

CLINICAL REVIEW

Application Type	Pediatric Supplemental New Drug Application
Application Numbers	NDA 201277 (b) (4) s008
Priority or Standard	Priority
Submit Dates	June 30, 2014
PDUFA Goal Date	December 30, 2014
Reviewer Name(s)	Anthony Fotenos, MD, PhD
Review Completion Date	
Established Name	Gadobutrol
Trade Name	Gadavist
Drug Class	Diagnostic magnetic resonance imaging gadolinium-based contrast agent
Applicant	Bayer HealthCare Pharmaceuticals
Formulation	1.0 M (604.72 g/L) solution
Dosing Regimen	0.1 mL/kg IV, followed by 5-10 mL saline flush, at rate of 1 mL/1-2 seconds
Indication(s)	For intravenous use in diagnostic magnetic resonance imaging to detect and visualize areas with disrupted blood brain barrier and/or abnormal vascularity of the central nervous system.
Intended Population(s)	Patients younger than age 2 years

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

We recommend approval of this eighth supplementary application to NDA 201277; specifically, that the central nervous system indication for Gadavist 0.1 mmol/kg be extended to include all pediatric patients (including term neonates).

1.2 Risk Benefit Assessment

Our recommendation is primarily based on integration of the sponsor's submitted preclinical, pharmacokinetic, and safety data; published accounts of postnatal renal development; and post-marketing experience with gadolinium-based contrast agents in pediatric patients younger than 24 months. In total, this evidence identifies no compelling reason why the favorable risk/benefit balance established as the basis of approval for Gadavist 0.1 mmol/kg in adults and older pediatric patients should not apply to pediatric patients younger than age 2 years.

1.3 Recommendations for Postmarket Risk Management Activities

The human kidney achieves its full complement of approximately one million nephrons by 36 weeks gestation, and it is reasonable to hypothesize that renally attributable safety risks associated with Gadavist may be higher in premature compared to term infants. It is also reasonable to hypothesize that regulatory approval for usage of Gadavist in term infants may lead to an increase in off-label usage in premature infants under uncommon circumstances when MR imaging with contrast is contemplated in this age group. In future quarterly safety updates and annual reports, in order to assess potential need for labeling clarification and/or additional study, we propose to request comment by the sponsor on any observed change in Gadavist usage amongst premature infants.

1.4 Recommendations for Postmarket Studies/Clinical Trials

We recommend updating to "fulfilled" the status of post-marketing requirement 1743-2. Specifically, study 91741 entitled, "Open-label, multicenter, pharmacokinetic, and safety study in children (term newborn infant 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)" fulfills requirement 1743-2. PH-36304 entitled, "Extended single dose toxicity study in neonatal (4 days old) rats" and PH-36683 entitled, "Repeated dose toxicity study in neonatal/juvenile rats" was found to fulfill requirement 1743-1 on November 9, 2012.

2 Introduction and Regulatory Background

On June 30, 2014, sponsor Bayer HealthCare Pharmaceuticals submitted a supplemental new drug application to expand its FDA-approved central nervous system (CNS) indication for Gadavist to include pediatric patients younger than age 2 years (hereafter also referred to as “young pediatric patients” and encompassing individuals born at 38 weeks gestation or older and alive less than 24 months per ICH E 11 “term newborn” and “infant/toddler” definitions). This document provides a primary clinical review of the sponsor’s application.

If approved for young pediatric patients, Gadavist will be the first gadolinium (Gd^{3+})-based contrast agent (GBCA) specifically marketable to this age group. The main reason to question use of GBCAs in young pediatric patients depends on understanding human postnatal renal development. This is because the most important safety risks associated with GBCAs can be divided conceptually into three categories, some of which depend on renal function: A) hypersensitivity reactions observed in a timeframe of minutes to hours post exposure; B) nephrogenic systemic fibrosis (NSF) observed in a timeframe of days to months; and C) the theoretical possibility of not-yet-observed long-term manifestations of gadolinium toxicity. Since renal impairment is the primary determinant of category B and likely also associated with category C, the direction and magnitude of renal function in young pediatric subjects compared to adult/older pediatric subjects is central to understanding relative risk and the overall risk/benefit balance for Gadavist in young pediatric patients.

Interestingly, discussion of postnatal glomerular development (the element of renal function most relevant for Gadavist) varies across the literature. For example, in a review on the, “Ontogeny of drug elimination by the human kidney,” Chen and colleagues write, “Presently, many believe that the clearance rate increases gradually after infancy, reaching functional adult levels in preschool years. This generally accepted belief is grossly erroneous; in fact, during preschool years the clearance rate of many drugs greatly exceeds adult rates” (Pediatr Nephrol 2006;21:160-168). Figure 1 illustrates the problem:

Figure 1: Postnatal development of glomerular filtration in relation to normalization method



Reviewer figure adapted from multiple published sources. *Top*: From Eur J Nucl Med Mol Imaging 2008;35:1669-1672, based on ⁵¹Cr EDTA blood sampling in 632 pediatric subjects ages 1 month to 16 years with normal kidney function on MAG3 imaging. *Middle*: From Pediatr Nephrol 2006; 21:160-168, based on AAPS PharmSci 2002;2(1):1-7, using serial mannitol sampling from 63 normal pediatric subjects ages 2 days to 12 years from 1949. *Bottom*: From Pediatr Nephrol 1991 5:5-11, based on data from 109 normal term and pre-term pediatric subjects ages 2 weeks to 12 years from seven publications between 1948 and 1975 using inulin and mannitol sampling. GFR = glomerular filtration rate.

Figure 1 shows how the answer to basic developmental questions, such as whether postnatal glomerular filtration rate (GFR) in infants is markedly (bottom panel) or mildly (middle panel) decreased compared to maximally functional levels, and whether maximally functional levels occur in pre-schoolers (middle panel), depends on the normalization method used to quantify GFR. Indeed, mean normal GFR is 26 mL/min/1.73m² for term newborns (UpToDate accessed 9/26/2014) and the bottom panel in Figure 1 shows how almost all normal pediatric subjects have GFR's < 60 mL/min/1.73m² during their first two months of life. Do normal pediatric subjects share the same risks as adult subjects with moderate (G3, defined as GFR 30-59 mL/min/1.73m²) and severe (G4, defined as GFR 15-29 mL/min/1.73m²) kidney disease? The dependence of ontogenical models on normalization method, published criticisms of body surface area (BSA) normalization (for example, Nephrol Dial Transplant 2009 24: 3593-3596 and Clin Physiol Func Imaging 2007 27:135-137), and the absence of dialysis from any list of normal developmental milestones all strongly suggest the answer is, "No." The clinical significance of an individual having <60 mL/min/1.73m² GFR is not the same in young pediatric compared to adult subjects.

Reviewer's summary comment: For any new GBCA indication in young pediatric subjects, the use of GFR cutoffs expressed in units normalized for BSA should be expressed in alternative non-normalized units/percentiles (eg, Figure 1 top panel) and/or qualitatively contextualized to avoid the misimpression that GFR < 60 mL/min/1.73m² has the same clinical significance in young pediatric compared to adult subjects.

