CLINICAL PHARMACOLOGY REVIEW

NDA:	**201-277; SE 08**
Submission Date:	**June 30, 2014**
Brand Name:	**Gadavist 1.0**
Generic Name:	**Gadobutrol Injection**
Formulations:	**Intravenous solution** **1.0 mmol Gd/mL (604.72 Gadavist mg/mL)**
Route of Administration:	**Intravenous injection**
Dosing Regimen:	**0.1 mmol/kg**
Indication:	**Gadavist is a gadolinium-based contrast agent indicated for intravenous use:** • **In diagnostic magnetic resonance imaging (MRI) in adults and children of all ages (including term neonates) to detect and visualize areas with disrupted blood brain barrier (BBB) and/or abnormal vascularity of the central nervous system.** • **For MRI of the breast to assess the presence and extent of malignant breast disease.**
Applicant:	**Bayer HealthCare Pharmaceuticals, Inc.**
Type of Submission:	**Efficacy Supplement (pediatric 0<2 years old; term new born infants to 23 months old toddlers)**
Relevant IND:	**IND 56,410**
OCP Division:	**DCP V**
ORM Division:	**DMIP**
Reviewer:	**Christy S. John, Ph.D.**
Team Leader (TL):	**Gene Williams, Ph.D.**
Pharmacometrics Reviewer/TL:	**Nitin Mehrotra, Ph.D.**

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1. EXECUTIVE SUMMARY

The clinical pharmacology review for this Gadavist efficacy supplement is abbreviated to include only relevant information and questions. For detailed clinical pharmacology QBR, please refer to the review by Dr. Christy John in DAARTS dated Feb 25, 2011.

Gadavist (gadobutrol injection) is a gadolinium based contrast agent that was approved in 2011 for the 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 (CNS). The purpose of this efficacy supplement is to extend the use of Gadavist to the pediatric population below 2 years of age (b) (4) To achieve this end, the applicant has conducted a pharmacokinetics study (91741) in children 0 to less than 2 years of age (term new born infants to 23 months toddlers).

A clinical dose of 0.1 mmol/kg is reasonable for use in pediatric population 2 years and younger based on similar PK observed compare to pediatrics 2-17 years of age. Based on the population PK analysis, the PK of the pediatric population aged 0 – < 2 years is found to be similar to the PK of the pediatric population aged 2 – 17 years. The results showed that similar AUC values were observed for the entire pediatric population aged 0 - < 2 years in study 91741, with a trend to slightly higher AUC values for the youngest subjects aged 0 - < 2 months. However, the AUC in 0 - < 2 month pediatrics was within the range of those observed in 12-17 year pediatrics. Thus, based on the similarity in AUC, no safety concern is expected in pediatric subjects aged 0 – < 2 years. Simulated plasma gadobutrol concentrations at 20 and 30 min post dose (C20 and C30) in 0-2 year pediatrics were reasonably similar to those of 2-17 year pediatrics. Considering the C20 and C30 value as indicators for imaging efficiency, similar signal/contrast-enhancement is expected to be achieved in the pediatric population aged 0 - < 2 years as was observed in pediatric subjects aged 2 – 17 years.

In conclusion, PK results at a dose of 0.1 mmol/kg in 0-2 year pediatrics are similar to older children and adults. Considering the C20 and C30 value as indicators for imaging efficiency, similar signal/contrast-enhancement is expected to be achieved in the pediatric population aged 0 - < 2 years as was observed in pediatric subjects aged 2 – 17.

1.1. RECOMMENDATIONS

The Office of Clinical Pharmacology, Divisions of Clinical Pharmacology V and Pharmacometrics have reviewed NDA 201-277 submitted on June 30, 2010. OCP finds this application acceptable provided mutually agreeable language on labeling can be reached. The proposed dose of 0.1 mmol/kg of gadobutrol in pediatrics 0-2 years of age is acceptable. This submission fulfills a Post Marketing Requirement (PMR 1743-2) from the original approval of March 14, 2011 to study the product in pediatric patients 0-2 years of age.

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1.2. PHASE IV COMMITMENTS: None

1.3. SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

Gadavist, a gadolinium based contrast agent was approved on March 14, 2011 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. The approved dose of Gadavist for this indication is 0.1 mmol/kg. The purpose of the current pediatric study 91741 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 newborn infants to toddlers 23 months of age inclusive) as the primary objective. This study (91741) was an open-label, multi-center, prospective study with a total of 43 pediatric subjects (9 subjects were less than 2 months of age).

Based on the population PK analysis, the PK of the pediatric population aged 0 – < 2 years in study 91741 is similar to the PK of the pediatric population aged 2 – 17 years at a dose of 0.1 mmol/kg. Pediatric patients received a standard dose of 0.1 mmol/kg BW gadobutrol. Within 8 hours after the gadobutrol injection, 3 blood samples for the evaluation of gadobutrol PK were to be drawn from each subject, i.e. 1 sample per time window (sparse sampling approach). The time windows were 15 to 60 min, 2 to 4 hours, and 6 to 8 hours post-injection, respectively. Each time window was subdivided into 4 sampling time intervals. In addition, eGFR was obtained prior to gadobutrol injection.

The table below compares the individual PK parameter estimates derived from the combined population PK analysis of 0-17 year pediatric data.

FDA **Table 1: Comparison of individual PK evaluation in pediatric population aged 0 - < 2 years (study 91741; binned by age: 0 - < 2 months and ≥ 2 - 23 months) versus pediatric population aged 2 – 17 years (study 310788, A43735; binned by age: 2 – 6 years, 7 – 11 years, and 12 – 17 years)**

Parameter	All (0-<2 years) [a]	0-<2 months [a]	≥2-23 months [a]	All (2-<17 years) [a]	2-6 years [a]	7-11 years [a]	12-17 years [a]
	N=43	N=9	N=34	N=130	N=45	N=39	N=46
CL/kg [L/h/kg]	0.128 (0.0529, 0.195)	0.0639 (0.0529, 0.0778)	0.133 (0.0803, 0.195)	0.0983 (0.0433, 0.215)	0.119 (0.0801, 0.215)	0.0994 (0.0433, 0.165)	0.0808 (0.0455, 0.103)
Vss/kg [L/kg]	0.524 (0.363, 1.04)	0.741 (0.659, 1.04)	0.479 (0.363, 0.804)	0.244 (0.109, 0.414)	0.332 (0.189, 0.414)	0.240 (0.158, 0.303)	0.196 (0.109, 0.285)
AUC [µmol*h/L]	781 (513, 1891)	1597 (1285, 1891)	757 (513, 1229)	1055 (412, 2285)	846 (412, 1331)	1025 (623, 2285)	1237 (946, 2211)

[a] Median (Minimum, Maximum)

AUC increased with increasing age from ≥ 2 months up to 17 years. Overall, AUC values widely overlapped across the entire pediatric population aged 0 – 17 years. Furthermore, simulated plasma concentrations in the time frame relevant for imaging, i.e., plasma concentrations at 20 min and 30 min after gadavist administration (C20, C30) (imaging/efficacy window) was compared to pediatric subjects over 2 years of age. As early plasma concentrations are considered to be a relevant parameter for MR imaging, gadolinium plasma concentrations at 20 min and 30 min after injection (C20, C30) were simulated for a total number of 200 virtual pediatric subjects for different age groups. The results of the simulations are summarized in **FDA Table 2.**

FDA Table 2: Comparison of simulated gadolinium plasma concentrations at 20 min (C20) and 30 min (C30) after i.v. bolus dose of 0.1 mmol/kg gadobutrol in pediatric population aged 0 - < 2 years versus pediatric population aged 2 – 17 years.

Parameter	All (0-<2 years) [a,b]	0-<2 months [a,b]	≥2-23 months [a,b]	All (2-<17 years) [a,b]	2-6 years [a,b]	7-11 years [a,b]	12-17 years [a,b]
	N=400	N=200	N=200	N=600	N=200	N=200	N=200
C_{20} [µmol/L]	290 (137, 461)	268 (133, 446)	300 (164, 509)	442 (221, 786)	362 (195, 628)	452 (255, 750)	518 (276, 867)
C_{30} [µmol/L]	249 (125, 380)	243 (122, 369)	254 (133, 392)	361 (200, 597)	309 (182, 479)	367 (211, 367)	436 (215, 681)

[a] Median (5th, 95th percentile)

[b] Statistics of 1000 simulations based on 5 different median weights and different typical CL values scaled to body weight corresponding to age group 0 - < 2 months (median age: 0.9 months, median body weight: 4.4 kg), age group 2 - 23 months (median age: 10.2 months, median body weight: 8.2 kg), age group 2 – 6 years (median age: 4 years, median body weight: 16 kg) , age group 7 – 11 years (median age: 9 years, median body weight: 31.1 kg) and age group 12 – 17 years (median age: 15 years, median body weight: 55.1 kg) with 200 virtual subjects per group.

Simulated C20 and C30 concentrations increased with increasing age across the entire pediatric population from age group 0 - < 2 months up to age group 17 years. Nevertheless, the 5th/95th percentile range of the two youngest age groups 0 - < 2 months and ≥ 2 - 23 months overlapped to a large extent with the 5th/95th percentile range of the older age groups 2 - 17 years.

In conclusion, similar AUC values were observed for the entire pediatric population aged 0 - 17 years, with a trend to slightly higher AUC values for the very young subjects aged 0 - < 2 months. AUC values widely overlapped across all age groups (0 - 17 years). Thus, based on the AUC, no safety concern is expected in pediatric subjects aged 0 – < 2 years after an IV injection of 0.1 mmol/kg gadobutrol. Simulated C20 and C30 concentrations were reasonably similar across all age groups (0 – 17 years). Thus, considering the C20 and C30 values as indicators for imaging efficiency, similar signal/contrast-enhancement is expected to be achieved in the pediatric population aged 0 - < 2 years as seen in pediatric subjects aged 2 – 17 years.

2. Question-Based Review:

2.1 What are the proposed dosage and route of administration?

The recommended dose of Gadavist for adults and children of all ages (including term neonates) is 0.1 ml/kg body weight (0.1 mmol/kg) to be administered as an intravenous bolus injection, manually or by power injector, at a flow rate of approximately 2 mL/second.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

To support the proposed indication, the applicant conducted a clinical study to evaluate the pharmacokinetics (PK) of gadobutrol in plasma at the standard approved dose of 0.1 mmol/kg BW in pediatric subjects from birth to less than 2 years of age (term newborn infants to toddlers 23 months of age inclusive). The population pharmacokinetic (PK) characteristics of gadobutrol were assessed in study 91741 conducted to evaluate the pharmacokinetic and safety in children (term newborn infants to 23 months of age) undergoing a contrast-enhanced magnetic resonance imaging with an intravenous (IV) injection of 0.1 mmol/kg body weight.

The primary objective of the study was to derive PK parameters such as clearance (CL), clearance normalized to body weight (CL/kg), volume of distribution at steady state (Vss), volume of distribution at steady state normalized to body weight (Vss/kg), area under the concentration-time curve (AUC), terminal half-life ($t_{1/2}$), and to simulate plasma concentrations in the time frame relevant for imaging, i.e., plasma concentrations at 20 min (C20) and to compare these PK values to the respective values determined for children aged 2 – 17 years. The applicant used the same model that was used for the original approval for pediatric patients over 2 years old.

2.3 Does the proposed dosing regimen 0.1 mmol/kg produce exposures in pediatric population aged 0 – < 2 years that are reasonably comparable to pediatrics aged 2 – 17 years and adults?

Yes, the proposed dosing regimen 0.1 mmol/kg produces overlapped AUC values (Figure 1), C20 (Figure 2) and C30 (Figure 3) concentrations across all age groups (0 – 2 months, 2 – 23 months, 2 – 6 years, 7 – 11 years and 12 – 17 years).

