 = Sufficient Visibility)				
	Reader#1 (N=314)	**Reader#2 (N=313)**	**Reader#3 (N=312)**	**Reader Average (N=315)**
Paired Gadovist	**1.78**	**2.28**	**1.76**	**1.93**
Paired Prohance	**1.77**	**2.25**	**1.72**	**1.90**
Difference	**.01**	**.03**	**.04**	**.03**
95% CI	**(- .03 , .06)**	**(- .02 , .10)**	**(- .02 , .09)**	**(-.01 , .06)**

Table(10): Gadovist versus ProHance Visualization Statistics by Lesion/Structure

Contrast Enhancement			
	Gadovist	**ProHance**	**Difference (95% CI)**
Lesions (N = 289)	**1.65**	**1.58**	**.07 (0 , .15)**
Normal Structures (N = 310)	**2.76**	**2.73**	**.03 (0 , .06)**
All (N = 316)	**2.26**	**2.22**	**.04 (0 , .08)**
Border Delineation			
	Gadovist	**ProHance**	**Difference**
Lesions (N = 289)	**2.29**	**2.22**	**.07 (- .03 , .18)**
Normal Structures (N = 310)	**2.81**	**2.79**	**.02 (- .01 , .05)**
All (N = 316)	**2.58**	**2.55**	**.04 (-.01 , .08)**
Internal Morphology			
	Gadovist	**ProHance**	**Difference**
Lesions (N = 289)	**1.68**	**1.59**	**.08 (0 , .16)**
Normal Structures (N = 310)	**2.14**	**2.14**	**0 (- .02 , .03)**
All (N = 316)	**1.93**	**1.90**	**.03 (- .01 , .06)**

Table(11): Mean# Lesions Gadovist versus ProHance

Statistics on Total # Detected Lesions				
	Reader#1 (N=336)	**Reader#2 (N=336)**	**Reader#3 (N=336)**	**Reader Average (N=336)**
Gadovist Mean #Lesions	**7.80 (SD=12.9)**	**9.63 (SD=15.0)**	**7.31 (SD=9.1)**	**8.25 (SD=11.4)**
ProHance Mean #Lesions Paired	**7.44 (SD=13.0)**	**9.62 (SD=15.8)**	**7.65 (SD=10.7)**	**8.24 (SD=11.8)**
Mean Difference in # Lesions	**.36 (SD=6.2)**	**.01 (SD=10.7)**	**-.34 (SD=6.6)**	**.01 (SD=5.7)**
95% CI on Mean Difference	**(-.30 , 1.04)***	**(-1.14 , 1.61)***	**(-1.05 , .36)**	**(- .60 , .62)***

Table(12): Comparisons of # Detected Lesions : Gadovist versus ProHance: (N = 336)

	Gadovist > ProHance	Gadovist = ProHance	ProHance > Gadovist	Difference (Gadovist –ProHance)
Reader#1	**32.4%**	**41.7%**	**25.9%**	**6.5% (-1.6.% , 14.7%)**
Reader#2	**35.4%**	**33.9%**	**30.7%**	**4.8% (-3.9% , 13.4%)**
Reader#3	**31.8%**	**36.9%**	**31.3%**	**.6% (-7.9% , 9.1%)**
Average	**33%**	**38%**	**29%**	**7% (-2% , 16%)**

Note: With P1 = (Column#1) /100 and P2 = (Column#3) /100 and N = 336:

95% CI on Difference $\approx$ *Difference +/- 1.96* $\sqrt{(P1+P2)/N}$

SECONDARY ENDPOINT RESULTS: DIAGNOSTICS

The secondary diagnostic endpoints were:

(Secondary Endpoint#1): Identifications of presence/absence of abnormal brain tissue:

(Secondary Endpoint#2): Subject Level identification of a malignant lesion:

(Secondary Endpoint#3): Subject Level Diagnoses

Table(13) presents:

A Majority Read Unenhanced versus Gadovist Paired versus ProHance Paired classifications of each the subject's primary lesions as benign/malignant in those cases where Truth was available.

A Majority Read Unenhanced versus Gadovist Paired versus ProHance Paired classifications of each the subject's brain tissue as Normal/Abnormal in those cases where Truth was available.

A Majority Read Unenhanced versus Gadovist Paired versus ProHance Paired classifications of each the subject's primary lesion exact diagnosis in those cases where Truth was available.

The results reveal similar Gadovist and ProHance performances, with both performances somewhat superior to Unenhanced performances.

Table(13): Majority Rule Patient Level Diagnostic Statistics

Majority Rule Statistics on Binary Classifications of Lesions (N = 292 Subjects) Truth: Benign = 199 Cases ; Malignant = 93 Cases			
	Unenhanced	**Gadovist Enhanced**	**ProHance Enhanced**
Sensitivity	**47%**	**67%**	**60%**
Specificity	**97%**	**98%**	**98%**
Majority Rule Statistics on Binary Classifications of Brain Tissue (N= 322 Subjects) Truth: Normal = 61 Cases ; Abnormal = 261 Cases			
	Unenhanced	**Gadovist Enhanced**	**ProHance Enhanced**
Sensitivity	**66%**	**76%**	**76%**
Specificity	**80%**	**80%**	**82%**
Majority Rule Statistics on Patient Level Exact Match Subject Level Diagnoses (N = 292 Subjects)			
	Unenhanced	**Gadovist Enhanced**	**ProHance Enhanced**
Match Percentage	**58%**	**64%**	**66%**

Tables (14) through (16) present the results above reader-by-reader.