2.1 Product Information

Gadavist belongs to the GBCA pharmaceutical class. Molecules of this class act as microscopic magnets to reduce local relaxation times, key physical tissue properties measured by magnetic resonance imaging (MRI). The contrast agent's registered trade name is Gadavist in the United States and Gadovist elsewhere. The active ingredient is gadobutrol. Other names include Gd-D03A-butriol, ZK 135079, and BAY 86-4875. Gadavist was originally approved by the FDA as a new molecular entity on March 14, 2011.

There are currently nine GBCAs approved for marketing in the United States, listed in order of original FDA approval, oldest first: Magnevist (1988), Prohance (1992), Omniscan (1993), Optimark (1999), Multihance (2004), Eovist (2008), Ablavar (2008), Gadavist (2011), and Dotarem (2013). GBCAs may be classified according to whether they are ionic or non-ionic; linear or macrocyclic; non-, weakly, or strongly protein-binding; and FDA-labeled as relatively higher or lower NSF-risk. Gadavist is macrocyclic, non-ionic, non-protein-binding, and relatively lower NSF-risk. Gadavist is the only GBCA formulated at a high (1.0 M) concentration.

Gadavist is currently indicated at a 1.0 M 1 ml/kg IV dose for use with MRI in adults and pediatric patients 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. The sponsor now proposes to expand this indication to include all pediatric patients (including term neonates), using the same dosing regimen.

2.2 Tables of Currently Available Treatments for Proposed Indications

No GBCA is currently FDA-approved for pediatric patients younger than age 2 years. Table 1 shows the pediatric approval of the GBCAs available for MRI of the CNS.

Table 1: Reviewer's tabulation of currently available contrast agents for MRI of the CNS

Proprietary Name	Nonproprietary Name	Approved for Pediatric Use
Magnevist	gadopentetate dimeglumine	Yes (age \geq 2y)
Prohance	gadoteridol	Yes (age \geq 2y)
Omniscan	gadodiamide	Yes (age \geq 2y)
Optimark	gadoversetamide	No
Multihance	gadobenate dimeglumine	Yes (age \geq 2y)
Dotarem	gadoterate meglumine	Yes (age \geq 2y)

Dotarem is approved for use in pediatric patients younger than age 2 years outside the United States. At a meeting of the FDA Center for Drug Evaluation and Research Medical Imaging Drugs Advisory Committee on February 14, 2013, focused on whether initial marketing approval for Dotarem should include pediatric patients younger than age 2 years, it was estimated that on the order of 20,000 patients per year in this age range currently receive contrast for MR imaging off-label in the United States. Based on survey results of pediatric radiology division leaders from 2010, it was estimated that the majority of pediatric patients receive relatively higher-NSF-risk agents (particularly Magnevist). Almost half of respondents also indicated that off-label doses higher than 0.1 mmol/kg were prescribed (Pediatri Radiol 2011 41:1271-1283).

2.3 Availability of Proposed Active Ingredient in the United States

Gadavist is the only marketed drug in the United States that contains gadobutrol.

2.4 Important Safety Issues With Consideration to Related Drugs

The package insert for Gadavist (and other GBCAs Multihance, Prohance, Eovist, Ablavar, and Dotarem associated with NSF at a relatively lower rate) carry a boxed warning quoted in the following indented text:

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities.

- The risk for NSF appears highest among patients with:
 - Chronic, severe kidney disease (GFR $<$ 30 mL/min/1.73m²), or
 - Acute kidney injury.
- Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (for example,

age > 60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.

The package insert for GBCAs associated with NSF at a relatively higher rate (Magnevist, Omniscan, and Optimark) carry the following boxed warning (difference highlighted in italics):

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities.

- *Do not administer [GBCA] to patients with:*
 - Chronic, severe kidney disease (GFR < 30 mL/min/1.73m²), or
 - Acute kidney injury.
- Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (for example, age > 60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 2 provides a timeline of the regulatory history surrounding pediatric use of Gadavist, based on the sponsor's summary and review of referenced regulatory database submissions.

Table 2: Reviewer's tabulation summarizing Gadavist's regulatory history

Date	Application	Description
07/15/1998	IND 56410	Original IND activation by Berlex
12/29/2003	IND 56410	IND reactivated by Berlex
04/04/2007	IND 56410	Bayer HealthCare Pharmaceuticals acquires Berlex
08/27/2007	IND 56410	End of Phase 2 agreement on design of phase II/III study 310788 of pediatric patients ages 2 to 17 years.
01/27/2011	NDA 201277	Clinical review of study 310788
02/15/2011	NDA 201277	Nonclinical review of neonatal rat study report PH-36304
03/14/2011	NDA 201277	Marketing approval for Gadavist's CNS indication in patients older than age 2 years, including pediatric post-marketing requirements (PMRs) for animal (1743-1) and human pharmacokinetic (1743-2) studies in patients younger than age 2 years, per the Pediatric Research Equity Act (PREA; 21 U.S.C. 355c)
04/08/2011	IND 56410	PMR 1743-2: design of pharmacokinetic/efficacy study 91741
07/27/2011	IND 56410	Clinical pharmacology agreement on study 91741 design
09/12/2012	NDA 201277	PMR 1743-1: preclinical review of neonatal rat repeat-dose study report PH-36683
11/09/2012	NDA 201277	PMR 1743-1 fulfillment letter
04/15/2014	NDA 201277	Pre-sNDA meeting response and meeting cancellation
06/30/2014	NDA 201277	Application for pediatric sNDA and fulfillment of PMR 1743-2 submitted

The FDA's approval letter of March 14, 2011 specifically described the sponsor's required pediatric assessments, quoted in the indented text, as follows:

- 1743-1. You must provide additional nonclinical (animal) data to support the safety of your product in the 0-23 month pediatric age group. These nonclinical data should be obtained from newborn to juvenile animals that model pediatric patients in this age group. The study will examine the safety of the product in newborn and neonatal animals, following a single dose and limited repeated dose administrations.
 - Final Protocol Submission: May, 2011
 - Study/Trial Completion: January, 2012
 - Final Report Submission: June, 2012
- 1743-2. Your study will examine patients 0-23 months of age who are referred for an MRI exam with contrast. A sufficient number of subjects will be studied to adequately characterize the pharmacokinetics of the product in this age group. At least 40 patients

will be evaluated in this study, and the study must include a sufficient number of subjects to adequately support the efficacy of Gadavist for central nervous system MRI.

- Final Protocol Submission: July, 2012
- Study/Trial Completion: March, 2014
- Final Report Submission: January, 2015

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Based on filing review August 12, 2014, the sponsor's application was found to be sufficiently complete to permit substantive review. The sponsor was notified August 26, 2014.

3.2 Compliance with Good Clinical Practices

The sponsor reports no deviation from the ethical principles detailed in the Declaration of Helsinki or specific ethical considerations and provisions for pediatric patients, as detailed in the International Conference on Harmonization document on clinical investigation of medicinal products in the pediatric population (E11).

3.3 Financial Disclosures

The sponsor reports adequate collection of financial disclosure forms and no disclosable information from all investigators and sub-investigators who enrolled study subjects.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

A Chemistry Manufacturing and Control (CMC) supplement to modify the syringe tip closure for Gadavist prefilled syringes was reviewed on 7/31/2013 and approved. A CMC supplement adding a 2 mL vial for patients less than 44 lbs was reviewed on 12/11/2013 and approved.