A population PK model was developed combining data from pediatrics 0-2 years and 2-17 years. The final population PK model included weight as covariate on CL and V. Apart from weight, eGFR was also included as covariate on CL and typical body weight-scaled CL values were estimated for age group 0 - < 2 months and age group ≥ 2 months. The estimates from the final population PK model were used to predict AUC, C20 and

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C30 and box plots were made to visually compare these exposure metrics between pediatrics 0-2 months, 2-23 months, 2-6, 7-11, 12-17 and 2-17 year pediatrics. The AUC obtained in 0-2 month old was higher than 2 month to 11 year pediatrics but it appears to be overlapping with 12-17 year old pediatrics. There was a trend of C20 and C30 increasing with age but there was substantial overlap in C20 and C30 between various age groups. For details on the applicant's analysis (objectives, methodology and conclusions) and FDA reviewer's independent analysis, please refer to Pharmacometrics review (Section 4.1)

Figure 1: Distribution of simulated AUC values for the pediatric populations aged 0 - < 2 months, 2 - 23 months, 2 – 6 years, 7 – 11 years and 12 - 17 years based on the final population PK, respectively (n = 200 in each group).

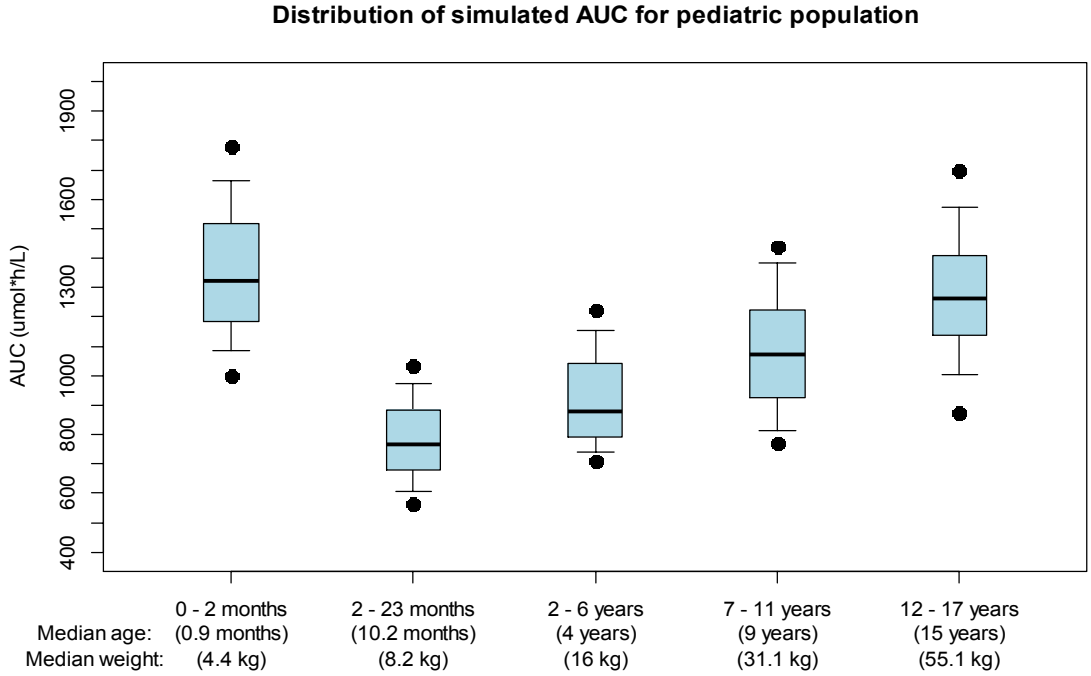

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Figure 2: Distribution of simulated gadobutrol plasma concentrations [µmol/L] at 20 minutes (C20) after i.v. bolus dose of 0.1 mmol/kg gadobutrol for the pediatric populations aged 0 - < 2 months, 2 - 23 months, 2 – 6 years, 7 – 11 years and 12 - 17 years based on the final population PK, respectively (n = 200 in each group).

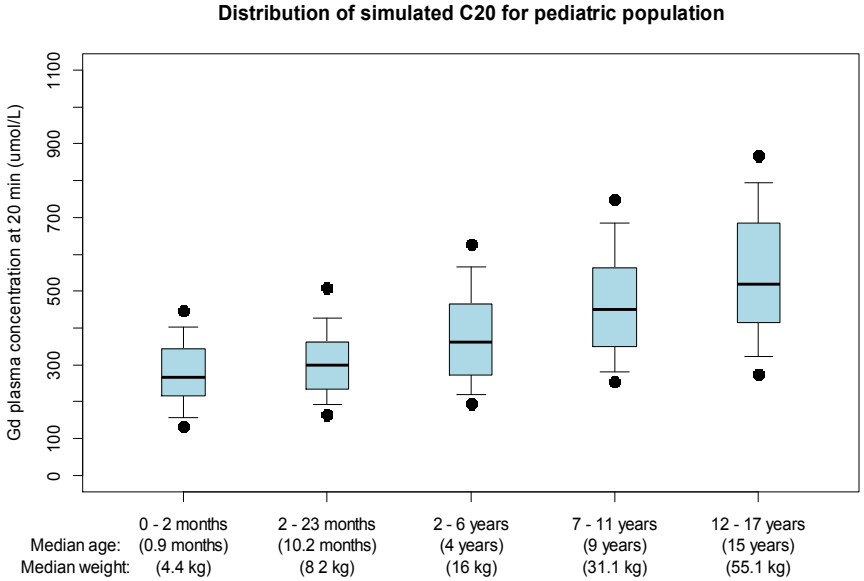
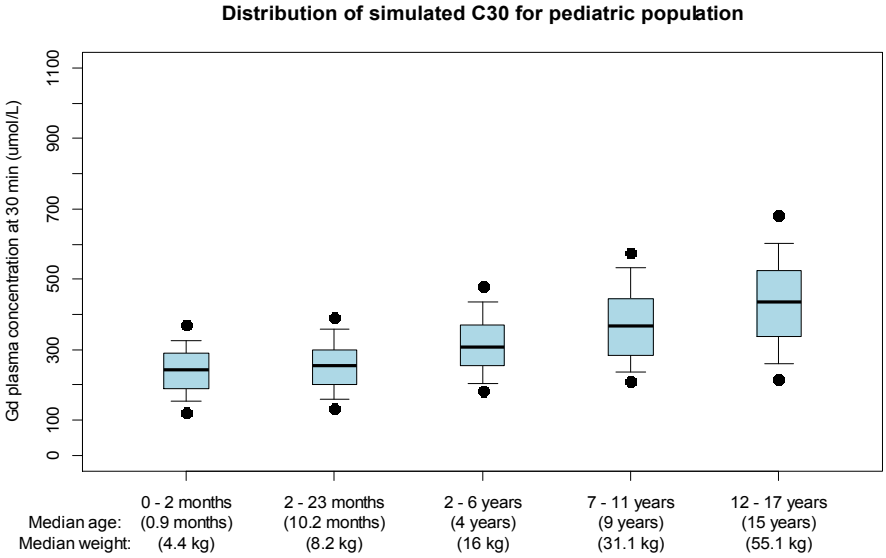


Figure 3: Distribution of simulated gadobutrol plasma concentrations [µmol/L] at 30 minutes (C30) after i.v. bolus dose of 0.1 mmol/kg gadobutrol for the pediatric populations aged 0 - < 2 months, 2 - 23 months, 2 – 6 years, 7 – 11 years and 12 - 17 years based on the final population PK, respectively (n = 200 in each group).



2.6 ANALYTICAL SECTION

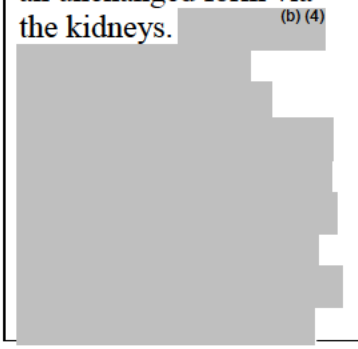
2.6.1 Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?
2.6.2 Were the analytical procedures used to determine drug concentrations in this NDA acceptable?

Plasma concentrations of Gd were measured using a validated inductive coupled plasma-mass spectrometric method. The lower limit of quantitation (LLOQ) is approximately 0.06 µmol/L (10 µg/L). For analysis, aliquots of the plasma sample were diluted to a maximum matrix content of 1% using 1% nitric acid. Internal standardization was performed by spiking with (b) (4) prior to analysis. Pharmacokinetic plasma samples were analyzed under the responsibility of the Department of (b) (4).

Please see original clinical pharmacology review by this reviewer in DARRTS (February 25, 2011) for details of the methods.

3. Detailed Labeling Recommendation:

Proposed by Sponsor	Reviewer's Recommendation
8.4 Pediatric Use (b) (4)	**8.4 Pediatric Use** The safety and effectiveness of Gadavist have been established in pediatric patients born at 38 weeks gestation or later based on imaging and pharmacokinetic data in 138 patients ages 2 to 17 years and 44 patients ages 0 to less than 2 years and extrapolation from adult data. The frequency, type, and severity of adverse reactions in pediatric patients were similar to adverse reactions in adults *[see Adverse Reactions (6.1)]*. No dose adjustment according to age is necessary in pediatric patients *[see Dosage and Administration (2.1), Clinical Pharmacology (12.3), and Clinical Studies (14.1)]*. The safety and effectiveness of Gadavist have not been established in premature infants. *NSF risk* No case of NSF associated with Gadavist or any other GBCA has been identified in pediatric patients ages 6 years and younger. Pharmacokinetic studies suggest that clearance of Gadavist is similar in pediatric patients and adults, including pediatric patients age younger than 2 years. No increased risk factor for NSF has been identified in juvenile animal studies of gadobutrol. Normal estimated GFR (eGFR) is around 30 mL/min/1.73m^2 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 age younger than 1 year have been conducted in patients with the following minimum eGFR: 31 mL/min/1.73m^2 (age 2 to 7 days), 38 mL/min/1.73m^2 (age 8 to 28 days), 62 mL/min/1.73m^2 (age 1 to 6 months), and 83 mL/min/1.73m^2 (age 6 to 12 months).
12.3 Pharmacokinetics *Distribution* After intravenous administration, gadobutrol is rapidly distributed in the extracellular space. After	**12.3 Pharmacokinetics** *Distribution* After intravenous administration, gadobutrol is rapidly distributed in the extracellular space. After a gadobutrol dose of 0.1 mmol/kg body weight, an average level of 0.59 mmol gadobutrol/L was measured in plasma 2 minutes after the injection and 0.3 mmol gadobutrol/L 60 minutes after the

a gadobutrol dose of 0.1 mmol /kg body weight, an average level of 0.59 mmol gadobutrol/L was measured in plasma 2 minutes after the injection and 0.3 mmol gadobutrol/L 60 minutes after the injection. (b) (4) 	injection. Gadobutrol does not display any particular protein binding. In rats, gadobutrol does not penetrate the intact blood-brain barrier.
Metabolism Gadobutrol is not metabolized.	*Metabolism* Gadobutrol is not metabolized.
Elimination Gadobutrol is excreted in an unchanged form via the kidneys. (b) (4) 	*Elimination* Values for AUC, body weight normalized plasma clearance and half-life are given in Table 3, below. Gadobutrol is excreted in an unchanged form via the kidneys. In healthy subjects, renal clearance of gadobutrol is 1.1 to 1.7 mL/(min·kg) and thus comparable to the renal clearance of inulin, confirming that gadobutrol is eliminated by glomerular filtration. Within two hours after intravenous administration more than 50% and within 12 hours more than 90% of the given dose is eliminated via the urine. Extra-renal elimination is negligible.

the renal clearance of insulin, confirming that gadobutrol is eliminated by glomerular filtration. Within two hours after intravenous administration more than 50% and within 12 hours more than 90% of the given dose is eliminated via the urine. The extrarenal elimination is negligible. (5.3.3.1 – 9746)	
Special populations Gender Gender has no clinically relevant effect on the pharmacokinetics of gadobutrol.	*Specific Populations* Gender Gender has no clinically relevant effect on the pharmacokinetics of gadobutrol.
Geriatric A single IV dose of 0.1 mmol/kg gadobutrol was administered to 15 elderly and 16 non-elderly subjects. AUC was slightly higher and clearance slightly lower in elderly subjects as compared to non-elderly subjects *[see Use in Specific Populations*	Geriatric A single IV dose of 0.1 mmol/kg Gadavist was administered to 15 elderly and 16 non-elderly subjects. AUC was slightly higher and clearance slightly lower in elderly subjects as compared to non-elderly subjects *[see Use in Specific Populations (8.5)]*.
	<u>Pediatric</u> The pharmacokinetics of gadobutrol were evaluated in two studies in a total of 130 patients age 2 to less than 18 years and in 43 patients less than 2 years of age (including term neonates). Patients received a single intravenous dose of 0.1 mmol/kg of Gadavist. The pharmacokinetic profile of gadobutrol in pediatric patients is similar to that in adults, resulting in similar values for AUC, body weight normalized

plasma clearance, as well as elimination half-life. Approximately 99% (median value) of the dose was recovered in urine within 6 hours (this information was derived from the 2 to less than 18 year old age group).