Table(14): Statistics on Classifications of Normal/Abnormal Brain Tissue

Sensitivity (N = 261)				
	Reader#1	**Reader#2**	**Reader#3**	**Majority**
Unenhanced	**62%**	**62%**	**66%**	**63%**
Gadovist Enhanced	**74%***	**76%***	**81%***	**76%***
ProHance Enhanced	**74%***	**76%***	**81%***	**76%***
Specificity (N = 61)				
	Reader#1	**Reader#2**	**Reader#3**	**Majority**
Unenhanced	**79%**	**75%**	**80%**	**80%**
Gadovist Enhanced	**84%**	**79%**	**71%**	**80%**
ProHance Enhanced	**87%**	**77%**	**72%**	**82%**
Accuracy (N = 267)				
	Reader#1	**Reader#2**	**Reader#3**	**Majority**
Unenhanced	**66%**	**65%**	**69%**	**67%**
Gadovist Enhanced	**76%***	**76%***	**78%***	**77%***
ProHance Enhanced	**77%***	**76%***	**79%***	**77%***

** = Statistically Significant Improvement over Unenhanced*

Table(15): Statistics on Classifications of Lesions

Sensitivity (N = 93)				
	Reader#1	**Reader#2**	**Reader#3**	**Majority**
Unenhanced	**52%**	**51%**	**48%**	**47%**
Gadovist Enhanced	**63%**	**68%**	**66%**	**67%**
ProHance Enhanced	**61%**	**59%**	**65%**	**60%**
Specificity (N = 199)				
	Reader#1	**Reader#2**	**Reader#3**	**Majority**
Unenhanced	**98%**	**91%**	**97%**	**97%**
Gadovist Enhanced	**98%**	**95%**	**97%**	**98%**
ProHance Enhanced	**98%**	**95%**	**97%**	**98%**
Accuracy (N = 292)				
	Reader#1	**Reader#2**	**Reader#3**	**Majority**
Unenhanced	**83%**	**78%**	**81%**	**81%**
Gadovist Enhanced	**87%**	**86%**	**87%**	**88%**
ProHance Enhanced	**86%**	**84%**	**86%**	**86%**

Table(16): Accuracy of Diagnosis (N = 292)

	Reader#1	**Reader#2**	**Reader#3**	**Majority**
Unenhanced	**52%**	**44%**	**46%**	**58%**
Paired Gadovist	**56%**	**49%**	**55%**	**64%**
Paired ProHance	**59%**	**47%**	**53%**	**66%**

3.2.3: Clinical Study 310124 Design/Endpoints

Unlike Study310123, Study 310124 does not include an active diagnostic control (ProHance). Other than for this missing feature, Study310124 is identical in design to Study 310123. Therefore, the description of the Protocol and endpoints presented directly below is identical to the description provided for Study310123.

Clinical Study 310124: Protocol

Study Title: A multicenter, open-label, Phase III Study to determine the Safety and Efficacy of Gadobutrol 1.0 molar (Gadovist) in patients referred for Contrast-Enhanced MRI of the Central Nervous System (CNS).

Study Efficacy Objectives
The primary Efficacy objectives focused on comparisons of paired Unenhanced plus Gadovist Contrast Enhanced MRI (hereafter: Paired) to Unenhanced MRI (hereafter: Unenhanced) with respect to visualization endpoints. There were four such endpoints, and evaluations of Paired images were required to be superior to evaluations of Unenhanced images for three of these endpoints. For the fourth endpoint- number of detected lesions- evaluations under Paired reads had to be non-inferior to evaluations under Unenhanced reads.

Several secondary endpoints addressed Efficacy in diagnostics (rather than visualization). Evaluation of the Paired versus Unenhanced reads proper to these secondary objectives, (such as efficacy for Sensitivity/Specificity), required a Standard of Reference (SOR), while the primary objectives did not. Note that in this Study, in contrast to Study 310123, where ProHance served as a Control, no efficacy comparisons to an approved modality were included.

Study Inclusion Criteria
Subjects were referred for a Contrast Enhanced MRI of the CNS based on current symptoms or on results from a previous imaging procedure. Subjects were referred either for MRI imaging of the brain and/or MRI imaging of the spine.
Note: Even if subjects were imaged for both brain and spine, the efficacy analyses were limited to one of these areas, presumably determined by the investigator.

Imaging Protocol
Subjects underwent one imaging consisting of Unenhanced MRI followed by Contrast Enhanced MRI.

Image Read Protocol
Three (expert radiologist) blinded readers independently read all Unenhanced and Paired Unenhanced plus Gadovist Enhanced MRI's.

Standard of Reference (SOR) Evaluations
The final Truth diagnosis was determined by (several) region specific independent Truth committees, each consisting of two experienced physicians in the neuroscience field. The diagnoses was by consensus, and was based on all information collected on the subjects within three months post study imagings, exclusive of the study specific image read results. Typical information included referral diagnoses, medical histories, histopathology, therapies, and alternative imagings.