4.3 Preclinical Pharmacology/Toxicology

In PH-36304 and PH-36683, the sponsor reports three main positive findings in pediatric rats ages 4 to 24 days: 1) reversible renal tubular vacuolation (an iodine- and gadolinium-contrast-class-wide phenomenon); 2) incompletely reversible atrophic clear cell tubules; and 3) pediatric-specific, dose-dependent gadolinium brain deposition associated with transiently increased microglia. Based on preclinical review, the estimated no-observed-adverse-effect level was 4.9 times the maximum human dose.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Gadolinium can carry up to 7 unpaired electrons and thus forms a strong internal, induced magnetic field in the presence of an externally applied magnetic field. This magnetism forms the basis for Gadavist's mechanism of action as an imaging contrast agent in the 0.1 to 1 nm range of each of gadolinium atom. Specifically, Gadavist increases the variation in nuclear relaxation times imaged by MRI devices, a property referred to as relaxivity.

4.4.2 Pharmacodynamics

Gadavist is physiologically inert. Thus, from the perspective of an image reader, injected Gadavist highlights the hematological system. Its localization follows the course of blood from injection site to vascular circulation/extracellular space to urinary excretion. The localization of Gadavist in a single static image thus depends on the timing of image acquisition relative to bolus injection. The distribution of the Gadavist in the brain also provides diagnostic information regarding pathological disruption of the blood brain barrier.

4.4.3 Pharmacokinetics

Gadavist is non-metabolized and renally excreted with a clearance rate comparable to inulin. The mean terminal half-life for plasma clearance is 1.8 hours.

The only new human trial data submitted with this pediatric application comes from study 91741, in which 44 pediatric patients younger than age 2 years were injected with Gadavist. The primary endpoint is pharmacokinetic. The rationale for study 91741, consistent with PMR 1743-2, is that safety and efficacy have already been established for Gadavist in adult and older pediatric patients and can be extrapolated to younger pediatric patients if the primary pharmacokinetic and secondary imaging endpoints in younger pediatric patients do not substantially differ. Our clinical perspective on the primary pharmacokinetic endpoints is thus deferred for discussion of efficacy in section 6, below.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The sponsor's application reported on two pre-clinical studies and one clinical study, summarized in Table 3 below.

Table 3: Reviewer's tabulation of study reports submitted with application

Report Identifier	Study Title	Associated PMR
PH-36304	Extended single dose toxicity study in neonatal (4 days old) rats	1743-1
PH-36683	Repeated dose toxicity study in neonatal/juvenile rats	1743-1
PH-37807	Study 91741: Exploratory population pharmacokinetic analysis of gadobutrol (Gadovist) in the Phase 1 study in pediatric patients aged 0-23 months	1743-2
PH-37277	Study 91741: Open-label, multicenter, pharmacokinetic, and safety study in children (term newborn infant 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)	1743-2

The sponsor also submitted PH-37523, a report on post-marketing safety study 14823 focused on adult and older pediatric subjects and thus essentially outside the scope specific to evaluation of Gadavist usage in pediatric patients younger than age 2 years.

5.2 Review Strategy

Our review focused on safety data and the clinical relevance of primary pharmacokinetic data from study 91741, as well as the sponsor's summary of postmarketing experience and independent literature. Efficacy endpoints based on diagnostic imaging interpretation from study 91741 were neither designed nor statistically powered to guide regulatory decision-making on an independent basis. They were mainly interpreted as low-quality evidence speaking to the validity of extrapolating from higher quality evidence in adults. Sections of the review template only relevant to the original NDA were omitted.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The package insert for Gadavist currently indicates two uses, quoted in the following indented text:

1. Gadavist is a gadolinium-based contrast agent indicated 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.
2. Gadavist is indicated for intravenous use with MRI to assess the presence and extent of malignant breast disease.

The sponsor proposes the following change for the first CNS indication (change highlighted in italics):

Gadavist is a gadolinium-based contrast agent indicated for intravenous use in diagnostic magnetic resonance imaging (MRI) (b) (4)

6.1.1 Methods

Efficacy assessment relies on the report for study 91741, entitled, “Open-label, multicenter, pharmacokinetic, and safety study in children (term newborn infant 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)” and dated April 3, 2014 (PH-37277).”

The sponsor reports five inclusion and 18 exclusion criteria. Essentially, young pediatric patients were approached for study participation after clinical referral for MR imaging with contrast and regardless of indication. Though such permissive inclusion criteria potentially benefit study generalizability, the exclusion of subjects with estimated glomerular filtration rate (eGFR) < 80% of normal limits study generalizability. Table 4 shows the minimum eGFR required for Gadavist injection (right column). The sponsor reports that eGFR was calculated using the Schwartz formula, which requires height, age, and serum creatinine as inputs.

Table 4: Sponsor's minimum GFR requirements for young pediatric patients (from PH-37277 Table 7-4)

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As the source for this table, the sponsor cites *Pediatr Nephrol* 1991: 5:5-11, which in turn cites a data book from 1974 without providing information on the sample or method of derivation. Nevertheless, these numbers appear grossly concordant with Figure 1 (bottom) and other independent sources (eg, *Eur J Nucl Med Mol Imaging* 2006:33:1477-1682).

Study participation involved four days of subject-investigator interactions: the first, for consent and history; the second and longest, for dose injection, MR imaging, and pharmacokinetic blood sampling at 15-60 min, 2-4 hours, and 6-8 hours post-injection, with exact sampling times within each time-block randomized per subject; the third, for assessing short-term adverse effects; and the last, seven days post-injection, for final safety assessment over the phone. At four weeks, investigators completed a form indicating "final diagnosis" presumably on the basis of available clinical information at the time.

For study 91741, clinically relevant endpoints based on image interpretation were secondary. The data consisted of investigator survey item selections on questions referring to image technical adequacy, post-drug image contrast quality, lesion detection, lesion/vessel contrast, lesion/vessel border delineation, lesion/vessel morphology, and lesion/vessel diagnosis. The methods for experimentally controlling image interpretation and survey item selection permitted considerable variability and bias. For example, MR acquisition sequences and sequence parameters could vary between subjects and study sites, with only a minimum set of sequences pre-specified per anatomical site. Investigators were all board-certified radiologists, responsible for completing separate semi-quantitative pre-drug and combined pre- and post-drug (hereinafter referred to as "paired") case report forms at the same time they were responsible for generating narrative radiology reports for patient care, requiring integration of pre- and post-drug images. Study investigators were aware of the purpose of the study, the identity of A vs A+B experimental comparators (available contemporaneously), and the role each comparator played in the study design when completing case report forms (also available contemporaneously). Only a single investigator interpreted each subject's images.