Table 3: Pharmacokinetics by Age Group

	0–<2 years N=43	**2–6 years N=45**	**7–11 years N=39**	**12–<18 years N=46**
AUC (µmolxh/L)	781	846	1025	1237
CL (L/hr/kg)	0.128	0.119	0.099	0.081
t1/2 (hrs)	2.91	1.91	1.66	1.68

4 APPENDICES

4.1. Pharmacometrics review

Pharmacometrics review

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1 Summary of Findings

1.1 Key Review Questions

The purpose of this review is to address the following key question.

1.1.1 Does the proposed dosing regimen 0.1 mmol/kg produce exposures in pediatric population aged 0 – < 2 years that are reasonably comparable to pediatrics aged 2 – 17 years and adults?

Yes, the proposed dosing regimen 0.1 mmol/kg produces overlapped AUC values (Figure 1), C20 (Figure 2) and C30 (Figure 3) concentrations across all age groups (0 – 2 months, 2 – 23 months, 2 – 6 years, 7 – 11 years and 12 – 17 years).
The AUC obtained in 0-2 month old was higher than 2 month to 11 year pediatrics but it appears to be overlapping with 12-17 year old pediatrics. The C20 and C30 increased with increasing age but there is substantial overlap between various age groups.

Figure 4: Distribution of simulated AUC values for the pediatric populations aged 0 - < 2 months, 2 - 23 months, 2 – 6 years, 7 – 11 years and 12 - 17 years based on the final population PK, respectively (n = 200 per group).

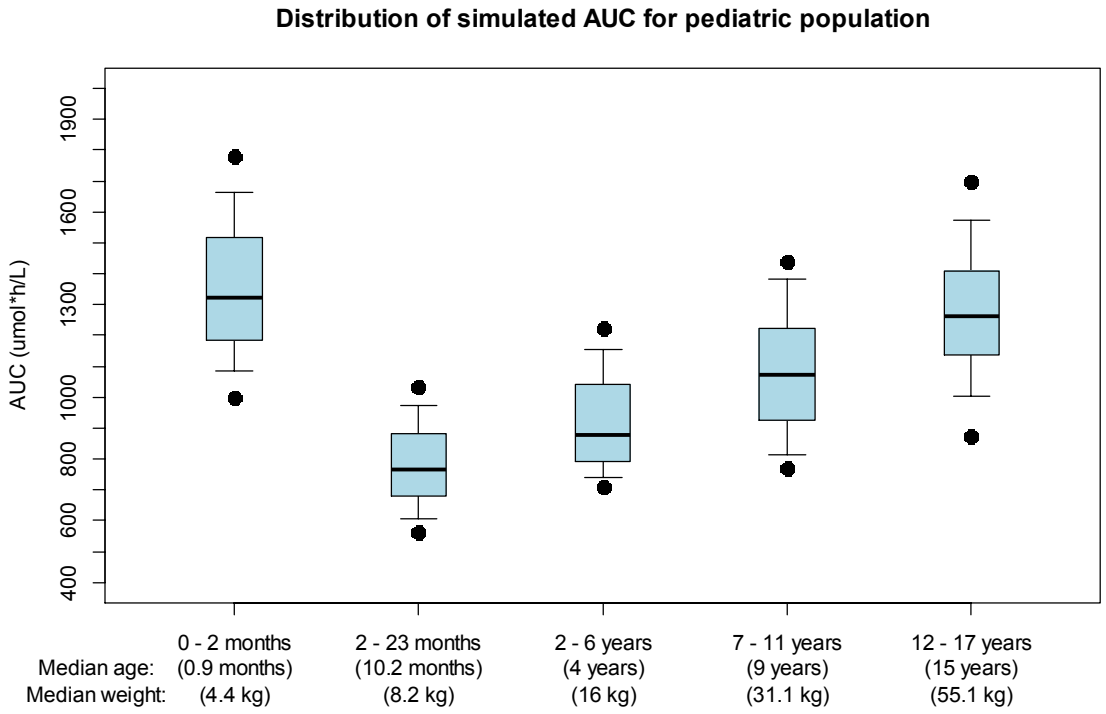

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Figure 5: Distribution of simulated gadobutrol plasma concentrations [µmol/L] at 20 minutes (C20) after i.v. bolus dose of 0.1 mmol/kg gadobutrol for the pediatric populations aged 0 - < 2 months, 2 - 23 months, 2 – 6 years, 7 – 11 years and 12 - 17 years based on the final population PK, respectively (n = 200 per group).

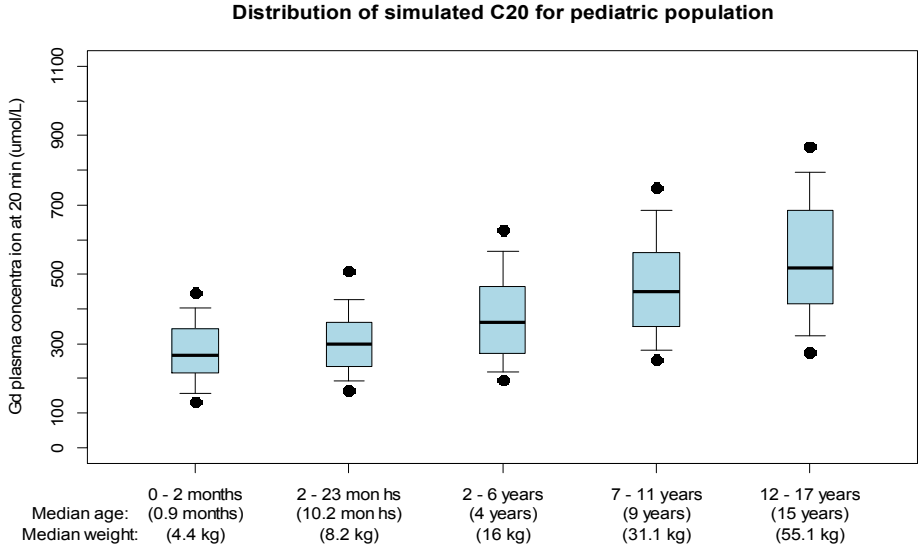
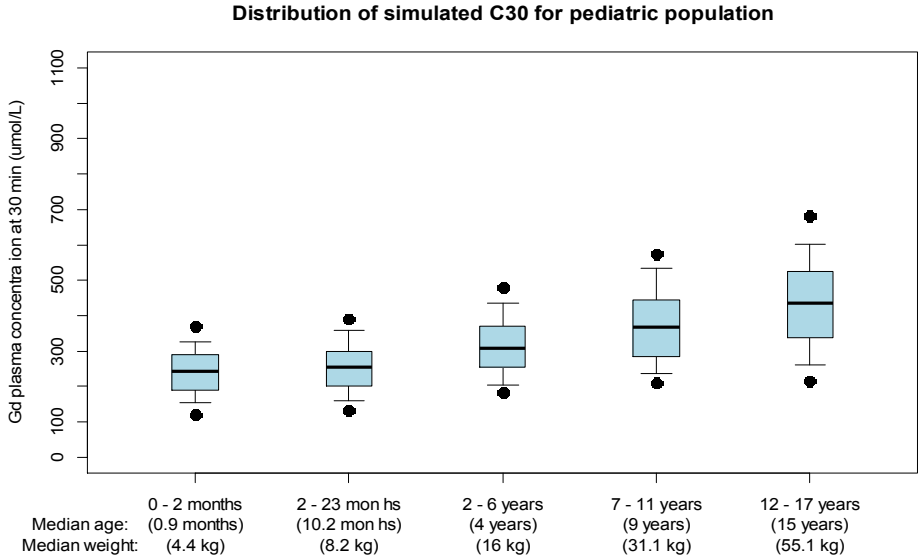


Figure 6: Distribution of simulated gadobutrol plasma concentrations [µmol/L] at 30 minutes (C30) after i.v. bolus dose of 0.1 mmol/kg gadobutrol for the pediatric populations aged 0 - < 2 months, 2 - 23 months, 2 – 6 years, 7 – 11 years and 12 - 17 years based on the final population PK, respectively (n = 200 per group).



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A population PK model was developed combining data from pediatrics 0-2 and 2-17 years. The model estimates were used to predict AUC, C20 and C30 and box plots were made to visually compare these exposure metrics between pediatrics 0-2 months, 2-23 months, 2-6, 7-11 and 12-17 years.
The primary basis of the dosing recommendations and approval will be based on the matching exposures observed in pediatrics 0-2 years to those observed in 2-17 years. C20 and C30 are the exposures following 20 and 30 minutes of gadobutrol dosing. C20 and C30 are considered to be relevant for efficacy as the MRI is usually conducted between 20 to 30 minutes after administration of the contrast agent. Therefore, similar exposures in pediatrics 0-2 years compared to 2-17 years is an indicator of similar imaging efficiency i.e. similar imaging efficiency, similar signal/contrast-enhancement is expected to be achieved. Furthermore, AUC is also compared between pediatrics aged 0-2 years and 2-17 years to demonstrate that 0.1 mmol/kg gadobutrol for pediatric patients aged 0-2 years is not expected to produce significant safety concerns.

1.2 Recommendations

Division of Pharmacometrics has reviewed this sNDA and recommends approval. We agree with the applicant's proposed dosing regimen of 0.1 mmol/kg in 0-2 year pediatric patients.

1.3 Label Statements

Please refer to clinical pharmacology QBR for detailed labeling recommendations.

2 Pertinent regulatory background

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. Gadavist® (gadobutrol) Injection was also approved for MRI of the breast to assess the presence and extent of malignant breast disease on June 11, 2014.
The current submission includes pharmacokinetic (PK) and safety data in children 0-<2 years of age from study 91741 to provide additional data in the pediatric population <2 years and to extend the use of gadobutrol at the same dose level of 0.1 mmol/kg (b) (4) to this population. The supplement is being submitted in fulfillment of a PMR. The primary basis on which approval is sought is matching PK which is consistent with the agreed upon PMR, the study was not designed to assess safety and efficacy.

3 Results of Applicant's Analysis

The applicant analyzed gadobutrol PK data of the pediatric population aged 0 - < 2 years in study 91741 alone for the dose selection in pediatrics and pediatric PK label statements. The methodology and results of applicant's analysis are summarized below.

3.1 Methods

Data from study 91741 were analyzed using nonlinear mixed-effects modeling with the NONMEM® software (Version 7.2.0, Icon Development Solutions, Ellicott City, Maryland USA) together with PsN/Xpose, SAS, S-PLUS, or R. Model selection was guided by the data and was based on visual inspection of diagnostic scatter plots, various GOF indicators, comparisons based on the minimum objective function (OFV) and analysis of estimates of population fixed and random effects parameters.

Criteria for inclusion of a covariate in the final model included: 1) statistical significance at P value < 0.001, 2) 95% confidence interval excludes 0, 3) a reduction of the amount of variability of the parameters.

A visual predictive check (VPC) evaluation and 1000 non-parametric bootstraps runs were performed to assess the performance of the final model and parameters.

3.2 Results and Discussion

3.2.1 Data

A total number of 43 pediatric subjects with 127 plasma concentrations from study 91741 were included in the population PK analysis. The NONMEM data file comprised 9 subjects aged < 2 months and 34 subjects ≥ 2 months with 25 and 102 plasma concentrations, respectively. The median age of all pediatric subjects was 7 months (range 0.2 - 23 months) and the median body weight was 7.2 kg (range 2.80-14.2 kg). The median estimated GFR (eGFR) was 69.0 mL/min/1.73 m^2 (range 33.4 - 121 mL/min/1.73 m^2) and 127 mL/min/1.73 m^2 (range 54.2 – 282 mL/min/1.73 m^2) for subjects aged 0 - 2 months and subjects aged 2 - 23 months, respectively.