Primary Study Objectives:

(First Primary Objectives): Superiority in Visualization:

The paired read of Unenhanced plus Gadovist Enhanced MRI must demonstrate Superiority to Unenhanced MRI simultaneously for three Visualization parameters:

(a): Degree of Contrast Enhancement
(b): Border Delineation
(c): Internal Morphology

(Second Primary Objective): Non-Inferiority in Lesion Detection

The paired read of combined Unenhanced plus Gadovist Enhanced MRI must demonstrate Non-Inferiority to Unenhanced MRI in total number of lesions detected.

Protocol/Algorithm for Primary Visualization Scores
The scoring for visualizations is very complex. The scoring protocol for each of the three visualization parameters involves a sequence of steps, addressed in detail in the appendix, but broadly described here as follows:

Each reader scores lesions and Normal Structures separately, using a graded scale that reflects increased clarity of visualization.

An overall reader score is then determined as an average of the separate Normal Structure and lesion scores.

The final overall score for the endpoint is the average of these scores across readers. It is this score that constitute the endpoint value.

Note: See the Appendix for a thorough description of the scoring method.

Contrast Enhancement Score for a lesion or structure:

1 = None ; 2 = Weak ; 3 = Clear ; 4 = Clear and Bright

Border Delineation Score for a lesion or structure:

1 = None ; 2 = Moderate ; 3 = clear but incomplete ; 4 = Clear and Complete

Internal Morphology Score for a lesion or structure:

1 = Poorly visible ; 2 = Moderately visible ; 3 = Sufficiently visible

THREE PRINCIPAL SECONDARY ENDPOINTS/OBJECTIVES

(Secondary Objective#1): Identifications of presence/absence of abnormal brain tissue:
Subject level evaluations for Presence/Absence of abnormal brain tissue will be recorded for all three reads - Paired Gadovist/Paired ProHance/Unenhanced. Success levels – Sensitivity, Specificity , Accuracy - will be determined with respect to a diagnostic SOR , and the differences in these levels will be evaluated.

(Secondary#2): Subject Level identification of a malignant lesion:
Paired Gadovist MRI will be compared to Unenhanced MRI for the detection of malignant lesions. All these comparisons involve Sensitivity/Specificity evaluations with respect to an SOR.

Note: The detection of malignant lesions does not require any characterization of these lesions beyond their malignancy. Also, as with (1), these evaluations are conducted at the subject level. Effectively, it appears that the design provides that this secondary endpoint allows for the evaluation of at most one malignant lesion per subject: the SOR determines for some select lesion that it is or is not malignant, and the various reads must both detect and correctly classify this lesion as Benign/Malignant. It is unclear if each subject must contribute a uniquely identified lesion for this analysis, or if subjects can contribute no such lesion, or several such lesions.

(Secondary#3): Subject Level Diagnoses
Paired Gadovist MRI will be compared to Unenhanced MRI for *exact* patient level diagnoses . The Reviewer's inference here is that the Secondary#2 binary classification endpoint is derived from this exact diagnosis endpoint.

3.2.4: Study 310124 Results

Table(17): Demographics

Age		**48 +/- 15 yrs**
Age Group	**< 45 yrs**	**149 (44%)**
	45 to 64 yrs	**145 (42%)**
	>= 65 yrs	**49 (14%)**
Gender	**Male**	**146 (43%)**
	Female	**197 (57%)**
Race	**Caucasian**	**68 (20%)**
	Hispanic	**87 (25%)**
	Asian	**161 (47%)**
	Other	**27 (8%)**
Country	**Argentina**	**85 (25%)**
	Columbia	**40 (12%)**
	South Korea	**100 (29%)**
	China	**59 (17%)**
	USA	**59 (17%)**

Comment:
The table suggests that the Hispanic population was essentially equivalent to the Argentine population, and did not include the Columbia population.

Table(18): Patient Disposition:

	Study310124
Subjects Enrolled	**347**
Completers (Dosed&Imaged)	**336**
Total Discontinued	**11**
Reasons:	
No Dosing	**4**
Withdrawal of Consent	**2**
Protocol Deviations	**4**
Adverse Event/Loss to Follow-Up	**1**
FAS (Full Analysis Set)	**321**
PPS (Per Protocol Set)	**314**

Table(19) below presents the Paired Gadovist versus Unenhanced results for the three visualization endpoints, both by individual reader and by reader average. The reader average was used to test the primary hypotheses. The success criterion was that the 95% 2-sided confidence intervals for Paired versus Unenhanced reads for the average read have their lower limits above zero. The table shows that all confidence intervals for these differences, both for the average read and for the individual readers, have lower limits well above zero. Thus, the criteria for efficacy for visualization endpoints was met.