For reference, the sponsor's complete eligibility criteria; schedule of procedures; and image interpretation survey questions/items are quoted in the indented blocks and Table 5, below:

Inclusion Criteria

1. Aged < 2 years (term newborn infants to toddlers 23 months of age inclusive) at the time of gadobutrol injection
2. Scheduled to undergo routine gadolinium-enhanced MRI of any body region
3. Signed and dated informed consent of the legal representative(s)
4. Able to comply with the study procedures such as availability at the study center for 8 hours after the MRI examination for PK blood sampling and for safety assessments at 24 ± 4 hours after the administration of gadobutrol
5. Their legal representative(s) was/were able to provide contact information for a follow-up telephone call at 7 ± 1 days post-injection

Exclusion Criteria

1. Clinically unstable subjects, e.g. subjects in whom fluctuations in safety parameters was observed during the study period due to underlying disease and/or treatment regimens such as polytrauma subjects
2. Subjects who had a change in chemotherapy ≤ 48 hours prior to and up to 24 hours after gadobutrol injection
3. Any planned intervention during the study and up to 24 hours after gadobutrol injection (excluding lumbar puncture)
4. Subjects who received or were planned to receive any investigational product within 48 hours before gadobutrol injection or during study participation
5. Subjects who received or were planned to receive any other contrast agent within 48 hours prior to gadobutrol injection or up to 24 hours after gadobutrol injection
6. Subjects with contraindication for MRI such as iron metal implants (e.g. aneurysm clips)
7. History of anaphylactoid or anaphylactic reaction to any allergen including drugs and contrast agents
8. Severe inborn or acquired heart rhythm anomalies
9. Congenital long QT syndrome or family history of congenital long QT syndrome
10. Any concomitant medication known to prolong the QT interval
11. Congenital heart defect or higher degree heart block
12. Uncorrected hypokalemia
13. Subject with known and clinically relevant deviations of available clinical laboratory parameters from reference ranges (e.g. more than 3 times upper limit of reference range), in particular with regard to liver/renal function and blood coagulation
14. Subject with renal insufficiency of any intensity, i.e. eGFR < 80% of age adjusted normal value calculated based on the Schwartz formula
15. Acute renal failure of any intensity, either due to hepato-renal syndrome or occurring in the peri-operative liver transplantation period
16. Previous participation in this study
17. Close affiliation with the study center, e.g. a close relative of the investigator or his/ her designee
18. Pediatric subject in institutionalized care (most vulnerable population)

Image interpretation survey questions/items

- Anatomical area evaluated (select 1 of 9, pre/paired)
 - brain
 - spine
 - head/neck
 - heart
 - thorax
 - abdomen
 - pelvic area
 - retroperitoneal area
 - musculoskeletal
- Basic technical adequacy for diagnosis (select 1 of 4, pre + paired)
 - region visualized with artifacts compromising quality and interpretability of images
 - only partial evaluation of images possible, region not covered adequately anatomically
 - region visualized with artifacts, partially compromising image quality but evaluation and diagnosis still possible
 - region clearly visualized, excellent quality
- Assessment of contrast quality (select 1 of 5, post)
 - none (eg, in case of non-enhancing vessel)
 - poor
 - moderate
 - good
 - excellent
- Presence of pathology (select 1 of 2, pre + paired)
 - yes
 - no
- Degree of contrast-enhancement in lesion or vessel (select 1 of 4, pre + paired)
 - no, lesion or vessel is not enhanced
 - moderate, lesion or vessel is weakly enhanced
 - good, lesion or vessel is clearly enhanced
 - excellent, lesion or vessel is clearly and brightly enhanced
- Border delineation of lesion or vessel (select 1 of 4, pre + paired)
 - none, no or unclear delineation of the boundary between the lesion or vessel and the surrounding tissue
 - moderate, some aspects of border delineation covered
 - good, almost clear delineation, but not complete on relevant slices
 - excellent, clear and complete delineation
- Visualization of lesion-internal morphology (lesion characterization) or homogeneity of vessel enhancement (select 1 of 3, pre + paired)
 - poor, the structure and internal morphology of the lesion or vessel is poorly visible

- moderate, the structure and internal morphology of the lesion or vessel is visible but sufficient information cannot be obtained
- good, the structure and internal morphology of the lesion or vessel is sufficiently visible for diagnostic purposes
- Diagnosis (select 1 of 58, pre + paired) and 4-week “final” diagnosis
 - brain - malignant brain lesion
 - brain - benign brain lesion
 - brain - brain malformation
 - brain - brain stroke (infarction / hemorrhage)
 - brain - CNS inflammation
 - brain - demyelinating disease of the brain
 - spine - malignant spinal cord lesion
 - spine - benign spinal cord lesion
 - spine - spinal cord malformation
 - spine - spinal chord trauma
 - spine - demyelinating disease of the spine
 - head / neck - malignant head / neck lesion
 - head / neck - benign head / neck lesion
 - head / neck - head / neck malformation
 - head / neck - head / neck inflammation
 - cardiac / heart - congenital heart malformation
 - cardiac / heart - cardiac vasculature malformation
 - cardiac / heart - myocarditis
 - cardiac / heart - cardiac ischemia
 - chest / thorax - malignant lung lesion
 - chest / thorax - benign lung lesion
 - chest / thorax - lung inflammation
 - abdomen - liver - malignant liver lesion
 - abdomen - liver - benign liver lesion
 - abdomen - liver - biliary tract malformation
 - abdomen - spleen - malignant splenic lesion
 - abdomen - spleen - benign splenic lesion
 - retroperitoneal - kidney - malignant renal lesion
 - retroperitoneal - kidney - benign renal lesion
 - retroperitoneal - kidney - renal malformation
 - retroperitoneal - adrenal gland - malignant adrenal gland lesion
 - retroperitoneal - adrenal gland - benign adrenal gland lesion
 - pancreas - pancreatic malformation
 - pancreas - pancreatitis
 - pancreas - malignant pancreatic lesion
 - pancreas - benign pancreatic lesion
 - pelvic area – reproductive organs - malignant ovarian lesion
 - pelvic area – reproductive organs - benign ovarian lesion
 - pelvic area – reproductive organs - ovarian torsion
 - pelvic area – reproductive organs - malignant testes lesion

- pelvic area – reproductive organs - benign testes lesion
- pelvic area – reproductive organs - testes torsion
- pelvic area – reproductive organs - genital malformation
- lower urinary tract - malignant bladder lesion
- lower urinary tract - benign bladder lesion
- lower urinary tract - urinary bladder malformation
- musculoskeletal - malignant bone lesion
- musculoskeletal - benign bone lesion
- musculoskeletal - malignant soft tissue lesion
- musculoskeletal - benign soft tissue lesion
- lymphatic system - malignant lymph node lesion
- lymphatic system - benign lymph node lesion
- MRA / vessels - vascular malformation
- MRA / vessels - vascular stenosis
- metastases - metastatic lesion
- not assessable
- no lesion / abnormality (normal)
- other – specify
- Additional diagnostic gain by the contrast-enhanced image set (select 1 of 3, post)
 - initial diagnosis unchanged
 - initial diagnosis changed – improved, ie more specific
 - initial diagnosis changed – new diagnosis
- Confidence in diagnosis (select 1 of 3, pre + post)
 - very confident
 - confident
 - not confident

Table 5: Sponsor's schedule of procedures (from final study protocol Table 7-1)

Assessment / procedure	Baseline visit (≤24 h pre-injection)	Immediately pre-injection ^a	Injection	Immediately post-injection	Immediately post MRI	Post MRI (15 – 60 min post-injection)	Post MRI (2 - 4 h post-injection)	Post MRI (6 - 8 h post-injection)	24±4 hours post-injection	7±1 days post-injection telephone contact ^f
Informed consent ^b	•									
Inclusion / exclusion criteria	•									
Demographic data	•									
Referral diagnosis	•									
Medical history	•									
Physical examination	•								•	
Adverse events	Continuous assessment from signing the informed consent until follow-up telephone contact									
Vital signs ^c	•	•			• ^d		•		•	
eGFR ^e		•								
Physical check ^f				•	•		•			
Blood sample for safety parameters	• ^g								•	
Blood sample for PK parameters ^h						• ^h	• ^h	• ^h		
Pulse oximetry and cardiac rhythm monitoring ⁱ		•		•	•					
Concomitant medications	•	•					•		•	• ⁱ
Gadobutrol injection			•							
MRI		•		•						

