U.S. Department of Health and Human Services
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Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation
Clinical Studies

NDA/BLA	NDA 201-277
Serial Number:	Pediatric Efficacy Supplement 008
Drug Name:	Gadavist® (Gadobutrol) Injection
Indication(s):	To expand the pediatric indication of Gadavist® (gadobutrol) Injection to include children 0-<2 years of age.
Applicant:	Bayer HealthCare Pharmaceuticals
Date(s):	NDA Submission: June 30, 2014 PDUFA Date:, December 30, 2014
Review Priority:	Priority
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Keywords: Post marketing, contrast enhanced, MRI, pediatric

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1. EXECUTIVE SUMMARY

Gadavist® (gadobutrol) Injection was approved by FDA on March 14, 2011 for intravenous use in diagnostic Magnetic Resonance Imaging (MRI) in adults and children (2 years of age and older) to detect and visualize areas with disrupted blood brain barrier (BBB) and/or abnormal vascularity of the central nervous system. Per agreement with the Division in pre-sNDA meeting comments of April 11, 2014, the sponsor submitted a supplemental New Drug Application (sNDA 201-277) (Final Report (PH-37277**))** toward fulfillment of the post-marketing requirement to expand the use for gadobutrol to children 0-< 2 years of age. This submission fulfills a Post Marketing Requirement (PMR) from the original approval of March 14, 2011 to study the product in pediatric patients 0-2 years of age.

This was an open-label, multi-center, prospective study with the primary objective to evaluate the PK of gadobutrol in plasma at the standard dose of 0.1 mmol/kg BW in pediatric subjects aged < 2 years (term neonates to toddlers 23 months of age inclusive).

The secondary objectives were the evaluation of efficacy and safety. Efficacy was evaluated as a secondary analysis by single onsite readers following the administration of gadobutrol at the standard dose of 0.1mmol/kg BW. The investigators qualitatively assessed the unenhanced image sets and the Combined (unenhanced + enhanced) image sets separately. The efficacy variables were evaluated descriptively. There was no comparison planned. Table 1 shows that the performance of Combined MRI is numerically better than Unenhanced MRI in several efficacy measures, but statistical inference cannot be drawn due to small sample size in this study.

Table 1: A Summary of Efficacy Variables (Secondary)

Variable	Unenhanced MRI (n=44)	Combined MRI (n=44)
Basic technical adequacy (Excellent - clearly visualized regions)	90.9% (40/44)	93.2% (41/44)
Contrast quality "good" or "excellent"	--	97.7% (43/44)
Degree of contrast-enhancement "good" or "excellent"	--	93.2% (41/44)
Border delineation of the lesions/vessels ratings "good" or "excellent"	75.0% (33/44)	97.7% (43/44)
Lesions detected	75.0% (33/44)	75.0% (33/44)
Lesion characterization "good"	61.6% (27/44)	97.7% (43/44)
Diagnoses		
no lesions/normal	22.7% (10/44)	25.0% (11/44)
congenital disease/ syndrome	13.6% (6/44)	18.2% (8/44)
other diagnoses	40.9% (18/44)	29.6% (13/44)
Confidence in diagnosis	86.4% (33/38)	97.7% (43/44)
A change in the diagnosis		11.4% (5/44)
A change in subject management		18.2% (8/44)

2. INTRODUCTION

Magnetic Resonance Imaging (MRI) has been used to provide reliable medical imaging information in subjects with vessel abnormalities and parenchymal organ disorders, e.g. neurological disorders for more than 30 years. The main purpose of MRI is to display and to demarcate focal pathologies of the central nervous system (CNS) and other body regions. It is well known that the use of contrast agents improves the detection and visualization of specific features of such pathologies.

2.1 Overview

Gadovist 1.0 / Gadavist is an extracellular contrast agent for enhancement of MRI. Gadobutrol has been approved in in more than 70 countries, including the European Union (EU) countries, Canada, Australia, South Africa, Mexico, New Zealand, Turkey, and several Eastern European and Asian countries for contrast enhancement in MRI of the arterial vasculature and contrast-enhanced (CE) MRI of the liver and kidneys. In Switzerland as well as in some other countries outside the EU, such as Canada and Australia, gadobutrol was approved for pediatric patients aged 2 - 17 years for all indications approved for adults in 2009 / 2010.