Table(19): Visualization Results for Gadovist

Contrast Enhancement (Scores: From 1 = No Enhancement through 4 = Clear and Bright Enhancement)				
	Reader#1 (N=301)	**Reader#2 (N=309)**	**Reader#3 (N=309)**	**Reader Average (N=311)**
Paired Read	**2.96**	**2.87**	**2.86**	**2.86**
Unenhanced Read	**.94**	**.93**	**.93**	**.93**
Difference	**2.03**	**1.94**	**1.93**	**1.94**
95% CI	**(1.93 , 2.12)**	**(1.86 , 2.03)**	**(1.84 , 2.02)**	**(1.85 , 2.02)**
Border Delineation (Scores: From 1 = No Delineation through 4 = Clear and Complete Delineation)				
	Reader#1 (N=301)	**Reader#2 (N=309)**	**Reader#3 (N=309)**	**Reader Average (N=311)**
Paired Read	**3.01**	**3.15**	**2.76**	**2.94**
Unenhanced Read	**2.17**	**1.98**	**1.64**	**1.92**
Difference	**.85**	**1.17**	**1.12**	**1.02**
95% CI	**(.76 , .93)**	**(1 .07 , 1.28)**	**(1.03 , 1.20)**	**(.94 , 1.10)**
Internal Morphology (Scores: From 1 = Poor Visibility through 3 = Sufficient Visibility)				
	Reader#1 (N=301)	**Reader#2 (N=309)**	**Reader#3 (N=309)**	**Reader Average (N=311)**
Paired Read	**2.40**	**2.46**	**2.25**	**2.35**
Unenhanced Read	**1.87**	**1.38**	**1.49**	**1.57**
Difference	**.53**	**1.08**	**.77**	**.78**
95% CI	**(.47 , .59)**	**(1 .00 , 1.17)**	**(.70 , .83)**	**(.72 , .84)**

Table(20) refines the presentation of visualization results for the average read by partitioning performances into visualization on lesions and visualization on normal structures. Again, all lower limits of CI's for Paired reads versus Unenhanced reads are above zero, but there is a pattern that reveals that visualization by paired reads is better on normal structures than it is on lesions

Table(20): Gadovist Average Read Visualization Statistics by Lesion/Structure

Contrast Enhancement			
	Average Paired	**Average Unenhanced**	**Difference (95% CI)**
Lesions (N = 273)	**2.29**	**.79**	**1.51 (1.35 , 1.66)**
Normal Structures (N = 289)	**3.33**	**1.01**	**2.32 (2.28 , 2.36)**
All (N = 311)	**2.86**	**.93**	**1.94 (1.85 , 2.02)**
Border Delineation			
	Average Paired	**Average Unenhanced**	**Difference**
Lesions (N = 273)	**2.42**	**1.42**	**1.00 (.85 , 1.15)**
Normal Structures (N = 289)	**3.37**	**2.28**	**1.09 (1.06 , 1.13)**
All (N = 311)	**2.94**	**1.92**	**1.02 (.94 , 1.10)**
Internal Morphology			
	Average Paired	**Average Unenhanced**	**Difference**
Lesions (N = 273)	**2.04**	**1.27**	**.77 (.65 , .89)**
Normal Structures (N = 289)	**2.61**	**1.77**	**.84 (.81 , .86)**
All (N = 311)	**2.35**	**1.57**	**.78 (.72 , .84)**

Table(21) presents lesion detection results by individual reader and by average read.
The Non-Inferiority lower limit of -.35 was met for the primary average read and for 2 of the 3 readers.

Table(21): Mean# Lesions and Differences in Mean #Lesions for Gadovist

Statistics on Total # Detected Lesions				
	Reader#1 (N=321)	**Reader#2 (N=321)**	**Reader#3 (N=321)**	**Reader Average (N=321)**
Mean #Lesions Unenhanced	**2.26 (SD=7.61)**	**3.77 (SD=11.8)**	**1.92 (SD=7.2)**	**2.65 (SD=6.3)**
Mean #Lesions Paired	**2.93 (SD=8.68)**	**3.60 (SD=10.4)**	**2.37 (SD=7.3)**	**2.97 (SD=6.7)**
Mean Difference in # Lesions	**.66 (SD=5.31)**	**-.17 (SD=8.8)**	**.45 (SD=4.2)**	**.32 (SD=3.5)**
95% CI on Mean Difference	**(.08 , 1.25)**	**(-1.13 , .80)***	**(.00 , .9)**	**(- .07 , .70)***

Table(22) below is intended to provide a better insight into the lesion detection performances of Paired versus Unenhanced reads. The categories are to be understood as follows:

"Unenhanced > Paired" means the Unenhanced Read detected more lesions than did the Paired Read
"Paired > Unenhanced" means the Paired Read detected more lesions than did the Unenhanced Read
"Unenhanced = Paired" means both reads detected the same number of lesions

The table does not present reaer-by-reader results, but instead pools the readers.

Table(22): Combined Reader/ Subject Comparisons of # Detected Lesions
(Number of Subjects = 321; Number of Reader Subjects = 963)

Unenhanced > Paired	**Unenhanced = Paired**	**Paired > Unenhanced**	**Difference (Paired – Unenhanced)**
11%	**65%**	**36%**	**25% (18% , 32%)**

Secondary Endpoint Results: Diagnostics

The secondary diagnostic endpoints were:

(Secondary Endpoint#1): Identifications of presence/absence of abnormal brain tissue:

(Secondary Endpoint#2): Subject Level identification of a malignant lesion:

(Secondary Endpoint#3): Subject Level Diagnoses

Table(23) presents:

A Majority Read Unenhanced versus Gadovist Paired classifications of each the subject's primary lesions as benign/malignant in those cases where Truth was available.