Reviewer's summary comments. 1) We note that the sponsor's eligibility criteria allow for non-CNS indications, meaning the overlap between adult/established (CNS) and pediatric/extrapolated (CNS and non-CNS) study populations is only partial. However, in view of the primary pharmacokinetic endpoint, tradeoffs involved in pediatric research, and the circulatory mechanism of GBCAs, we do not believe these population differences substantially limit the validity of extrapolation. 2) Routine clinical practice will likely not reflect sponsor's operational definition of renal insufficiency for study exclusion, reflecting ongoing controversy/challenge in the field around how best to quantify postnatal glomerular function. 3) Methodological deficiencies substantially limit our ability to interpret the sponsor's secondary efficacy endpoints related to image interpretation.

6.1.2/3 Demographics/Subject Disposition

The sponsor reports nested subject groups of size n=47 (referred), n=44 (injected), and n=43 (injected per-protocol). Of the n=47 group, the sponsor problematically reports one subject (SID 10020008, age 18.4 months) was excluded for being older than 24 months. Two subjects (age 7 and 10.4 months) were excluded for having eGFR values < 80% normal. All in the n=44 group were injected with Gadavist. Of the n=44 group, one subject (age 21 months) should have been injected with a dose of 1.1 mL, but instead received a dose of 0.11 mL. The n=43 group was used for the primary pharmacokinetic analysis of efficacy and the n=44 group was used for the safety and secondary efficacy analysis.

Members of the n=44 group ranged in ages from 0.2 to 23 months; assuming a 30-day month, the youngest subjects were 6-day-olds. By design, the age distribution was non-uniform, with 11 subjects 2 months or younger (and 9 younger than 2 months). Nine investigators recruited

subjects across three countries, mostly Germany (32), but also the United States (8) and Canada (4). Forty of the 44 subjects (91%) were white. Thirty-one (70%) were referred for MR imaging of the brain, head/neck, or spine, consistent with the approved CNS indication; the remainder were referred for body (13) or musculoskeletal (1) imaging. Two (age 7 and 10 months) had eGFR values below the inclusion criteria cut-offs shown in Table 3; nevertheless, these two subjects were included in the safety and efficacy analyses. Overall, of the 47 subjects referred for MRI, 4 (9%) had eGFR values below the sponsor's 80%-normal cutoff.

For reference, Table 6 provides the sponsor's tabular demographic summary of the n=44 group.

Table 6: Sponsor's tabular demographic summary (from PH-37277 Table 8-3)

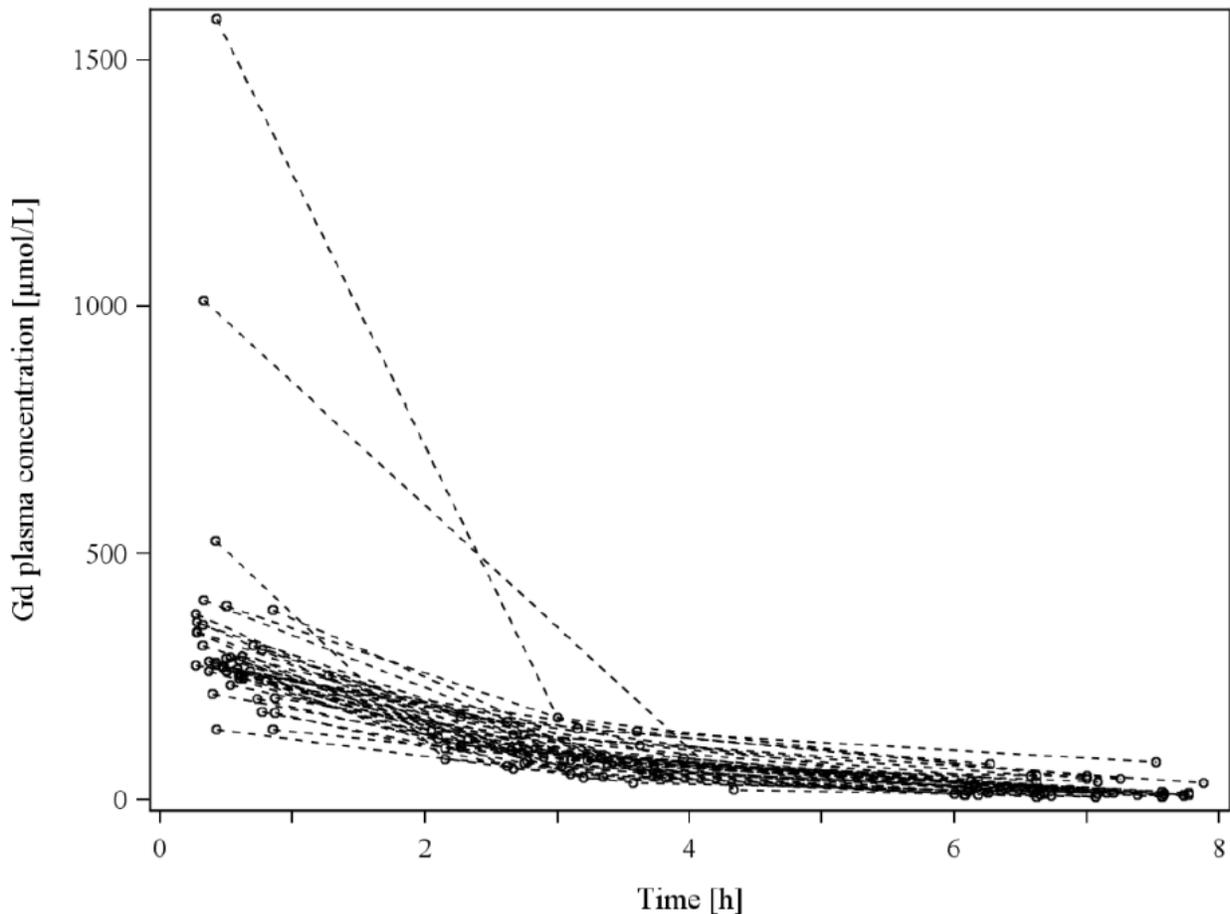
	Total N=44 (100%)
Sex (n [%])	
Male	26 (59.1%)
Female	18 (40.9%)
Race (n [%])	
White	40 (90.9%)
Black or African American	2 (4.5%)
Not reported	1 (2.3%)
Multiple	1 (2.3%)
Ethnicity (n [%])	
Not Hispanic or Latino	39 (88.6%)
Hispanic or Latino	4 (9.1%)
Not reported	1 (2.3%)
Age all subjects (months)	
n	44
Mean (SD)	8.8 (7.1)
Range (Min - Max)	0.2 - 23.0
Median	7.0
Baseline Weight (kg)	
n	44
Mean (SD)	7.7 (3.0)
Range (Min - Max)	2.8 - 14.2
Median	7.4
Baseline Height (cm)	
n	44
Mean (SD)	68.5 (11.5)
Range (Min - Max)	49.0 - 91.5
Median	68.8

Reviewer's summary comment: No major deficiency is identified involving demographics or subject disposition in study 91741.