3.2.2 Visual predictive check based on the previous model

Firstly, the applicant applied the previously developed population PK model for the pediatric population aged 2-17 years to fit the gadobutrol plasma concentration data of the current study population. This previous population PK model was a linear two compartment model with inter-individual variability in CL and V1. Body weight was the major covariate to scale the PK parameters CL and V1, using an allometric model with scaling coefficients of 0.75 for CL and 1 for V1. Estimated GFR, normalized to 1.73 m² BSA, also had a significant positive linear impact on gadobutrol clearance. The VPC result showed that this model seemed to describe the variability in pediatric population aged 2 - 23 months adequately (Figure 4). However, it appeared to under-predict concentration in subjects aged < 2 months (Figure 5).

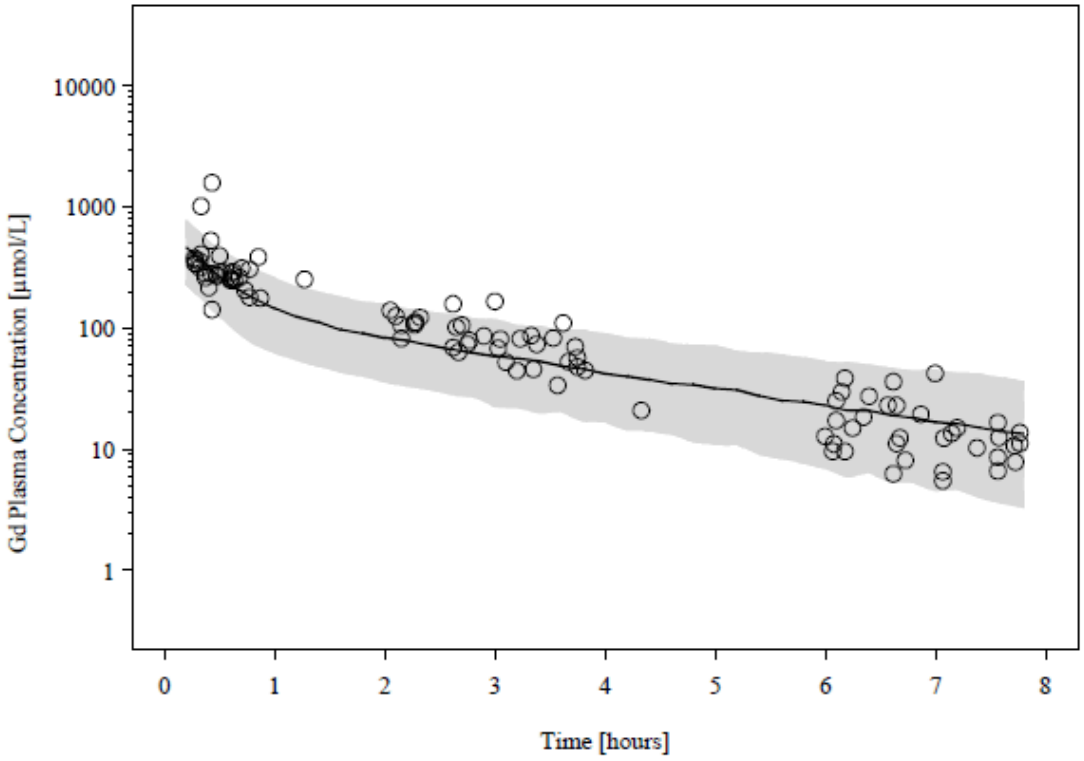

Figure 7: Visual predictive check performed with the previous model for the plasma concentrations of age group 2 - 23 months. (Shaded area: 5th and 95th percentiles of the simulations. Open circles: individual observations. Solid line: median of the simulations)

(Source: Applicant's Population PK Report for pediatric patients aged 0 – 23 months, p25)

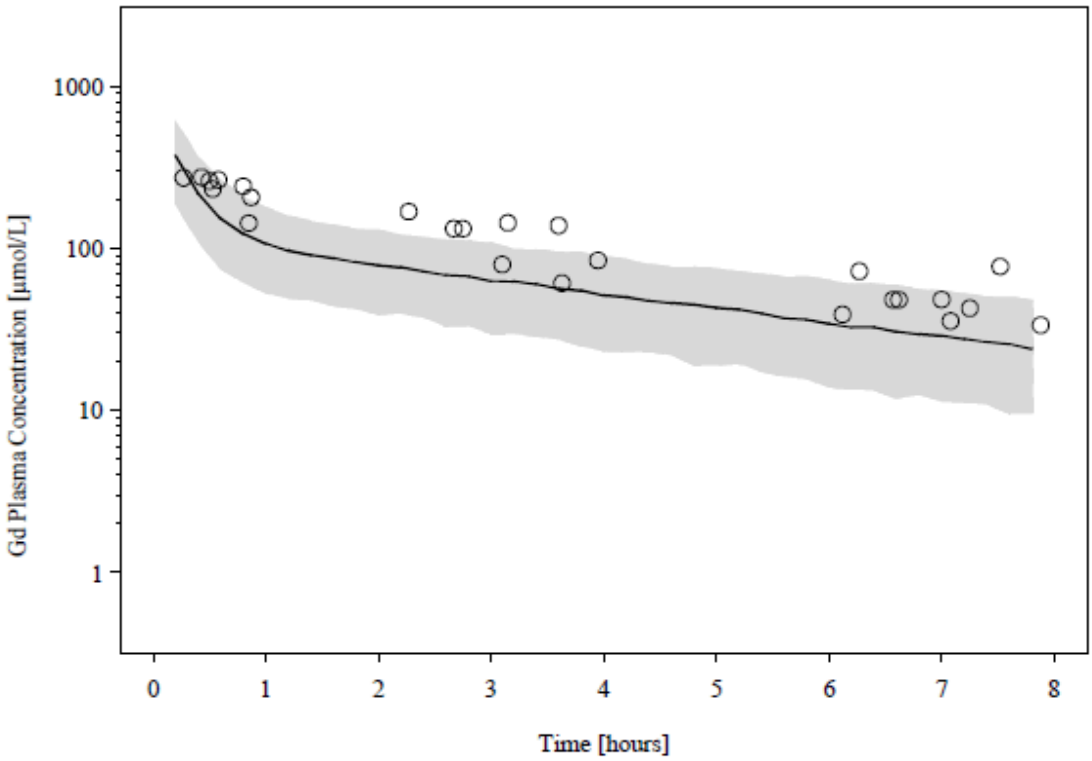

Figure 8: Visual predictive check performed with the previous model for the plasma concentrations of age group 0 - 2 months. (Shaded area: 5th and 95th percentiles of the simulations. Open circles: individual observations. Solid line: median of the simulations)

(Source: Applicant's Population PK Report for pediatric patients aged 0 – 23 months, p26)

3.2.3 Model refinement

Thus, the applicant decided to refine the previous model for the purpose of best fit to the data. The refined final model for the pediatric subjects aged 0 - < 2 years is summarized as follows:

- The pharmacokinetics of gadobutrol in the pediatric population aged 0 - < 2 years were described by a linear two-compartment model with elimination from the central compartment.
- Inter-individual variability was identified for CL, residual variability was described by a proportional error model.
- Body weight was the major covariate to scale the PK parameters total body clearance (CL) and central volume of distribution (V1), using an allometric model with scaling coefficients of 0.75 for CL and 1 for V1.

- In addition to body weight, age had a significant impact on gadobutrol clearance. Different typical body weight-scaled CL values were estimated for age group 0 - < 2 months and age group 2 - 23 months.

Compared to the previous model, this refined model fixed typical value of Q to the final estimate of the previous analysis, excluded inter-individual variability of V1 and impact of eGFR on CL. Instead this model included age as a categorical covariate on CL such that separate CL was estimated for 0-2 months and 2-23 months. GOF plots and VPC results showed that the refined model reasonably described the data, including the data of the very young subjects aged < 2 months, adequately. Bootstrap analysis confirmed the ruggedness of the model. Table 1 shows the final parameters estimates. The VPC results depicted in Figure 6 and Figure 7 show that this refined model describes the data from pediatric population aged 0-< 2 months and 2-23 months, adequately.

Table 1: Applicant's Final Population PK Model Parameter Estimates.

Parameter	Unit	Estimate	RSE [%][a]	LLCI[b]	ULCI[c]	Description
Fixed Effects						
$CL/WGHT^{0.75}$_AGEG_1	$L/h/kg^{0.75}$	0.129	5.60	0.115	0.143	Systemic clearance normalized to body weight to a power of 0.75 for age group 0 - < 2 months
V1/WGHT	L/kg	0.193	8.81	0.160	0.226	Central volume of distribution normalized to body weight to a power of 1
Q	L/h	1.32 FIX	-	-	-	Inter-compartmental clearance
V2	L	0.604	13.8	0.441	0.767	Peripheral volume of distribution
$CL/WGHT^{0.75}$_AGEG_2	$L/h/kg^{0.75}$	0.224	3.92	0.207	0.241	Systemic clearance normalized to body weight to a power of 0.75 for age group ≥ 2 months
Random Effects						
Inter-individual variability[d]						
IIV_CL (CV)	%	16.2	24.6	11.7	19.8	Inter-individual variability of CL
Residual error						
SIGMA prop (CV)	%	19.8	29.4	12.9	24.8	Proportional residual error of gadolinium plasma concentrations

(Source: Applicant's Population PK Report for pediatric patients aged 0 – 23 months, p28)

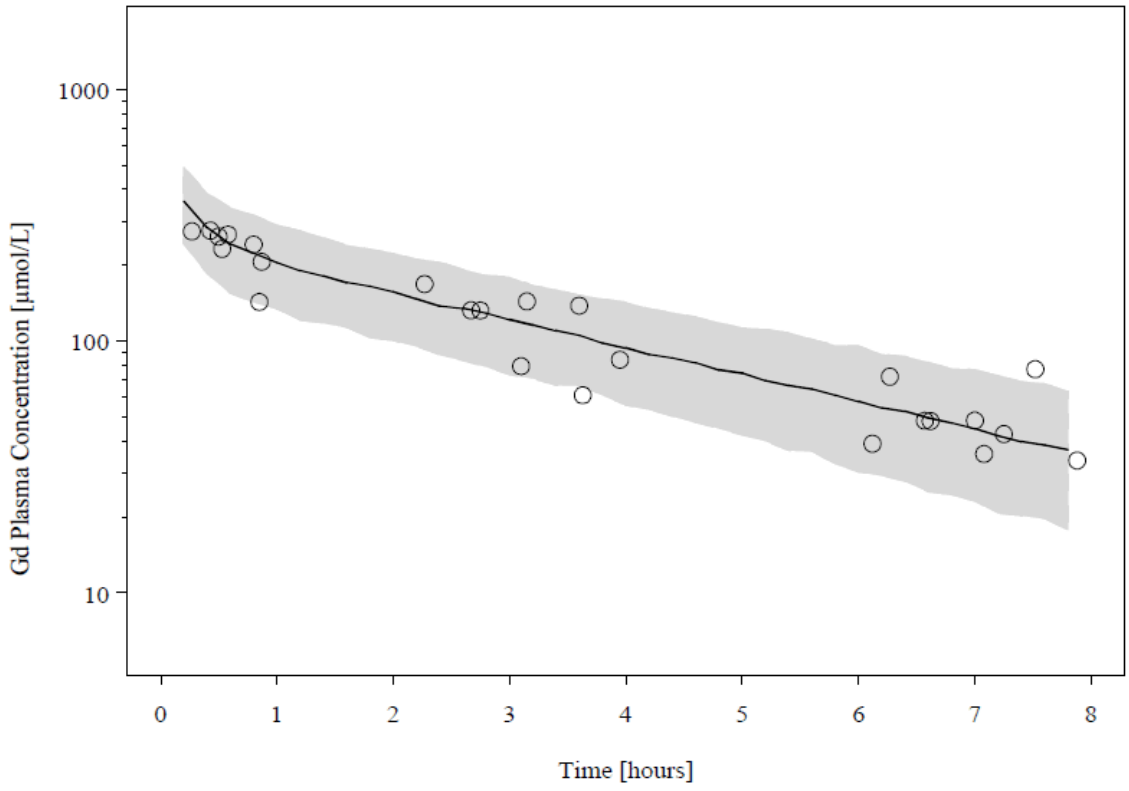

Figure 9: Visual predictive check for Gd plasma concentrations of age group 1 (0-<2 months), semilog scale: 90% prediction interval and median of simulated Gd plasma concentrations versus time based on the final population PK model overlaid with all observed concentrations.