A Majority Read Unenhanced versus Gadovist Paired Paired classifications of each the subject's brain tissue as Normal/Abnormal in those cases where Truth was available.

A Majority Read Unenhanced versus Gadovist Paired classifications of each the subject's primary lesion exact diagnosis in those cases where Truth was available.

The results reveal similar Gadovist both performances to be somewhat superior to Unenhanced performances, except for Specificity in classification of brain tissue.

Table(23): Majority Rule Patient Level Diagnostic Statistics

Majority Rule Statistics on Binary Classifications of Lesions (N = 321 Subjects) Truth: Benign = 198 Cases ; Malignant = 63 Cases		
	Unenhanced	**Gadovist Enhanced**
Sensitivity	**57%**	**78%**
Specificity	**93%**	**92%**
Majority Rule Statistics on Binary Classifications of Brain Tissue (N= 321 Subjects) Truth: Normal = 40 Cases ; Abnormal = 199 Cases		
	Unenhanced	**Gadovist Enhanced**
Sensitivity	**75%**	**84%**
Specificity	**73%**	**60%**
Majority Rule Statistics on Patient Level Exact Match Subject Level Diagnoses (N = 321 Subjects)		
	Unenhanced	**Gadovist Enhanced**
Match Percentage	**52%**	**61%**

Tables (24) through (26) present the results above reader-by-reader.

Table(24): Statistics on Classifications of Normal/Abnormal Brain Tissue

Sensitivity (N = 199)				
	Reader#1	**Reader#2**	**Reader#3**	**Majority**
Unenhanced	**75%**	**75%**	**77%**	**75%**
Gadovist Enhanced	**84%***	**84%***	**80%***	**84%***
Specificity (N = 40)				
	Reader#1	**Reader#2**	**Reader#3**	**Majority**
Unenhanced	**73%**	**65%**	**70%**	**73%**
Gadovist Enhanced	**60%**	**58%**	**63%**	**60%**
Accuracy (N = 239)				
	Reader#1	**Reader#2**	**Reader#3**	**Majority**
Unenhanced	**75%**	**73%**	**76%**	**75%**
Gadovist Enhanced	**80%***	**80%***	**77%***	**80%***

* *= Statistically Significant Improvement over Unenhanced*

Table(25): Statistics on Classifications of Lesions

Sensitivity (N =63)				
	Reader#1	**Reader#2**	**Reader#3**	**Majority**
Unenhanced	**57%**	**65%**	**65%**	**57%**
Gadovist Enhanced	**73%**	**81%**	**81%**	**78%**
Specificity (N = 198)				
	Reader#1	**Reader#2**	**Reader#3**	**Majority**
Unenhanced	**93%**	**87%**	**90%**	**90%**
Gadovist Enhanced	**92%**	**86%**	**89%**	**90%**
Accuracy (N = 261)				
	Reader#1	**Reader#2**	**Reader#3**	**Majority**
Unenhanced	**84%**	**82%**	**84%**	**82%**
Gadovist Enhanced	**87%**	**85%**	**87%**	**87%**

Table(26): Accuracy of Diagnosis (Individual reader N = 261)

	Reader#1	Reader#2	Reader#3
Unenhanced	**48%**	**44%**	**47%**
Paired Gadovist	**54%**	**52%**	**54%**

3.3 Evaluation of Safety

There were no standard Safety issues. However, Gadovist is a gadolinium product, and these products present special problems for renally impaired subjects. In particular, a specific disease (NSF) has emerged among a subset of renally impaired subjects imaged with gadolinium agents, and the labeling for some of these agents now includes a warning proper to this liability, in light of the observed risks emerging from NSF reports.

Table(27): NSF Reports on Gadolinium Agents (As of Feb 2009)

	Administrations (Millions)	NSF Reports (Single Agent)
Omniscan	**47**	**438**
Magnevist	**95**	**135**
Optimark	**.8**	**7**
MultiHance	**6**	**0**
ProHance	**12.3**	**1**
Dotarem	**22.4**	**1**
Primovist	**.15**	**0**
Vasovist	**.05**	**0**
Gadovist	**6**	**2**

This table provides some of the evidence that prompted contra-indication warnings for severely renally impaired subjects in Magnevist, Omniscan and Optimark labelings.

An Advisory Committee meeting was convened on January 21 2011 to discuss the weight of current evidence regarding the risk of NSF for Gadovist. The committee concluded that the evidence does not suggest that Gadovist poses a significant NSF risk, and therefore does not require a contraindication warning in its labeling. Details are provided in the clinical review of this NDA.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

No significant patterns contrary to the overall evaluations emerged in the subgroup analyses.