6.1.4 Analysis of Primary Endpoints

The primary endpoints of the sponsor's application are pharmacokinetic. Accordingly, Figure 2 shows the sponsor's graph of measured plasma gadolinium concentration in relation to time post injection.

Figure 2: Sponsor's graph of measured plasma gadolinium (Gd) concentration in relation to time post injection (from PH-37807 Figure 11-1)

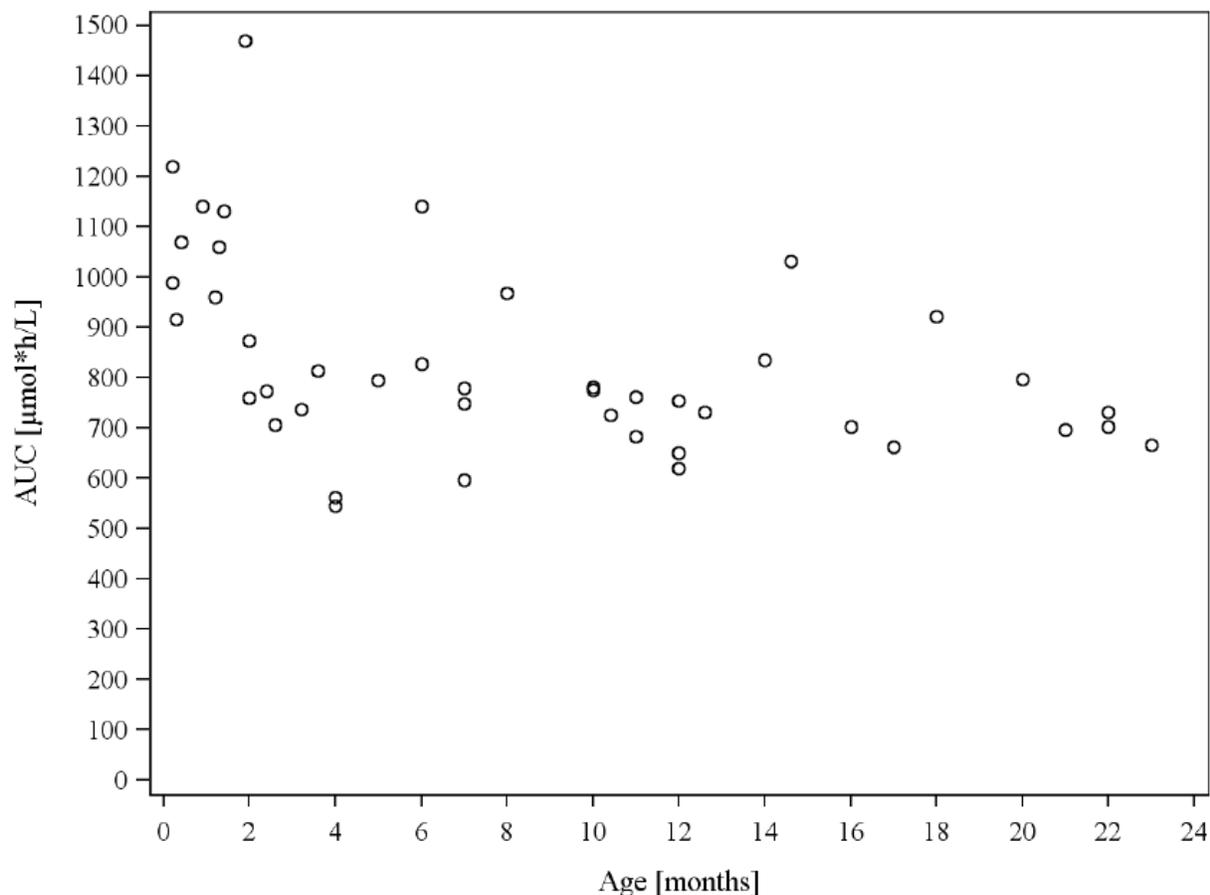


Each line represents an individual subject and connects three measured points derived from blood samples drawn per subject between 0-2, 2-4, and 4-6 hours post injection.

Figure 2 makes clear that the measured initial gadolinium concentrations of two subjects (age 4 and 6 months) were extremely high relative to the rest of the n=44 group. In at least one of these subjects, in response to an information request, the sponsor confirmed that only a single catheter was in place for both Gadavist injection and blood sampling, in support of a methodological (not physiological) explanation.

These two outlying measurements were thus excluded from the pharmacokinetic conversion of individual gadolinium plasma concentrations into the pivotal result to inform dosing: the sponsor's graph of area-under-the-curve (AUC) for Gadavist in relation to age, shown in Figure 3.

Figure 3: Sponsor's graph of area-under-the-curve (AUC) for Gadavist in relation to age (from PH-37807 Figure 11-5)



Each point represents a measurement-derived estimate of an individual's total exposure to Gadavist, integrating from injection to complete excretion.

Figure 3 suggests that Gadavist exposure is mildly (~30%), not markedly, elevated between months 0-2 compared to months 2-23, a plateau-like period of minimal change.

Indeed, placing the plateau-like period of Gadavist clearance between ages 2 to 23 months in the context of previously reviewed pharmacokinetic data from pediatric subjects ages 2 to 17 years (study 31078) supports the concept of a super-normal period for glomerular filtration during pre-school years (as previously discussed, see Figure 1B). For example, the sponsor reports median AUC is 1070 $\mu\text{mol}\cdot\text{h/L}$ for ages younger than 2 months (n=9), 751 $\mu\text{mol}\cdot\text{h/L}$ for ages 2 to 23

months (n=34), and 1167 $\mu\text{mol}\cdot\text{h}/\text{L}$ for ages 12 to 17 years (n=46). In units of hours for half-life, the corresponding median age-group values are $t_{1/2} = 2.6, 1.5,$ and $1.7,$ respectively. For reference, Table 7 shows the sponsor's complete tabulation of measured PK values by age-group for pediatric patients ages 0 to 17 years.

Table 7: Sponsor's comprehensive summary of measured PK values by age-group for pediatric patients (from PH-37807 Table 11-4)

Parameter	All (0 - < 2 years) a, b	0 - < 2 months a, b	$\geq 2 - 23$ months a, b	All (2 - 17 years) a, c	2 - 6 years a, c, d	7 - 11 years a, c, d	12 - 17 years a, c, d
	N=43	N=9	N=34	N=130	N=45	N=39	N=46
CL/kg [L/h/kg]	0.128 (0.0666, 0.184)	0.0920 (0.0666, 0.109)	0.133 (0.0870, 0.184)	0.10 (0.05, 0.22)	0.13 (0.08, 0.22)	0.10 (0.05, 0.17)	0.09 (0.05, 0.11)
V_{ss}/kg [L/kg]	0.277 (0.236, 0.409)	0.330 (0.311, 0.409)	0.267 (0.236, 0.344)	0.20 (0.09, 0.29)	0.24 (0.14, 0.29)	0.19 (0.14, 0.23)	0.18 (0.09, 0.25)
AUC [$\mu\text{mol}\cdot\text{h}/\text{L}$]	776 (544, 1470)	1070 (916, 1470)	751 (544, 1140)	999 (397, 2163)	815 (397, 1283)	969 (590, 2163)	1167 (905, 2017)
$t_{1/2}$ [h]	1.62 (1.16, 3.37)	2.63 (2.34, 3.37)	1.46 (1.16, 2.16)	1.69 (1.17, 2.62)	1.75 (1.28, 2.32)	1.61 (1.17, 2.62)	1.65 (1.36, 2.33)
MRT [h]	2.18 (1.57, 4.68)	3.60 (3.17, 4.68)	1.97 (1.57, 2.98)	1.94 (1.03, 3.37)	1.88 (1.07, 2.85)	1.83 (1.03, 3.37)	2.03 (1.50, 3.00)

Parenthesis contain 5th through 95th percentile ranges; central values represent medians.