Shaded area: 5th and 95th percentiles of the simulations
Open circles: individual observations
Solid line: median of the simulations
Dashed line (gray): lower limit of quantification (LLOQ)
(Source: Applicant's Population PK Report for pediatric patients aged 0 – 23 months, p126)

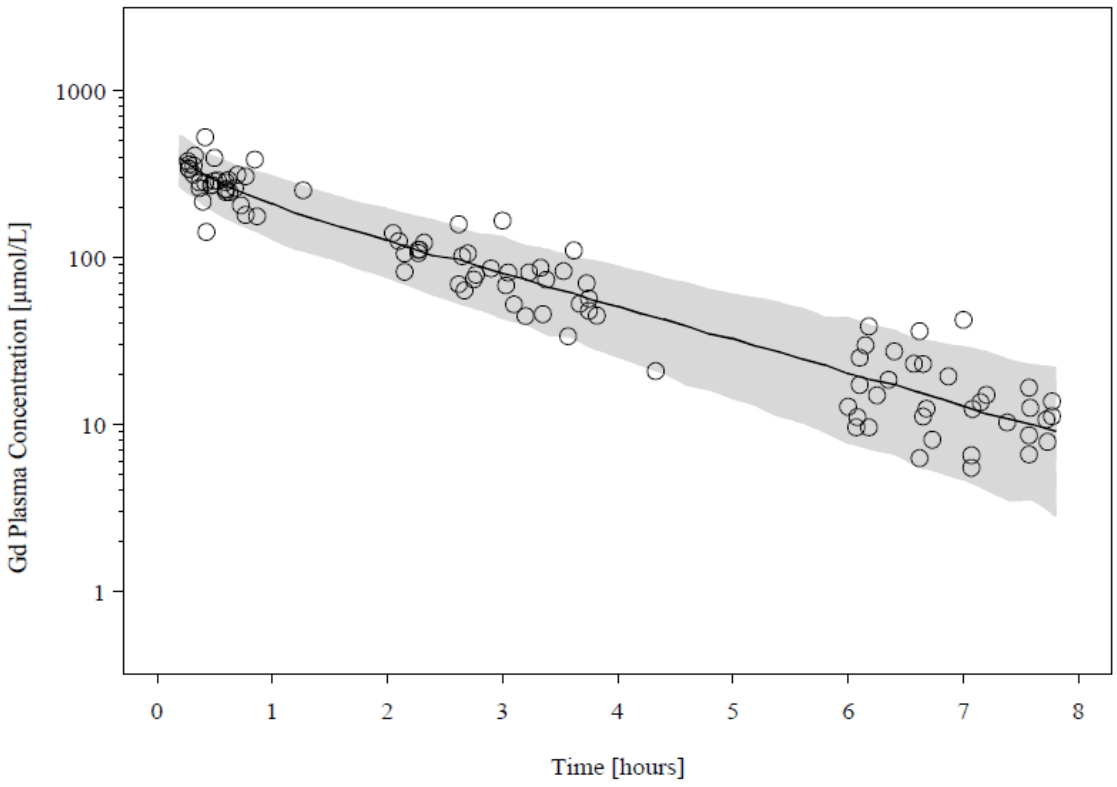

Figure 10: Visual predictive check for Gd plasma concentrations of age group 2 (≥ 2 months), semilog scale: 90% prediction interval and median of simulated Gd plasma concentrations versus time based on the final population PK model overlaid with all observed concentrations, except for concentrations above 1000 µmol/L.

Shaded area: 5th and 95th percentiles of the simulations
Open circles: individual observations
Solid line: median of the simulations
Dashed line (gray): lower limit of quantification (LLOQ)
(Source: Applicant's Population PK Report for pediatric patients aged 0 – 23 months, p129)

3.2.4 Individual PK evaluation based on the final population PK model

The refined model was used to calculate the individual posthoc parameter estimates and derived PK parameters, as described in Table 2. The median CL normalized to body weight was lower (by 31%) in 0-2 month old pediatrics compared to the older subjects. Hence, the median values of individual AUC, individual $t_{1/2}$, and individual MRT values were higher (1.4-fold, 1.8-fold, and 1.8-fold, respectively) in this group compared to the older subjects (> 2 moths). Nevertheless, AUC ranges of the two age groups overlapped.

Table 2: Summary of individual posthoc estimates and derived PK parameters of all pediatric subjects and by age group based on the final population PK model (PPS; all ages: N=43, age group 0 - < 2 months: N=9, age group ≥ 2 months: N=34).

Parameter	Age Group	Median	95% CI[a]	Minimum	Maximum
CL [L/h]	**All ages**	**0.981**	**0.799 - 1.17**	**0.263**	**2.10**
	0 - < 2 months	0.371	0.283 - 0.459	0.263	0.459
	≥ 2 months	1.07	0.923 – 1.28	0.566	2.10
CL/kg [L/h/kg]	**All ages**	**0.128**	**0.121 – 0.135**	**0.0666**	**0.184**
	0 - < 2 months	0.0920	0.0849 – 0.104	0.0666	0.109
	≥ 2 months	0.133	0.128 – 0.141	0.0870	0.184
V_{ss} [L]	**All ages**	**1.99**	**1.80 – 2.40**	**1.14**	**3.34**
	0 - < 2 months	1.45	1.20 – 1.59	1.14	1.59
	≥ 2 months	2.19	1.96 – 2.53	1.38	3.34
V_{ss}/kg [L/kg]	**All ages**	**0.277**	**0.259 – 0.294**	**0.236**	**0.409**
	0 - < 2 months	0.330	0.311 – 0.388	0.311	0.409
	≥ 2 months	0.267	0.256 – 0.283	0.236	0.344
AUC [µmol*h/L][b]	**All ages**	**776**	**736 - 834**	**544**	**1470**
	0 - < 2 months	1070	959 - 1220	916	1470
	≥ 2 months	751	706 - 781	544	1140
$t_{1/2}$ [h]	**All ages**	**1.62**	**1.46 – 1.79**	**1.16**	**3.37**
	0 - < 2 months	2.63	2.52 – 3.33	2.34	3.37
	≥ 2 months	1.46	1.42 – 1.67	1.16	2.16
MRT [h]	**All ages**	**2.18**	**1.94 – 2.40**	**1.57**	**4.68**
	0 - < 2 months	3.60	3.39 – 4.57	3.17	4.68
	≥ 2 months	1.97	1.90 – 2.25	1.57	2.98

[a] 95% CI: 95% confidence interval of the median

[b] Administered dose: 0.1 mmol/kg gadobutrol

(Source: Applicant's Population PK Report for pediatric patients aged 0 – 23 months, p31)

3.2.5 Comparison of pediatric population 0 - < 2 years (current study) versus pediatric population 2 – 17 years (study 310788, A43735)

The applicant compared individual key PK parameters as well as the simulated C20 and C30 concentrations of the current study to the respective values previously derived for the pediatric population aged 2 – 17 years.

Although AUC increased with increasing age from ≥ 2 months up to 17 years by approximately 55%, AUC values widely overlapped across the entire pediatric population aged 0 – 17 years as shown in Figure 8.

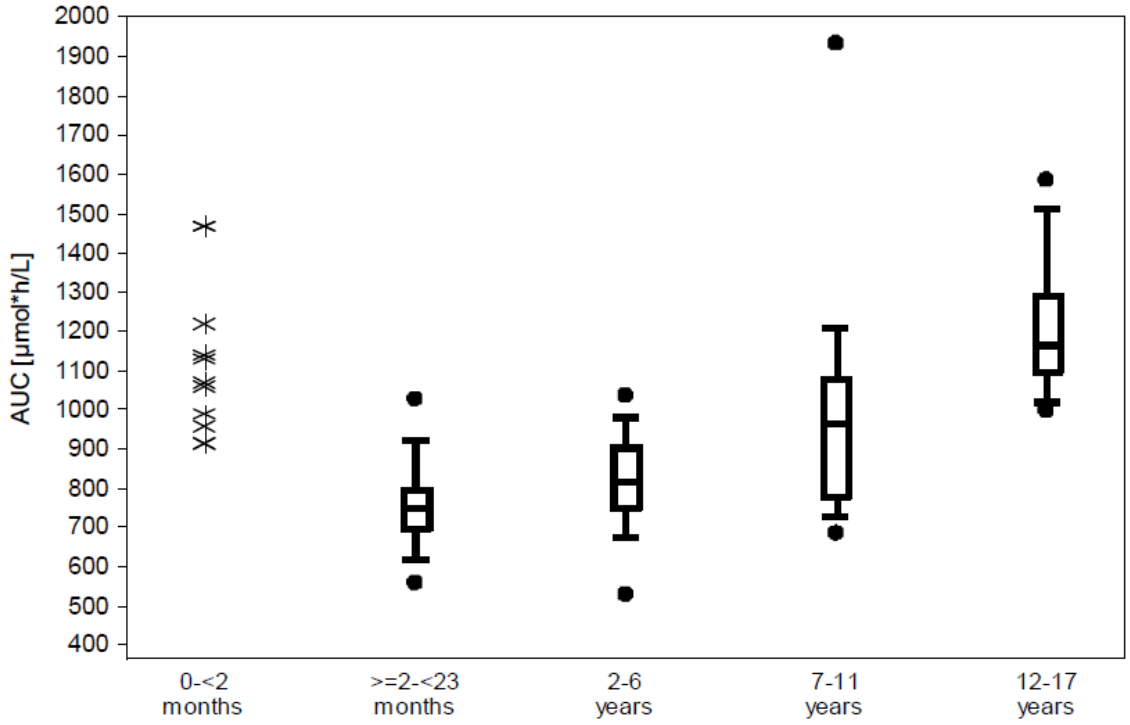

Figure 11: Distribution of estimated AUC values for the pediatric populations aged 0 - < 2 years (binned by age: 0 - < 2 months (N=9) and ≥ 2 - 23 months (N=34)) and 2 – 17 years (binned by age: 2 – 6 years (N=45), 7 – 11 years (N=39), and 12 – 17 years (N=46)) based on the refined and previous population PK model, respectively.

In the box plot, 10%-point, 25%-point, median, 75%-point and 90%-point are shown from the top, and the marks of "•" mean 5%- and 95%-points. For the youngest age group (0 - < 2 months) the estimated individual AUC values are shown instead of a box plot because of the small number of subjects (N=9).
(Source: Applicant's Population PK Report for pediatric patients aged 0 – 23 months, p38)

Simulated C20 and C30 concentrations, which are considered to be a relevant parameter for MR imaging, increased with increasing age across the entire pediatric population from age group 0 - < 2 months up to age group 17 years as presented in Figure 9 and Figure 10, respectively. Nevertheless, the 5th/95th percentile range of the two youngest age groups 0 - < 2 months and ≥ 2 - 23 months overlapped to a large extent with the 5th/95th percentile range of the older age groups 2 - 17 years.