Table(28): Contrast Enhancement by Gender

Study310123				Study310124		
	Image	Score			Image	Score
Male (N=136)	Enhanced	2.3		Male (N=130)	Enhanced	2.8
	Baseline	1.0			Baseline	1.0
	Difference	1.3			Difference	1.8
Female (N=180)	Enhanced	2.3		Female (N=181)	Enhanced	2.9
	Baseline	1.0			Baseline	.9
	Difference	1.3			Difference	2.0

Table(29): Contrast Enhancement by Age

Study310123				Study310124		
	Image	Score			Image	Score
<=65 (N=242)	Enhanced	2.2		<=65 (N=266)	Enhanced	2.8
	Baseline	1.0			Baseline	.9
	Difference	1.2			Difference	1.9
65 < (N=74)	Enhanced	2.2		65 < (N=45)	Enhanced	3.1
	Baseline	1.0			Baseline	1.0
	Difference	1.2			Difference	2.1

Table(30): Contrast Enhancement by Race

Study310123				Study310124		
	Image	**Score**			**Image**	**Score**
Caucasian (N=177)	**Enhanced**	**2.2**		**Caucasian (N=58)**	**Enhanced**	**2.7**
	Baseline	**1.0**			**Baseline**	**.9**
	Difference	**1.2**			**Difference**	**1.8**
Asian (N=97)	**Enhanced**	**2.4**		**Asian (N=151)**	**Enhanced**	**3.0**
	Baseline	**1.0**			**Baseline**	**.9**
	Difference	**1.4**			**Difference**	**2.1**
Hispanic (N=23)	**Enhanced**	**2.5**		**Hispanic (N=80)**	**Enhanced**	**2.8**
	Baseline	**1.0**			**Baseline**	**.9**
	Difference				**Difference**	**1.9**
Black (N=18)	**Enhanced**	**2.2**		**Black (N=8)**	**Enhanced**	**2.2**
	Baseline	**1.0**			**Baseline**	**.9**
	Difference	**1.2**			**Difference**	**1.3**
Other (N=1)	**Enhanced**	**2.8**		**Other (N=14)**	**Enhanced**	**2.7**
	Baseline	**1.0**			**Baseline**	**.9**
	Difference	**1.8**			**Difference**	**1.6**

Table(31): Border Delineation by Gender

Study310123				Study310124		
	Image	**Score**			**Image**	**Score**
Male (N=136)	**Enhanced**	**2.6**		**Male (N=130)**	**Enhanced**	**2.8**
	Baseline	**2.0**			**Baseline**	**1.9**
	Difference	**.6**			**Difference**	**.9**
Female (N=180)	**Enhanced**	**2.6**		**Female (N=181)**	**Enhanced**	**3.0**
	Baseline	**2.0**			**Baseline**	**1.9**
	Difference	**.6**			**Difference**	**1.1**

Table(32): Border Delineation by Age

Study310123				Study310124		
	Image	**Score**			**Image**	**Score**
<=65 (N=254)	**Enhanced**	**2.9**		**<=65 (N=267)**	**Enhanced**	**3.4**
	Baseline	**2.2**			**Baseline**	**2.5**
	Difference	**.7**			**Difference**	**.9**
65 < (N=75)	**Enhanced**	**3.0**		**65 < (N=45)**	**Enhanced**	**3.5**
	Baseline	**2.2**			**Baseline**	**2.6**
	Difference	**.8**			**Difference**	**.9**

Table(33): Border Delineation by Race

Study310123				Study310124		
	Image	**Score**			**Image**	**Score**
Caucasian (N=1862)	**Enhanced**	**2.8**		**Caucasian (N=57)**	**Enhanced**	**3.2**
	Baseline	**2.3**			**Baseline**	**2.7**
	Difference	**.5**			**Difference**	**.5**
Asian (N=97)	**Enhanced**	**3.0**		**Asian (N=151)**	**Enhanced**	**3.5**
	Baseline	**2.0**			**Baseline**	**2.6**
	Difference	**1.0**			**Difference**	**.9**
Hispanic (N=25)	**Enhanced**	**2.9**		**Hispanic (N=81)**	**Enhanced**	**3.4**
	Baseline	**1.4**			**Baseline**	**2.2**
	Difference	**1.5**			**Difference**	**1.2**
Black (N=20)	**Enhanced**	**3.0**		**Black (N=7)**	**Enhanced**	**3.0**
	Baseline	**2.3**			**Baseline**	**2.8**
	Difference	**.7**			**Difference**	**.2**
Other (N=1)	**Enhanced**	**3.5**		**Other (N=16)**	**Enhanced**	**3.4**
	Baseline	**2.8**			**Baseline**	**2.6**
	Difference	**.7**			**Difference**	**.8**

Table(34): Internal Morphology by Gender

Study310123				Study310124		
	Image	**Score**			**Image**	**Score**
Male (N=141)	**Enhanced**	**2.4**		**Male (N=132)**	**Enhanced**	**2.7**
	Baseline	**1.7**			**Baseline**	**1.9**
	Difference				**Difference**	
Female (N=188)	**Enhanced**	**2.4**		**Female (N=180)**	**Enhanced**	**2.8**
	Baseline	**1.8**			**Baseline**	**2.1**
	Difference	**.6**			**Difference**	**.7**