In contrast to this pharmacokinetic evidence supporting a non-linear developmental model for Gadavist clearance/exposure, estimates for plasma concentration at 20 (C_{20}) and 30 (C_{30}) minutes suggest a mildly up-sloping developmental trajectory. These plasma concentration values are important because they represent a clinically reasonable surrogate for the magnitude of image contrast added by drug injection. For example, the sponsor reports C_{20} estimates of 313 $\mu\text{mol}/\text{L}$ for ages younger than 2 months, 341 $\mu\text{mol}/\text{L}$ for ages 2 to 23 months, and 518-523 $\mu\text{mol}/\text{L}$ for ages 12 to 17 years. These figures suggest the magnitude of image contrast added by drug injection may be somewhat less in young pediatric patients compared to adult and older pediatric patients, despite overlap between age groups in terms of percentile range. Together, the combined pharmacokinetic data suggest that the Gadavist dose of 0.1 mL/kg in young pediatric patients represents a reasonable compromise between two clinically competing interests: one, in terms of safety/AUC, potentially favoring a lower dose and the other, in terms of efficacy/concentration, potentially favoring a higher dose.

Reviewer's summary comment: Sponsor's primary pharmacokinetic endpoints support extrapolation of benefit that is similar or reduced in young pediatric patients compared to the benefit at developmental maturity. Sponsor's primary pharmacokinetic endpoints support extrapolation of risk that is similar or mildly increased in pediatric patients younger than 2 months and similar or mildly decreased in pediatric patients ages 2 to 23 months compared to the risk at developmental maturity. In any case, the clinical meaningfulness of any true risk differences is likely less than the range spanned for currently indicated uses in older patients with $e\text{GFR} > 60 \text{ mL}/\text{min}/1.73\text{m}^2$. We conclude that the extrapolated balance of benefit-to-risk remains acceptable and optimal or near-optimal for Gadavist 0.1 mL/kg in young pediatric patients, favoring extension of the approved CNS indication to this age group.

6.1.5 Analysis of Secondary Endpoints

We have little confidence making independent inferences about efficacy for Gadavist in young pediatric patients on the basis of the sponsor's reported secondary imaging interpretation endpoints, given the methodological deficiencies discussed above in section 6.1.1. The reported results we find least problematic pertain to investigators' multiple-choice selections of descriptions for imaging border delineation and morphology, briefly summarized below.

Investigators selected the best imaging descriptor "Excellent, clear and complete delineation" under the heading "Border delineation of lesions/vessels" on pre-contrast images for 24 (55%) of 44 of subjects. In reference to the paired pre- and post-drug images, investigators selected the same best descriptor for 42 (95%) of 44 subjects.

Investigators selected the best imaging descriptor, "Good, the structure and internal morphology of the lesion or vessel is sufficiently visible for diagnostic purposes" under the heading "Visualization of lesion-internal morphology (lesion characterization) or homogeneity of vessel enhancement" on pre-contrast images for 27 (62%) of 44 subjects. In reference to the paired pre- and post-drug images, investigators selected the same best descriptor for 43 (98%) of 44 subjects.

Reviewer's summary comment: In the context of more definitive adult efficacy and pharmacokinetic surrogate (ie, plasma concentration) data, sponsor's limited secondary endpoints based on imaging interpretation are not inconsistent, favoring extrapolation of a diagnostic benefit in terms of improved lesion visualization for Gadavist 0.1 mL/kg to young pediatric patients.

7 Review of Safety

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

As of February 26, 2014, the sponsor reports that 6330 subjects have been exposed to Gadavist across 41 phase II-IV studies; this number is increased from the previously reviewed sample size of 5748. Of these 6330 study subjects, 138 were pediatric patients ages 2 to 17 years (study 36304, previously reviewed) and 44 were pediatric patients younger than 24 months (study 91741).

7.1.2 Categorization of Adverse Events

The sponsor reports that adverse events (AEs) were categorized according to MedDRA version 16.1. Only events that were new starting between the period of injection and 72 hours (treatment

emergent adverse events, TEAEs) were categorized as AEs; later events were described separately. The sponsor categorized adverse drug events (ADRs) using a lower suspicion for causality for serious compared to non-serious AEs.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The demographics of the target population of central interest, young pediatric patients, is the same for safety as the n=44 study 91741 group reviewed for efficacy in section 6.1.2/3, above. Each subject was exposed to a single dose of 1.0 M Gadavist 0.1 mL/kg IV. The sponsor reports the mean volume of study drug administered was 0.75 mL. All subjects completed the full schedule of planned safety evaluations.

For comparison, whereas over 90% of the n=44 group of young pediatric patients were white, the sponsor reports that the overall n=6330 safety group was somewhat more diverse: 60% Caucasian, 30% Asian, 5.5% Hispanic, and 1.5% Black.

7.2.4 Routine Clinical Testing

For study 91741, the sponsor reports that safety testing included the following:

- Continuous assessment for adverse events
- At baseline visit \leq 24 hours pre-injection
 - Vital signs
 - Medical history and physical exam
 - Blood sampling
 - General chemistry (Na, K, Cl, BUN)
 - Hematology (Hct/Hgb, platelets, RBC, WBC)
 - Medication check
- At visit for injection/MRI
 - Vital signs
 - Blood sampling
 - Creatinine/eGFR
 - Pulse oximetry and cardiac rhythm monitoring
 - Medication check
- At 24-hour follow-up visit
 - Vital signs
 - Physical exam
 - Blood sampling
 - General chemistry (Na, K, Cl, BUN)
 - Hematology (Hct/Hgb, platelets, RBC, WBC)
 - Medication check

- At 7-day telephone contact
 - Medication check

Reviewer summary comments. 1) The design for routine laboratory testing did not include pre- and post-drug creatinine, lowering sensitivity in the event of asymptomatic Gadavist-induced kidney injury; 2) The delay between GBCA dosing and NSF ranges from days to years (median ~60 days), meaning post-marketing data is most sensitive for detection of NSF.

7.3 Major Safety Results

7.3.1 Deaths

The sponsor reports no deaths associated with study 91741 or any other study involving pediatric subjects.

7.3.2 Nonfatal Serious Adverse Events

The sponsor reports nonfatal serious adverse events (infected cyst and sedation-related respiratory failure) involving two subjects in study 91741, neither of which were attributed to Gadavist. After review of sponsor's narrative event descriptions, we agree with the sponsor's causal attribution.