2.1.1 Regulatory History

The sponsor's NDA submitted on May 13, 2010 resulted in an approval on March 14, 2011 for the following indications and usage:

Gadavist is a gadolinium-base contrast agent indicated for intravenous use in diagnostic MRI in adults and children (2 years of age and older) to detect and visualize areas with disrupted blood brain barrier (BBB) and/or abnormal vascularity of the central nervous system and/or abnormal vascularity of the central nervous system.

Gadavist (gadobutrol) Injection was also approved earlier for MRI of the breast to assess the presence and extent of malignant breast disease.

Per agreement with the Division in pre-sNDA meeting comments of April 11, 2014, the sponsor submitted a supplemental New Drug Application (sNDA 201-277) supplement 008 toward fulfillment of the post-marketing requirement to expand the use for gadobutrol to children 0-< 2 years of age.

2.1.2 Doses

The standard dose of 0.1 mmol/kg BW was used in pediatric subjects aged <2 years (term newborn infants to toddlers 23 months of age inclusive).

2.1.3 Identified Studies in the review

This sNDA is supported by a single pharmacokinetic (PK) and safety study #91741 (Final Report (PH-37277**))** of gadobutrol in children 0-<2 years of age.

2.1.4 Analysis Populations

The study was conducted in 9 centers in Canada, Germany and the USA between May 2012 and November 2013 and evaluated term neonates to toddlers 23 months of age inclusive undergoing a CE-MRI with intravenous injection of 0.1 mmol/kg BW gadobutrol for any body-region.

Overall 47 subjects were enrolled and 3 subjects failed screening because they did not meet the eligibility criteria. They did not receive the study drug and did not complete the study.

- **Safety Analysis Set (SAF):** A total of 44/47 subjects (93.6%) were administered gadobutrol, completed the study medication and were valid for the safety analysis set (SAF).

- **Full Analysis Set (FAS):** A total of 44/47 subjects (93.6%) were valid for the full analysis set (FAS).

- **Per-protocol Set (PPS):** The protocol defined population had 43 subjects as 1 subject had a major protocol deviation.

A total of 9 subjects were less than 2 months of age and were included in all 3 analysis sets (FAS, SAF and PPS).

2.2 Data Sources

The sNDA was submitted as an electronic submission, and is available in darrts.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Summary data were provided related to the qualitative evaluation of the secondary efficacy data. A qualitative evaluation of all mandatory images was performed by the investigator at each study center. Assessment was provided for the unenhanced image sets and for the combined (unenhanced and enhanced) image sets separately. Assessment was performed qualitatively within body regions/target organs of interest e.g. within the brain, the spine, the liver, the kidneys, the vessels, etc. using a predefined scoring system for certain parameters. All results and scores were recorded in the eCRF for unenhanced MRI and combined unenhanced and enhanced MRI.

These qualitative assessments by a single on-site investigator at each center has limitations and evaluations may be biased.

3.2 Evaluation of Efficacy

3.2.1 Study Design

Study #91741 (Report #PH-37277) was an open-label, multicenter, pharmacokinetic, and safety study in children (term newborn infants to 23 months of age) undergoing a contrast-enhanced MRI with an intravenous injection of 0.1 mmol/kg BW gadobutrol 1.0 M (Gadovist 1.0).

Only pediatric subjects without renal impairment (eGFR >80% of age "standard/mean" values) scheduled for routine CE-MRI of any anatomical area were enrolled in this study who were scheduled to undergo routine gadolinium enhanced MRI of any body region and able to comply with the following study procedures:

- Availability for 8 hours post-injection for PK blood sampling and for the safety follow-up assessments at 24 ± 4 hours post-injection

- Provide contact information for a follow-up telephone call at 7 ± 1 days post-injection

3.2.2 Objective

The primary objective of the study was to evaluate the pharmacokinetics (PK) of gadobutrol in plasma at the standard dose of 0.1 mmol/kg BW in pediatric subjects aged < 2 years (term neonates to toddlers 23 months of age inclusive).

The secondary objectives were the evaluation of efficacy and safety. Efficacy was evaluated as a secondary analysis following the administration of gadobutrol at the standard dose of 0.1 mmol/kg BW. The investigators qualitatively assessed the unenhanced image sets and the combined image sets separately. The efficacy variables were evaluated descriptively.