Table(35): Internal Morphology by Age

Study310123				Study310124		
	Image	**Score**			**Image**	**Score**
<=65 (N=246)	**Enhanced**	**1.9**		**<=65 (N=266)**	**Enhanced**	**2.3**
	Baseline	**1.3**			**Baseline**	**1.5**
	Difference	**.6**			**Difference**	**.8**
65 < (N=74)	**Enhanced**	**1.9**		**65 < (N=44)**	**Enhanced**	**2.4**
	Baseline	**1.4**			**Baseline**	**1.6**
	Difference	**.5**			**Difference**	**.8**

Table(36): Internal Morphology by Race

Study310123				Study310124		
	Image	Score			Image	Score
Caucasian (N=186)	Enhanced	2.4		Caucasian (N=57)	Enhanced	2.7
	Baseline	1.9			Baseline	2.3
	Difference	.5			Difference	.4
Asian (N=97)	Enhanced	2.3		Asian (N=151)	Enhanced	2.8
	Baseline	1.6			Baseline	2.1
	Difference	.7			Difference	.7
Hispanic (N=25)	Enhanced	2.4		Hispanic (N=81)	Enhanced	2.7
	Baseline	1.1			Baseline	1.6
	Difference	1.3			Difference	1.1
Black (N=20)	Enhanced	2.4		Black (N=7)	Enhanced	2.6
	Baseline	1.8			Baseline	2.5
	Difference	.6			Difference	.1
Other (N=1)	Enhanced	2.9		Other (N=16)	Enhanced	2.8
	Baseline	2.3			Baseline	2.1
	Difference	.6			Difference	.7

Table(37): Mean Lesion Counts by Gender

Study310123				Study310124		
	Image	#Lesions			Image	#Lesions
Male (N=144)	Enhanced	7.2		Male (N=135)	Enhanced	2.8
	Baseline	6.9			Baseline	2.2
	Difference	.3			Difference	.6
Female (N=192)	Enhanced	9.1		Female (N=186)	Enhanced	3.1
	Baseline	9.0			Baseline	3.0
	Difference	.1			Difference	.1

Table(38): Mean Lesion Counts by Age

Study310123				Study310124		
	Image	#Lesions			Image	#Lesions
[45, 65) (N=261)	Enhanced	6.7		[45, 65) (N=275)	Enhanced	2.6
	Baseline	6.7			Baseline	3.2
	Difference	0			Difference	-.6
65 < (N=75)	Enhanced	13.8		65 < (N=46)	Enhanced	3.0
	Baseline	12.9			Baseline	2.1
	Difference	.9			Difference	-.9

Table(39): Mean Lesion Counts by Race

Study310123				Study310124		
	Image	**#Lesions**			**Image**	**#Lesions**
Caucasian (N=192)	**Enhanced**	**7.3**		**Caucasian (N=61)**	**Enhanced**	**4.0**
	Baseline	**7.5**			**Baseline**	**4.0**
	Difference	**-.2**			**Difference**	**0**
Asian (N=97)	**Enhanced**	**10.6**		**Asian (N=152)**	**Enhanced**	**2.7**
	Baseline	**9.6**			**Baseline**	**2.3**
	Difference	**1.0**			**Difference**	**.4**
Hispanic (N=25)	**Enhanced**	**3.0**		**Hispanic (N=82)**	**Enhanced**	**2.8**
	Baseline	**3.3**			**Baseline**	**2.6**
	Difference	**-.3**			**Difference**	**.2**
Black (N=21)	**Enhanced**	**12.6**		**Black (N=8)**	**Enhanced**	**7.3**
	Baseline	**12.5**			**Baseline**	**3.5**
	Difference	**.1**			**Difference**	**3.8**
Other (N=1)	**Enhanced**	**1.3**		**Other (N=18)**	**Enhanced**	**.8**
	Baseline	**1.0**			**Baseline**	**1.1**
	Difference	**.3**			**Difference**	**-.3**

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

No significant Efficacy issues or standard Safety arose in the review of this submission.
The Safety issue proper to Gadolinium agents – occurrences of NSF – was addressed at the Advisory Committee Meeting dedicated to this submission and convened on January 21 2011. The committee determined that Gadovist did not present a significant risk for NSF, and therefore no warning would be attached to Labeling.

5.2 Conclusions and Recommendations

Gadovist(Gadobutrol) is a gadolinium based contrast agent proposed by Bayer for MRI visualization of the central nervous system (CNS). There are currently five gadolinium agents approved by the FDA for this indication. The reviewer considers the two primary Phase III studies submitted by the Sponsor under NDA201277 (Study310123 and Study310124) as supportive of the proposed visualization claim and therefore recommend approval.

APPENDICES

Appendix(1): Details on the Scoring System

(A): Regions/Lesions to be scored

(1): If the region under investigation was the brain, then four Normal Brain Structures and up to five lesions (the five largest) were scored for each of the three visualization parameters. If the region under investigation is the spine, lesions alone were to be scored.

(2): If the region determined for the subject was the brain, then those Normal Structures that were lesion free were scored for visualization exactly as lesions were scored, and contributed a "non-lesion" component to the visualization score in a manner detailed below. However, if any Normal Structure contained a lesion, then it was the lesion and not the structure that was scored for visualization. Thus, for instance, if, for some reader, there were two lesion-free structures, two structures with a single lesion in each, and two additional lesions detected outside these structures, then the visualization score had a Normal Structure component with two contributors, and a lesion component with four contributors.