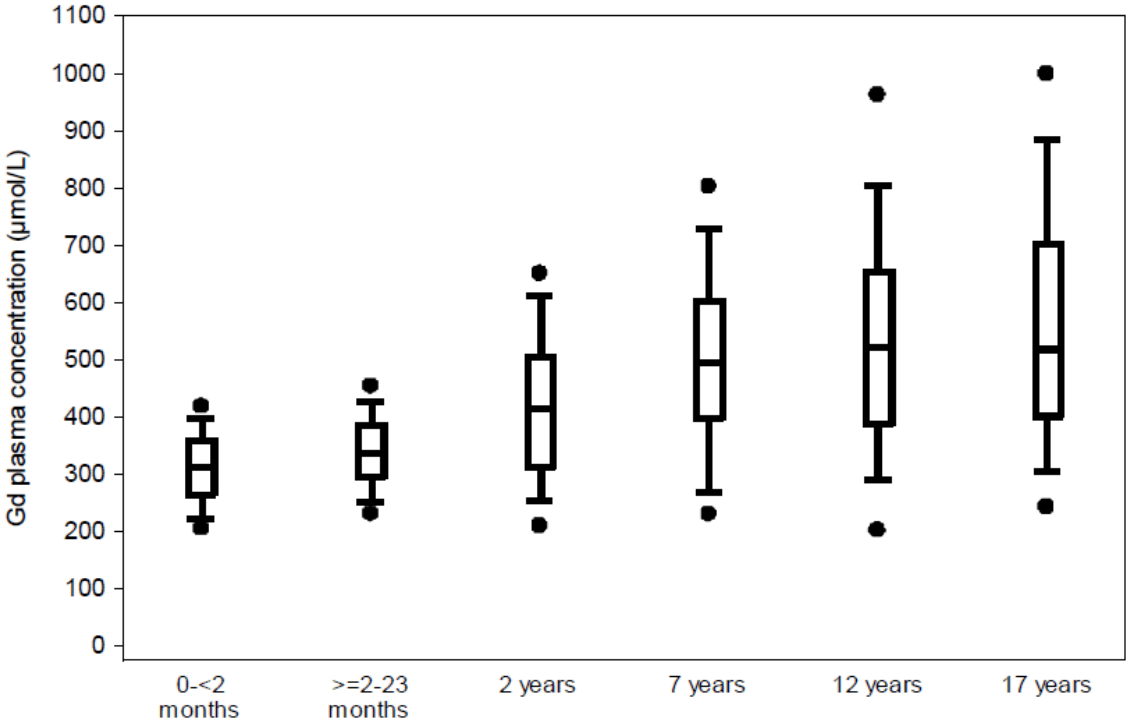

Figure 12: Distribution of simulated gadobutrol plasma concentrations [µmol/L] at 20 minutes (C20) after i.v. bolus dose of 0.1 mmol/kg gadobutrol for the pediatric populations aged 0 - < 2 years (simulated for 0 - < 2 months (N=9) and ≥ 2 - 23 months (N=34)) and 2 – 17 years (simulated for 2 years (N=199), 7 years (N=200), 12 years (N=200), and 17 years (N=200)) based on the final population PK model in pediatric population aged 0 – 2 years and aged 2 – 17 years, respectively.

In the box plot, 10%-point, 25%-point, median, 75%-point and 90%-point are shown from the top, and the marks of "•" mean 5%- and 95%-points.
(Source: Applicant's Population PK Report for pediatric patients aged 0 – 23 months, p39)

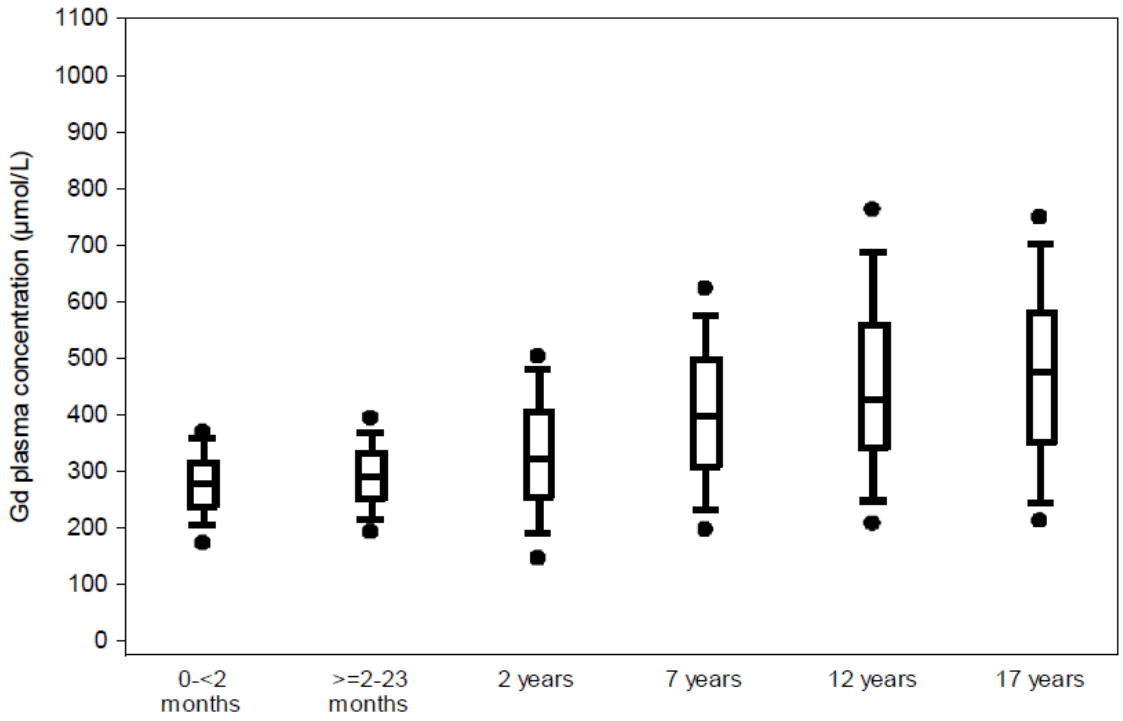

Figure 13: Distribution of simulated gadobutrol plasma concentrations [µmol/L] at 30 minutes (C30) after i.v. bolus dose of 0.1 mmol/kg gadobutrol for the pediatric populations aged 0 - < 2 years (simulated for 0 - < 2 months (N=9) and ≥ 2 - 23 months (N=34)) and 2 – 17 years (simulated for 2 years (N=199), 7 years (N=200), 12 years (N=200), and 17 years (N=200)) based on the final population PK model in pediatric population aged 0 – 2 years and aged 2 – 17 years, respectively.

In the box plot, 10%-point, 25%-point, median, 75%-point and 90%-point are shown from the top, and the marks of "•" mean 5%- and 95%-points.
(Source: Applicant's Population PK Report for pediatric patients aged 0 – 23 months, p40)

Based on this comparison the applicant concludes the following:

- Similar AUC values were observed for the entire pediatric population aged 0 - < 2 years in study 91741, with a trend to slightly higher AUC values for the very young subjects aged 0 - < 2 months.
- AUC values widely overlapped across all age groups (0 - 17 years). Thus, based on the systemic exposure which is the main safety related PK parameter, no safety concern is expected in pediatric subjects aged 0 – < 2 years after an IV injection of 0.1 mmol/kg gadobutrol.
- Simulated C20 and C30 concentrations showed high similarity across all age groups (0 – 17 years). Thus, considering the C20 value as an indicator for imaging efficiency, similar signal/contrast-enhancement is expected to be achieved in the

pediatric population aged 0 - < 2 years as seen in pediatric subjects aged 2 – 17 years.

Reviewer's Comments

We do not agree with the applicant's modeling strategy. The applicant refined a population PK model based on a previous analysis of pediatric population aged 2 – 17 years (study 310788). Then applicant used the refined model to estimate PK parameters in 0-2 year pediatrics (N=43, 127 plasma concentrations in study 91741). Given the availability of PK data from pediatric population aged 0 - 2 years (current study 91741) and 2 – 17 years (study 310788, A43735), a combined population PK model should have been utilized with all the PK data available from pediatric patients aged 0 – 17 years to examine whether the PK is comparable in pediatric patients across all age groups (0 – 17 years) at the same dose level of 0.1 mmol/kg.

Therefore, the reviewer used all the available data to develop the population PK model and use the model to compare PK in 0-2 year pediatrics and pediatrics 2-17 years. It is worth noting that even though the methodology of the applicant and the reviewer is different, the conclusions remain the same i.e. dose of 0.1 mmol/kg produces reasonably similar exposures in pediatrics 0-2 months when compared with pediatrics 2-17 years of age. Please refer to section 4 below for more details.

4 Reviewer's Analysis

4.1 Objectives

Analysis objectives are:

1. To develop a population PK model with all the available PK data from pediatric patients aged 0 – 17 years.
2. To compare derived AUC and simulated C20 and C30 across all age groups (0 – 17 years) based on the model to determine if the proposed 0.1 mmol/kg produces exposures in pediatric patients aged 0 – 2 years that are reasonably similar to that of pediatric population aged 2 - 17 years.

4.2 Methods

4.2.1 Data Sets

Data sets used are summarized in Table 3: Analysis Data Sets.

Table 3: Analysis Data Sets

Study Number	Name	Link to EDR
Study 91741	imp16152-pk-002.xpt	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Gadobutorol_201277_LL\Applicant Data and Reports\dataset\16152\analysis\legacy\datasets
Study 310788	imp13267pk010.xpt	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM

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		Reviews\Gadobutorol_201277_LL\Applicant Data and Reports\NDA 201277\0000\m5\datasets\a40794\analysis
PopPK modeling	imp16152-pk-pediatric.csv	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Gadobutorol_201277_LL\PPK Analyses\Final Model
PopPK simulation	imp16152_pk_pediatric_sim.csv	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Gadobutorol_201277_LL\PPK Analyses\Final Model

4.2.2 Software

NONMEM software (Version 7.2.0, Icon Development Solutions, Ellicott City, Maryland USA) together with PsN (Version 4.2.0, http://psn.sourceforge.net/) and Pirana (Version 2.9.0, http://www.pirana-software.com/) were used to develop population PK model and to generate the final individual PK parameters. R (Version 3.0.3, http://www.r-project.org/) was used for NONMEM dataset creation, goodness-of-fit (GOF) and VPC assessment.

4.2.3 Models

A two-compartment model including body weight as scaling factor for the parameters CL and V1 for both pediatric populations aged 0 -<2 years and 2 - 17 years was refined. The following components were re-evaluated:

- The need to estimate the power of body weight as a scaling factor for CL and V1.
- Covariates needed to explain variability in addition to body weight.
    - Linear model, Hill's model and power model were tested for the effect of eGFR on CL;
    - Stepwise model (different typical body weight-scaled CL value for very young population, eg. aged 0-2 months or 0-6 months) and Hill's model were tested for the effect of age on CL.

Plots of clearance estimates against each intrinsic factor (body weight, eGFR and age), the reduction in the IIV, physiological understanding, and the objective function value (OFV) were considered in determining the impact each covariate had on the individual's clearance estimate.

4.3 Results

4.3.1.1 Model refinement

The key runs of the model refinement are summarized in Table 4.
As a starting point, a two-compartment model with inter-individual variability on CL and V1 (run1) was built as a base model. Four different allometric models with a bodyweight-dependent maturational exponent were tested:

- fix the scaling factor of 0.75 for CL and 1 for V1 (run8)
- fix the scaling factor of 0.75 for CL and estimate that for V1 (run10)

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- estimate the scaling factor for Cl and fix 1 for V1 (run12)
- estimate scaling factors for both CL and V1 (run14)

The best model for body weight covariate model was found to be model run14 with estimated scaling factors of 0.812 for CL and 0.911 for V1. Based on this model, other covariates models were tested for the effect of eGFR and age on CL.

A significant decrease of OFV (-51.523) was found when eGFR was introduced linearly in the CL model (run40). In addition to body weight and eGFR, age has an additional impact on CL (run48), which was needed to explain the reduced renal function during the first few weeks after birth due to age related adaptations in renal function (**Figure 11**). Different typical body weight-scaled CL values were therefore estimated for age group 0 - < 2 months and age group ≥ 2 months. After incorporating the effects of eGFR and age on CL, parameter estimate of the exponent of the power model for body weight on CL was approximately 0.735, which is very close to the exponent value of 0.75. The increase in the OFV was negligible (+0.164, run68) when it fixed to 0.75. The backward elimination step demonstrated significant decrease in OFV after addition of the covariates (run81 – run83). Table 5 shows the population estimates of the final population PK model (run84) for the pediatric patients aged 0 – 17 years. All parameters were estimated with adequate precision.