The focus of this review is the evaluation of the secondary efficacy variables.

3.2.5 Demographic and Baseline Characteristics

Study 91741 evaluated term neonates to toddlers 23 months of age inclusive undergoing a CE-MRI with intravenous injection of 0.1 mmol/kg BW gadobutrol of any body region. The study was conducted in 9 centers in Canada, Germany and the USA between May 2012 and November 2013.

Overall 47 subjects were enrolled and 3 subjects failed screening because they did not meet the eligibility criteria. They did not receive the study drug and did not complete the study.

The mean age of the children was 8.8 (± 7.1) months with a range of 0.2 – 23 months. A total of 9 subjects were in the range on 0-2 months and 35 subjects ≥ 2 months.

Mean weight at baseline was 7.7 kg (± 3.0) and mean height at baseline was 68.5 cm (± 11.5). The majority of subjects was White (40/44, 90.9%)

3.3 Results and Conclusions

A summary of the secondary efficacy variable results is as follows:

The **primary anatomical areas** (body regions, target organs) evaluated for MRI were brain (n=21 subjects), retroperitoneal area (n=7), head/neck (n=5), spinal cord (n=5), chest/thorax (n=2), pelvic area (n=2), abdomen, and lymphatic system (each n=1). Evaluation of the CNS body region (brain and spine) constituted 54.5% of the overall indications spontaneously referred to this study.

The **basic technical adequacy** of the images was “excellent” in the vast majority of subjects (i.e. clearly visualized regions) in both unenhanced MRI (40/44 subjects, 90.9%) and combined MRI (41/44 subjects, 93.2%).

Overall **contrast quality** was assessed as “good” or “excellent” in all but one subject (43/44, 97.7%) in combined MRI independent of the body region.

Lesions were detected in 33/44 subjects (75.0%) in both unenhanced and combined MRI. In the majority of subjects (29/4, 65.9%), 1 lesion was detected in both image sets; in 2/44 (4.6%) subjects, 2 lesions were detected in both image sets. In 1 subject with metastases of a left adrenal neuroblastoma, the number of lesions was not visualized with unenhanced MRI, but combined MRI showed 10 lesions.

The **degree of contrast-enhancement** in the combined MRI was "good" or "excellent" in 41/44 subjects (93.2%). In 3/44 subjects (6.8%), lesions/vessels were not enhanced (subjects were diagnosed with a structural malformation in the lung, a congenital disease/syndrome in the kidney, with metastases of a thoracic neuroblastoma in the liver).

Border delineation of the lesions/vessels showed higher ratings of "good" and "excellent" (43/44, 97.7%) in the combined MRI set compared to unenhanced MRI (33/44, 75.0%). At combined MRI, 1/44 (2.3%) subjects each was rated with "good" and "no" border delineation compared to 6/44 (13.6%) subjects with "moderate" and 5/44 (11.4%) with "no" in unenhanced MRI.

Lesion characterization evaluated as "good" was higher at combined MRI (43/44, 97.7%) compared to unenhanced MRI (27/44, 61.6%). At combined MRI, there were no subjects with "moderate" and 1/44 (2.3%) with "poor" lesion characterization assessed compared to 11/44 (25.0%) subjects with "moderate" and 6/44 (13.6%) subjects with a "poor" assessment in unenhanced MRI.

Diagnoses reported for unenhanced MRI and combined MRI diagnoses were mainly no lesions/normal (unenhanced: 10/44, 22.7%; combined: 11/44, 25.0%), congenital disease/ syndrome (unenhanced: 6/44, 13.6%; combined: 8/44, 18.2%), and other diagnoses (unenhanced: 18/44, 40.9%; combined: 13/44, 29.6%). Almost each subject had an individual diagnosis specified by the investigator.

In the majority of subjects (24/44, 54.6%), the combined image set allowed an **additional diagnostic gain**, i.e. the initial diagnosis was changed to an improved diagnosis. In 1 subject, the diagnosis changed to a new diagnosis. In 19/44 subjects (43.2%), the diagnosis remained unchanged.