Further Refinement: *Lesions found in Normal Structures contributed to the five Lesions for Efficacy analyses, even if there were larger lesions outside these structures.*

(B): Visualization Scoring System

Enhancement Score for a lesion or structure (Four Levels):
1 = None ; 2 = Weak ; 3 = Clear ; 4 = Clear and Bright

Border Delineation Score for a lesion or structure (Four levels):
1 = None ; 2 = Moderate ; 3 = Clear but Incomplete ; 4 = Clear and Complete

Internal Morphology Score for a lesion or structure (Three Levels):
1 = Poorly Visible ; 2 = Moderately Visible ; 3 = Sufficiently Visible

(C): Overall Individual Reader Scores for each Visualization parameter:

First: Paired reads:
For lesions in Paired Reads: A reader's scores for the (at most five) principal lesions (large or in Normal Structures) are summed. Let there be LP such lesions; let their summed score be SLP.

For lesion-free Normal Structures: A reader's scores for these structures are summed. Let there be NP such structures; let their summed score be SNP.

Next: Unenhanced reads:
Identical procedure, with outcomes LU , SLU , NU , SNU

Now let L be the larger of LP and LU ; N be the larger of NP and NU

Then:
The reader's overall Paired score is: (1/ 2) { SLP/L + SNP/N }
The reader's overall Unenhanced score is: (1/ 2) { SLU/L + SNU/N }

Note that the denominator depends on both the Paired and the Unenhanced reads.
This modification is intended to "correct" for cases where the reader does not detect the same number of lesions under the different types of read.

Overall Visualization Score for the Reader (Paired or Unenhanced)

Overall Visualization Score for the Subject = (1/ 3) { Reader Scores across Readers)

CHECK LIST

Number of Pivotal Studies: 2

Trial Specification
Specify for each trial:

Protocol Number (s): Study310123
Phase: 3
Control: Unenhanced MRI Image as Comparator (Baseline)
Blinding: Open-Label
Number of Centers: 51
Region(s) (Country): US, Germany , Japan
Duration: Imaging Session: 1 Day
Treatment Arms: Cross-Over Imaging
Treatment Schedule: (Single Injection 1mmol/kg)
Randomization: No
Primary Endpoint: Image Visualization
Primary Analysis Population: FAS: Subjects with Image Evaluations
Statistical Design: Superiority in Visualization of Enhanced over Baseline Images
Adaptive Design: No
Primary Statistical Methodology: T-Test for Matched Pairs
Interim Analysis: No
Sample Size: FAS = 336
Sample Size Determination: Was it calculated based on the primary endpoint variable and the analysis being used for the primary variable?
Statistic = T-Test for Matched Pairs
Power= 90%
α = **.05**

- Was there an **Alternative Analysis** in case of violation of assumption; e.g., Lack of normality, Proportional Hazards Assumption violation. No
- Were there any major changes, such as changing the statistical analysis methodology or changing the primary endpoint variable? No
- Were the **Covariates** pre-specified in the protocol? N/A
- Did the Applicant perform **Sensitivity Analyses**? N/A
- How were the **Missing Data** handled? Excluded
- Was there a **Multiplicity** involved? No
- **Multiple Secondary Endpoints**: Are they being included in the label? No

Were Subgroup Analyses Performed Yes. Standard
Were there any **Discrepancies** between the protocol/statistical analysis plan vs. the study report? No

- Overall, was the study positive **Yes**

Protocol Number (s): Study310124
Phase: 3
Control: Unenhanced MRI Image as Comparator (Baseline)
Blinding: Open-Label
Number of Centers: 22
Region(s) (Country): US, South America , China , South Korea
Duration: Imaging Session: 1 Day
Treatment Arms: Cross-Over Imaging
Treatment Schedule: (Single Injection 1mmol/kg)
Randomization: No
Primary Endpoint: Image Visualization
Primary Analysis Population: FAS: Subjects with Image Evaluations
Statistical Design: Superiority in Visualization of Enhanced over Baseline Images
Adaptive Design: No
Primary Statistical Methodology: T-Test for Matched Pairs
Interim Analysis: No
Sample Size: FAS = 321
Sample Size Determination: Was it calculated based on the primary endpoint variable and the analysis being used for the primary variable? Yes
Statistic = T-Test for Matched Pairs

Power= 90%

α = **.05**

- Was there an **Alternative Analysis** in case of violation of assumption; e.g., Lack of normality, Proportional Hazards Assumption violation. No
- Were there any major changes, such as changing the statistical analysis methodology or changing the primary endpoint variable? No
- Were the **Covariates** pre-specified in the protocol? N/A
- Did the Applicant perform **Sensitivity Analyses**? N/A
- How were the **Missing Data** handled? Excluded
- Was there a **Multiplicity** involved? No
- **Multiple Secondary Endpoints**: Are they being included in the label? No

Were Subgroup Analyses Performed Yes. Standard
Were there any **Discrepancies** between the protocol/statistical analysis plan vs. the study report? No

- Overall, was the study positive **Yes**

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

/s/

ANTHONY G MUCCI
02/23/2011

RAJESHWARI SRIDHARA
02/24/2011
I concur with the recommendations of the reviewer