7.3.3 Dropouts and/or Discontinuations

The sponsor reports no dropouts or discontinuations associated with adverse effects in study 91741.

7.3.4 Significant Adverse Events

For study 91741, the sponsor reports that one subject (age 23 months) experienced an episode of emesis during the injection/MR imaging visit. Event severity was categorized as mild and might have been caused by Gadavist or the routine sedation procedure required for MRI in this age group.

For comparison to the overall safety profile for Gadavist suggested by sponsor's analysis of the n=6330 group, 3.7% experience ADRs; nausea is the second most common (1.2%). Table 8 shows the sponsor's tabulated summary of all ADRs identified in $\geq 0.1\%$ of subjects.

Table 8: Sponsor's tabulated summary of all ADRs identified in $\geq 0.1\%$ of study subjects (from 2.7.4 Summary of Clinical Safety Table 2-6)

Adverse drug reaction	Incidence (%) (N = 6330 subjects)
Headache	1.5
Nausea	1.2
Dizziness	0.5
Dysgeusia	0.4
Feeling hot	0.4
Injection site reaction (various kinds) ^a	0.4
Vomiting	0.4
Rash (includes generalized, macular, papular, pruritic rash)	0.3
Erythema	0.2
Pruritus (includes generalized)	0.2
Dyspnea	0.1
Hypersensitivity/anaphylactoid reaction cumulative ^b	0.1
Paresthesia	0.1

Reviewer's summary comment. The safety data reported for Gadavist use in 44 young pediatric patients are in line with the currently labeled risks derived from larger studies in adult and older pediatric patients.

7.4 Supportive Safety Results

For study 91741, the sponsor reports no common or unexpected pre-to-post-drug change in measured laboratory parameters, vital signs, or cardiac rhythm, including no evidence for post-drug elevation in BUN.

8 Postmarket Experience

Between initial marketing in Switzerland in 1999 and February 26, 2014, the sponsor estimates that more than (b) (4) patients have received injections of Gadavist across the 104 countries in which the drug is approved and the 69 in which it is marketed. Market surveys suggest approximately (b) (4) doses have been administered off-label to young pediatric patients.

The sponsor reports that 18 deaths have occurred as a result of hypersensitivity/anaphylactoid reactions to Gadavist. No deaths have been attributed to the drug for patients younger than age 31 years.

The sponsor reports awareness of NSF in 11 individuals who were also exposed to Gadavist. No cases have been reported since 2009 and none have involved pediatric patients. The sponsor attributes likely causality to Gadavist (as opposed to other confounding GBCAs) in three cases.

The accumulated prevalence of NSF from any cause worldwide is approximately 500, including ~10 in pediatric patients, all age 6 years or older (Pediatr Nephrol 2014 29:1927-37).

In its sNDA, the sponsor included report PH-37523 on its phase IV study 14823 entitled, “GARDIAN, Gadovist in Routine Diagnostic MRI – Administration in Non-selected patients.” In this study, investigators from 17 countries completed forms on 23,708 patients who received MR imaging with Gadavist from Aug 7, 2010 through March 11, 2014. Investigators provided information on patient demographics, medical conditions including eGFR and dialysis, dosing and MRI indication, contrast quality, and adverse events observed during the period of MRI visit. The study protocol called for 90-day phone follow-up of patients with $eGFR \leq 60$ mL/min/1.73m² (n = 131); however, 71% were lost to follow-up. The sponsor classified patients younger than age 18 years as pediatric patients (n=1,142); however, only 4 were less than age 2 years, meaning there was essentially no overlap in the scope of the GARDIAN study and the sponsor’s supplementary application to extend the CNS indication for Gadavist to include pediatric patients younger than age 2 years. The sponsor reports that adverse drug reactions were observed in 170 patients (0.7%). These were fully concordant with currently labeled safety risks. Adverse reactions were similar between adult and pediatric patients age 2 to 18 years, except no serious adverse event was reported in the pediatric age range.

A published prospective study from Canada of safety and efficacy for Gadavist 0.1 mL/kg in 60 pediatric patients younger than age 2 years (including infants born prematurely) involved subject follow-up over a 4-month period (Magn Res Ins 2013 3:1-12). Exclusion criteria included “renal impairment” without specification of eGFR cutoffs. Zero adverse drug events were identified, adding to evidence of Gadavist safety in young pediatric patients. Using clinical, pathological, or follow-up imaging studies to establish the diagnostic reference standard for 57 subject-lesions, expected and observed accumulation of contrast was concordant in 24 of 24 “enhancing” lesions and 33 of 33 “non-enhancing” lesions, adding to evidence of Gadavist efficacy in young pediatric patients.

Reviewer’s summary comment. Despite extensive post-marketing exposure to GBCAs, no case of NSF has ever been identified in pediatric patients younger than age 6 years.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

- Section 5 Warning and Precautions
 - Add following sentence to 5.1 Nephrogenic Systemic Fibrosis

- No case of NSF has been identified in pediatric patients age ≤ 6 years [*see Use in Specific Populations (8.4)*]
- Section 8 Use in Specific Populations
 - Add the following sentence to 8.4 Pediatric Use
 - The safety and effectiveness of Gadavist have been established in pediatric patients born at or later than 38 weeks gestation based on imaging and pharmacokinetic data in 138 patients ages 2 to 17 years and 44 patients age younger than 2 years and extrapolation from adult data
 - Add the following sentence to 8.4 Pediatric Use
 - The safety and effectiveness of Gadavist have not been established in premature infants.
 - Add the following paragraph to 8.4 Pediatric Use
 - NSF risk.
 - No case of NSF associated with Gadavist or any other GBCA has been identified in pediatric patients younger than age 6 years. Pharmacokinetic studies suggest that clearance of Gadavist is similar in pediatric patients and adults, including pediatric patients younger than age 2 years. No increased risk factor for NSF has been identified in juvenile animal studies. Normal estimated GFR (eGFR) is around 30 mL/min/1.73m² at birth and increases to mature levels around 1 year of age, reflecting growth in both glomerular function and relative body surface area. Clinical studies in pediatric patients younger than age 1 year have been conducted in patients with the following minimum eGFR: 31 mL/min/1.73m² (ages 2 to 7 days), 38 mL/min/1.73m² (ages 8 to 28 days), 62 mL/min/1.73m² (ages 1 to 6 months), and 83 mL/min/1.73m² (ages 6 to 12 months).
- Section 14 Clinical Studies
 - Add the following paragraph to 14.1 MRI of the CNS
 - Pediatric patients
 - One study of 44 pediatric patients younger than age 2 years and another study of 138 pediatric patients ages 2 to 18 years supported extrapolation of adult CNS efficacy findings. For example, comparing pre-contrast vs paired pre- and post-contrast images, investigators selected the best of four descriptors under the heading “Visualization of lesion-internal morphology (lesion characterization) or homogeneity of vessel enhancement” in 27/44 (62%) vs 43/44 (98%) of patients younger than age 2 years and in 108/138 (78%) vs 111/138 (80%) of patients ages 2 to 18 years.

9.3 Advisory Committee Meeting

No advisory committee meeting was held for this pediatric supplement..

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/s/

ANTHONY F FOTENOS
11/07/2014

BRENDA Q YE
11/07/2014

I agree with Dr. Fotenos' assessment.