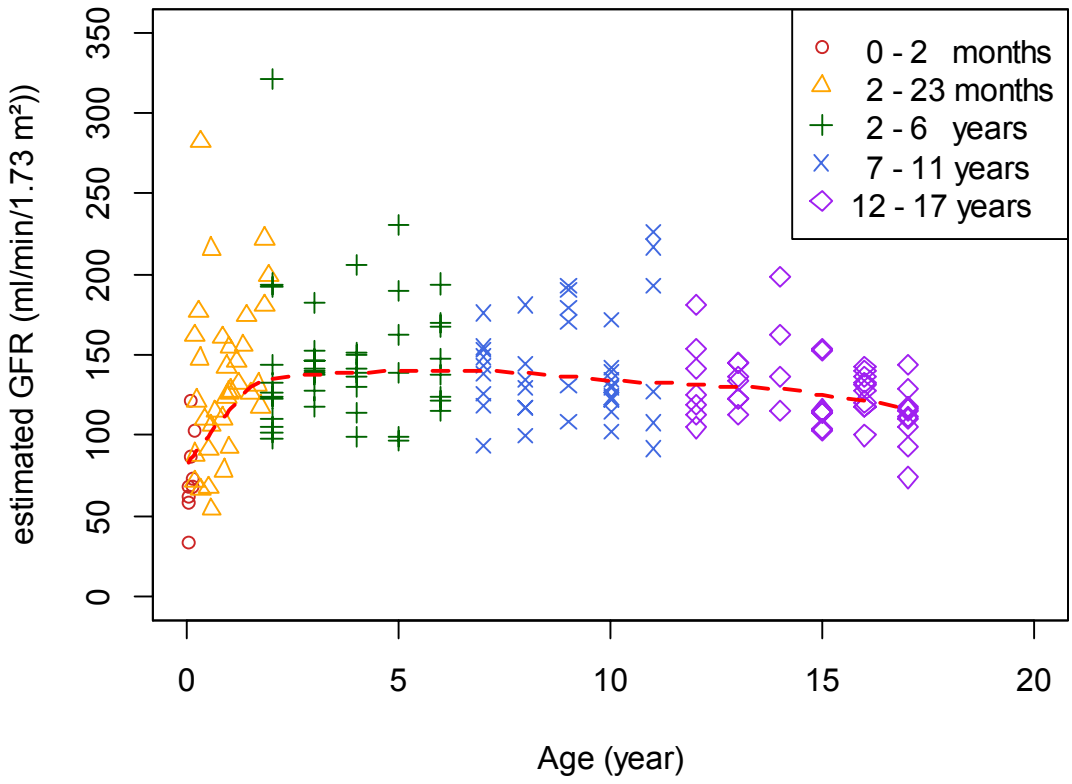

Figure 14: Correlation between estimated GFR and age based on the study data.

Table 4: Summary of key runs during development of population PK model

#Run	*#Ref*	*Description*	*OFV*	*ΔOFV*	*Min.*	*Cov.*	*Sign.*
Base model							
1		2-compartment model with first order absorption and elimination, IIV for CL and V1	4510.037		Successful	OK	4.3
Covariate model (body weight)							
8	1	WT on CL (Fix); WT on V1 (Fix)	4232.138	-277.899	Successful	OK	4.7
10	1	WT on CL (Fix); WT on V1 (Est)	4227.434	-282.603	Successful	OK	4.3
12	1	WT on CL (Est); WT on V1 (Fix)	4223.597	-286.440	Successful	OK	4.1
14	1	WT on CL (Est); WT on V1 (Est)	4222.343	-287.694	Successful	OK	6.3
Covariate model (eGFR, age)							
40	14	WT on CL (Est); WT on V1 (Est); eGFR on CL (linear)	4170.820	-51.523	Successful	OK	4.2
41	14	WT on CL (Est); WT on V1 (Est); eGFR on CL (Power)	4172.317	-50.026	Successful	OK	4.0
42	14	WT on CL (Est); WT on V1 (Est); eGFR on CL (Hill's)	4175.969	-46.374	Successful	OK	4.5
44	14	WT on CL (Est); WT on V1 (Est); AGE on CL (different TVCL for age 0 – 2 months)	4176.806	-45.537	Successful	OK	4.6
45	14	WT on CL (Est); WT on V1 (Est); AGE on CL (different TVCL for age 0 – 6 months)	4197.708	-24.635	Successful	OK	4.1
46	14	WT on CL (Est); WT on V1 (Est); AGE on CL (Hill's)	4172.870	-49.473	Successful	OK	4.6
48	40	WT on CL (Est); WT on V1 (Est); eGFR on CL (linear); AGE on CL (different TVCL for age 0 – 2 months)	4139.895	-30.925	Successful	OK	4.4
68	48	WT on CL (Fix); WT on V1 (Est); eGFR on CL (linear); AGE on CL (different TVCL for age 0 – 2 months)	4140.059	+ 0.164	Successful	OK	4.6
80	68	Full model, same as run68	4140.059		Successful	OK	4.6
Covariate model (Backward elimination)							
81	80	Full model, WT on V1 (Fix to 1)	4153.513	+13.454	Successful	OK	5.2
82	80	Full model, remove eGFR on CL	4177.207	+37.148	Successful	OK	4.4
83	80	Full model, remove AGE on CL	4171.668	+31.609	Successful	OK	4.6
Final model							
84	80	Final model, same as run68	4140.059		Successful	OK	4.6

Reference ID: 3661632

Table 5: Gadobutrol pediatric population estimates of the final PK model (Run84)

Parameter	*Unit*	*Estimate*	*RSE[%]*	*LLCI*	*ULCI*	*Description*
Fixed Effects						
$CL/WGHT^{0.75}$ (Age < 2 months)	$L/h/kg^{0.75}$	0.224	2.20	0.214	0.234	Systemic clearance normalized to body weight to a power of 0.75 for age 0 - < 2 months
$CL/WGHT^{0.75}$ (Age >= 2 months)	$L/h/kg^{0.75}$	0.110	13.2	0.082	0.138	Systemic clearance normalized to body weight to a power of 0.75 for age ≥ 2 months
$V1/WGHT^{SV}$	L/kg^{SCL}	0.440	7.10	0.379	0.501	Central volume of distribution normalized to body weight to a power of 1
SV		0.742	4.00	0.299	0.544	Power of body weight as a scale factor on V1
Q	L/h	0.272	9.90	0.219	0.325	Inter-compartmental clearance
V2	L	1.95	14.4	1.399	2.501	Peripheral volume of distribution
eGFR_CL	%	0.421	14.8	0.299	0.544	Percent increase/decrease in CL per 1% change in estimated GFR at baseline relative to median (130 ml/min/1.73 m²)
Random Effects (Inter-individual variability)						
IIV_CL	%CV	18.8 [17%][a]	26.5	9.04	28.6	Inter-individual variability of CL
IIV_V1	%CV	22.0 [34%] [a]	36.5	6.26	37.7	Inter-individual variability of V1
Residual error						
SIGMA prop	%CV	27.5 [18%] [a]	14.5	19.7	35.3	Proportional residual error of gadolinium plasma concentrations

[a] Shrinkage for IIV of CL, V1 and residual error.

4.3.1.2 Model validation

Goodness-of-fit plots of the final model are presented in Figure 12. The plots show a random and equal distribution of the observed versus predicted concentrations around the line of identity for each age groups. Weighted residuals (WRES) are randomly distributed around 0 when plotted over time or population predicted concentrations.

Table 6 and Figure 13 shows the reduction in the inter-individual variation of gadobutrol clearance (CL) as a function of body weight, eGFR and age after 1) the inclusion of body weight as a covariate (run14), 2) the subsequent inclusion of eGFR as a covariate (run40) and 3) the subsequent inclusion of age as a covariate (run48). Visual inspection of the difference between the base model (Figure 13, 1st row, 2nd column) and body weight covariate model by weight (Figure 13, 2nd row, 2nd column) indicates that the BW covariate model could mostly correct the trend between clearance and body weight. However, there still appears to be a correlation between eGFR and inter-individual variation of clearance (Figure 13, 2nd row, 3rd column). Accounting for the individual eGFR on CL leads to the disappearance of correlation between eGFR and η_{CL} (Figure 13, 3rd row, 3rd column) and a decrease of 3.8% in inter-individual variability of CL. Incorporating age as a factor on clearance eliminates the majority of the remaining bias for the youngest population (0 - < 2 months; Figure 13, 3rd row, 4th column) in the model prediction as seen from the near symmetrical distribution about zero in the panels on the 4th row of Figure 13.

Figure 14 and Figure 15 present the results of the visual predictive check (VPC) by comparing the 90% prediction interval of the simulated concentrations with the observed concentrations. The model appears to describe the overall variability in each age population adequately. Individual concentration-time plots showed the final population PK model could fit the observed data well both for pediatric population aged 0 – 2 months (Figure 16) and 2 – 23 months (Figure 17). Individual concentration-time plots for pediatric population aged 2-17 years were not shown here.

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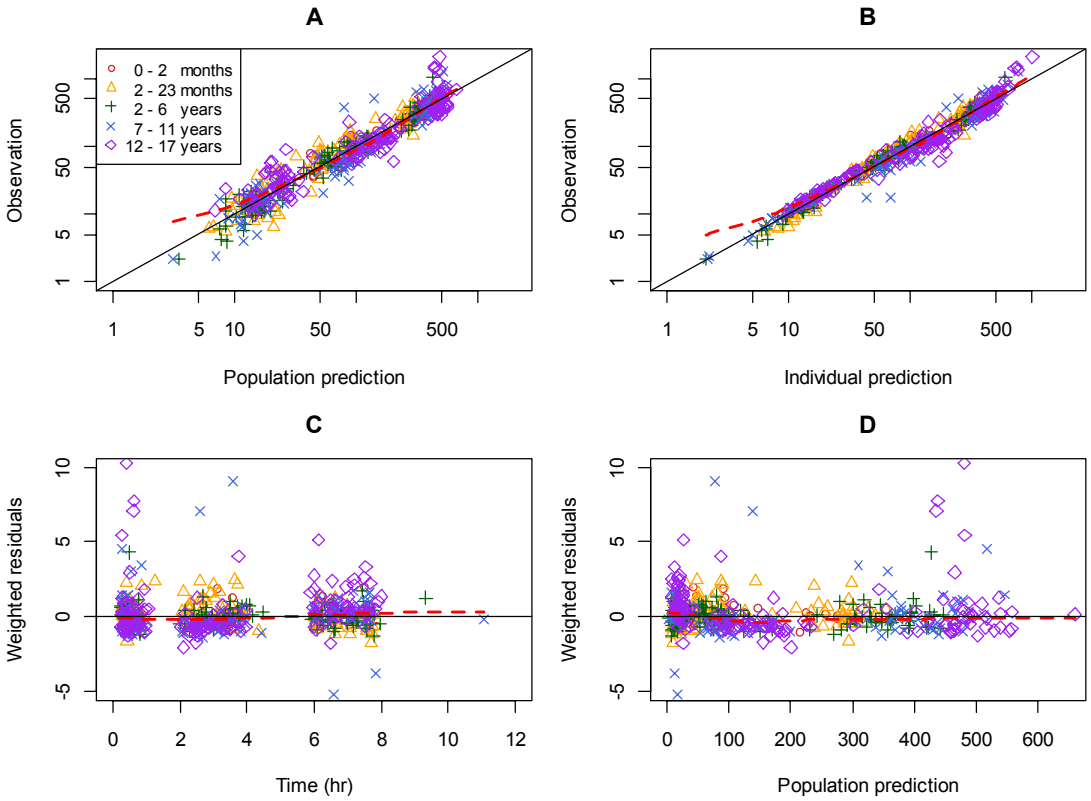

Figure 15: Goodness-of-fit plots of the final model (run84).

Table 6: Comparison of inter-individual variability of the estimates of CL & V1 between base model and covariate models.