Overall, the **confidence in diagnosis** assessed as confident and very confident was higher in the combined MRI (43/44 subjects, 97.7%) compared to unenhanced MRI (33/38 subjects, 86.4%). The diagnosis was rated as "not confident" in 1 subject in the combined MRI and compared to 6/44 (13.6%) subjects in unenhanced MRI. The one subject with the "not confident" finding had

this assessment in both the unenhanced and the combined MRI, while 5 subjects had an improved confidence in combined MRI.

A **change in subject management** was reported for 8/44 subjects (18.2%), whereas in 36/44 subjects (81.8%) the management remained unchanged from unenhanced MRI to combined MRI. The change in subject management was observed in the body regions retroperitoneal, brain, and pelvic area.

The most common reported **final diagnoses** were “congenital disease/syndrome”, “no lesions/ normal” (each 6/44, 13.6%), “malignant” lesions (4/44, 9.1%), and “other “(24/44, 54.5%).

A **change in the diagnosis** from unenhanced to combined MRI was reported in 5/44 subjects (11.4%). A change in the diagnosis from unenhanced MRI to final diagnosis was reported in 11/44 subjects (25.0%). A change in the diagnosis from combined MRI to final diagnosis was reported in 12/44 subjects (27.3%).

The results are given in the following Table 2:

Table 2: A Summary of Efficacy Variables (Secondary)

Variable	Unenhanced MRI (n=44)	Combined MRI (n=44)
Basic technical adequacy (Excellent - clearly visualized regions)	**90.9% (40/44)**	**93.2% (41/44)**
Contrast quality "good" or "excellent"	**--**	**97.7% (43/44)**
Degree of contrast-enhancement "good" or "excellent"	**--**	**93.2% (41/44)**
Border delineation of the lesions/vessels ratings "good" or "excellent"	**75.0% (33/44)**	**97.7% (43/44)**
Lesions detected	**75.0% (33/44)**	**75.0% (33/44)**
Lesion characterization "good"	**61.6% (27/44)**	**97.7% (43/44)**
Diagnoses		
no lesions/normal	**22.7% (10/44)**	**25.0% (11/44)**
congenital disease/ syndrome	**13.6% (6/44)**	**18.2% (8/44)**
other diagnoses	**40.9% (18/44)**	**29.6% (13/44)**
Confidence in diagnosis	**86.4% (33/38)**	**97.7% (43/44)**
A change in the diagnosis		**11.4% (5/44)**
A change in subject management		**18.2% (8/44)**

The performance of Combined MRI is numerically better than Unenhanced MRI in several efficacy measures, but statistical inference cannot be drawn due to small sample size in this study.

3.4 Evaluation of Safety

Safety data in 44 young children in this study are in line with the currently labeled risks derived from larger studies in older children and adults. Despite extensive post-marketing exposure to GBCAs no case of NSF has ever been identified in children ≤ 6 years. The details are available in the clinical report.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Results based on Gender, Race, Age, and Geographic Region were not reported due to the nature of data (pediatric patients < 2 years of age), efficacy evaluation being qualitative and secondary, 91% of the subjects being white, 20% of the subjects were less than 2 months of age and small sample sizes in various subgroups.

4.2 Other Special/Subgroup Populations

There were no special/subgroup populations identified.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The primary objective in this study was to evaluate the PK of gadobutrol in plasma at the standard dose of 0.1 mmol/kg BW in pediatric subjects aged < 2 years (term neonates to toddlers 23 months of age inclusive).

The secondary objectives were the evaluation of efficacy and safety. Efficacy was evaluated as a secondary analysis following the administration of gadobutrol at the standard dose of 0.1 mmol/kg BW. The investigators qualitatively assessed the unenhanced image sets and the Combined (unenhanced + enhanced) image sets separately. The efficacy variables were evaluated descriptively. There were no statistical issues in this study.

5.2 Conclusions and Recommendations

This sNDA contained a qualitative evaluation of the several efficacy measures which were secondary endpoints. There was no comparison planned. The results show that the performance of Combined (unenhanced + enhanced) MRI is numerically better than Unenhanced MRI in several efficacy measures, but statistical inference cannot be drawn due to small sample size in this study. However, the evidence in 44 young children less than 2 years of age in this study is in line with the larger studies in older children and adults. This reviewer concludes that the sponsor has met protocol defined objectives.

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/s/

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11/04/2014

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I concur with the primary reviewer.

THOMAS E GWISE
11/04/2014