Model	*Ref.*	*Description*	*IIV of CL*			*IIV of V1*		
			Estimate [%CV]	*RSE [%]*	*Shrinkage [%]*	*Estimate [%CV]*	*RSE [%]*	*Shrinkage [%]*
Run1		Base model	40.6	7.4	2.5	52.1	23.6	62.5
Run14	Run1	+ BW on CL & V1	24.1	8.5	10.7	27.8	17.6	32.4
Run40	Run14	+ eGFR on CL	20.3	11.9	14.2	23.8	15.5	32.0
Run48	Run40	+ AGE on CL	18.5	14.6	17.2	21.7	17.2	34.0

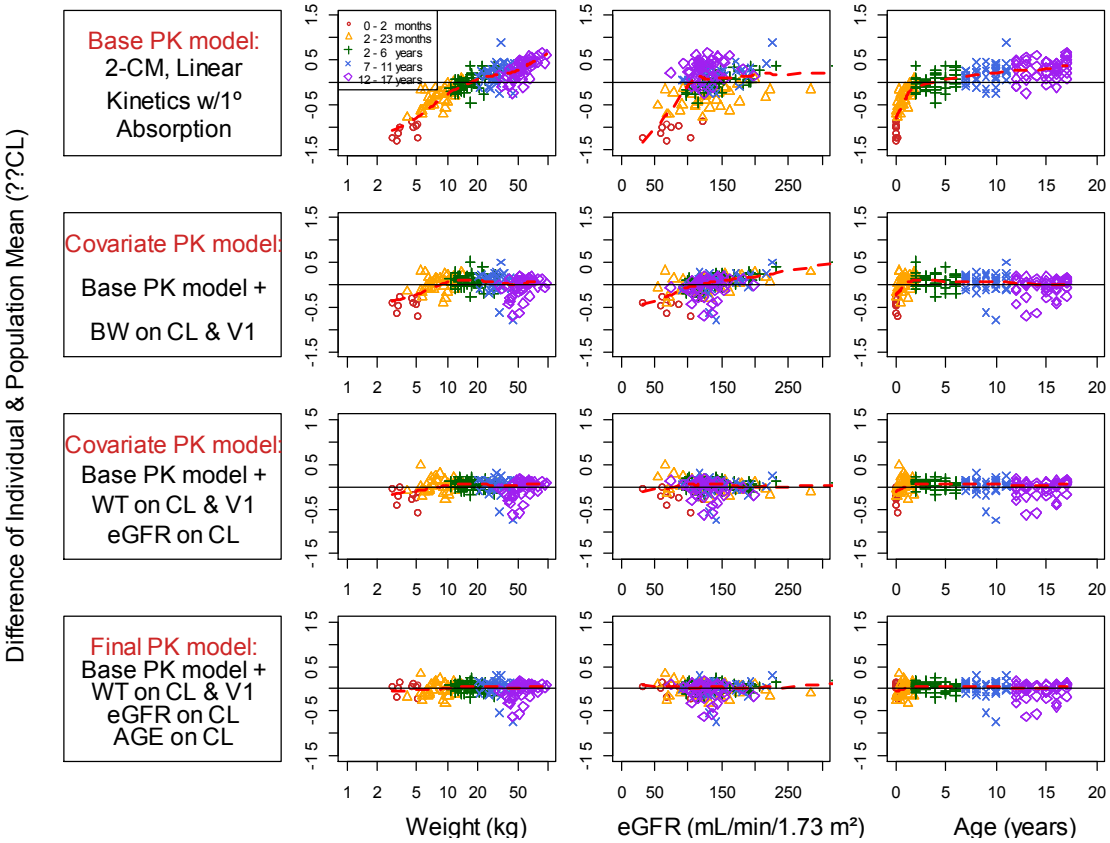

Figure 16: Including body weight, eGFR and age as covariates on clearance significantly reduce the inter-individual variability of the clearance estimates.

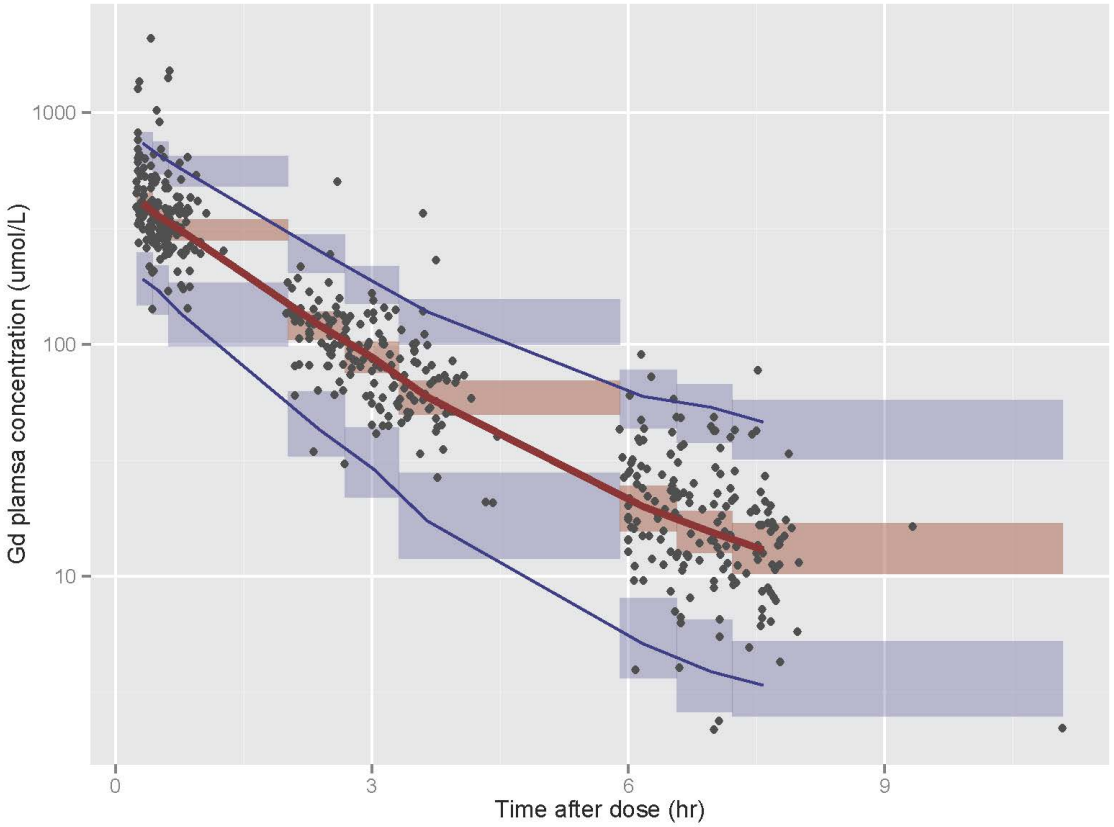

Figure 17: Visual Predictive Check of for the final model. (Solid cycles: observations; red lines: 50% predicted percentiles; blue lines: 95% prediction intervals; orange rectangles: 95% confidence intervals of 50% predicted percentiles; blue rectangles: 95% confidence intervals of 5% predicted percentiles and 95% predicted percentiles)

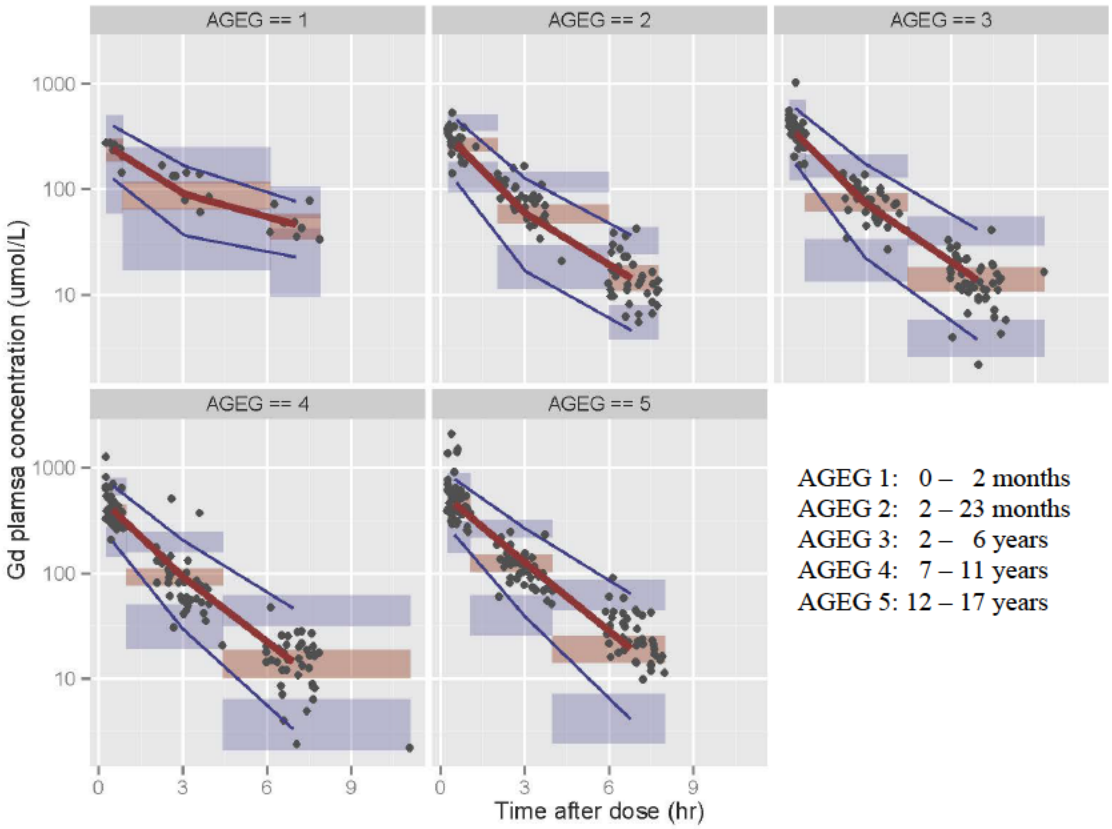

Figure 18: Visual Predictive Check for the final model stratified by age group. (Solid cycles: observations; red lines: 50% predicted percentiles; blue lines: 95% prediction intervals; orange rectangles: 95% confidence intervals of 50% predicted percentiles; blue rectangles: 95% confidence intervals of 5% predicted percentiles and 95% predicted percentiles)

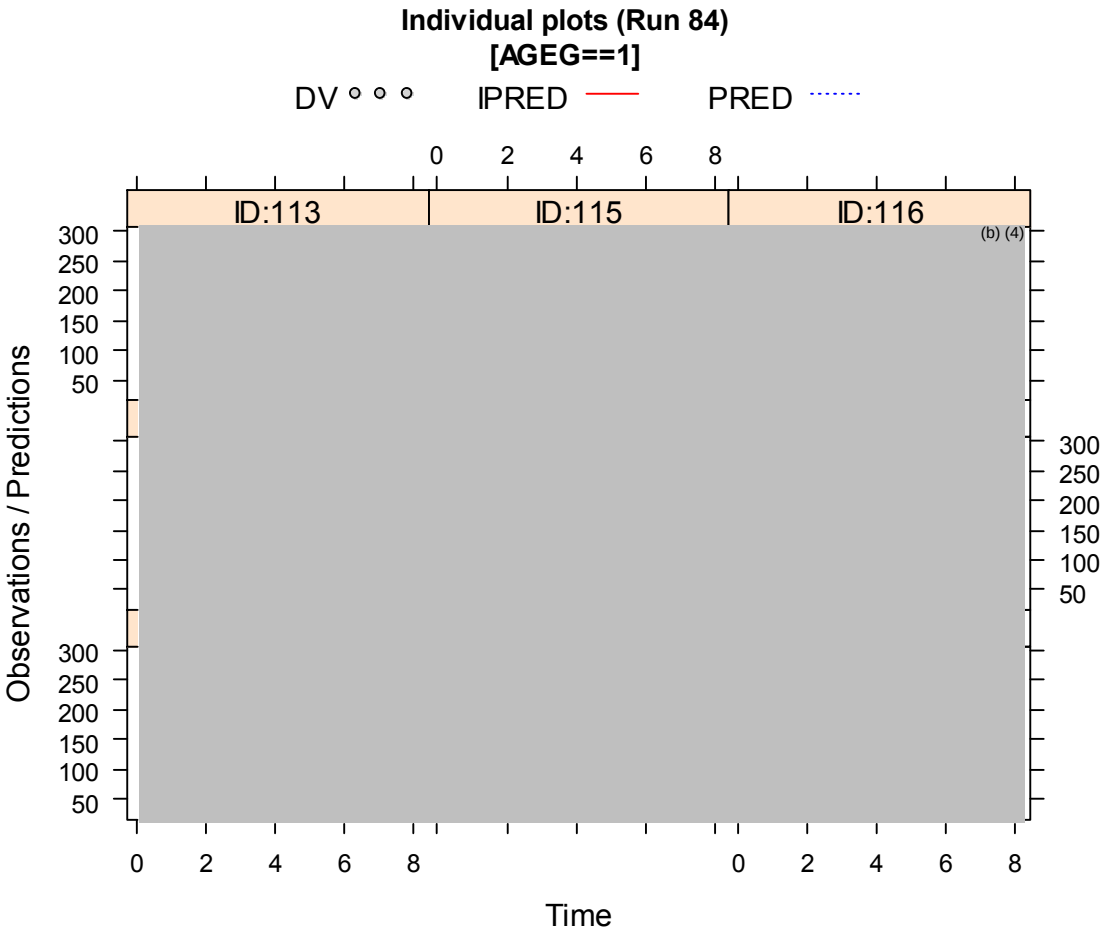

Figure 19: Individual concentration-time plots for the pediatric population aged 0 - < 2 months (linear scale).

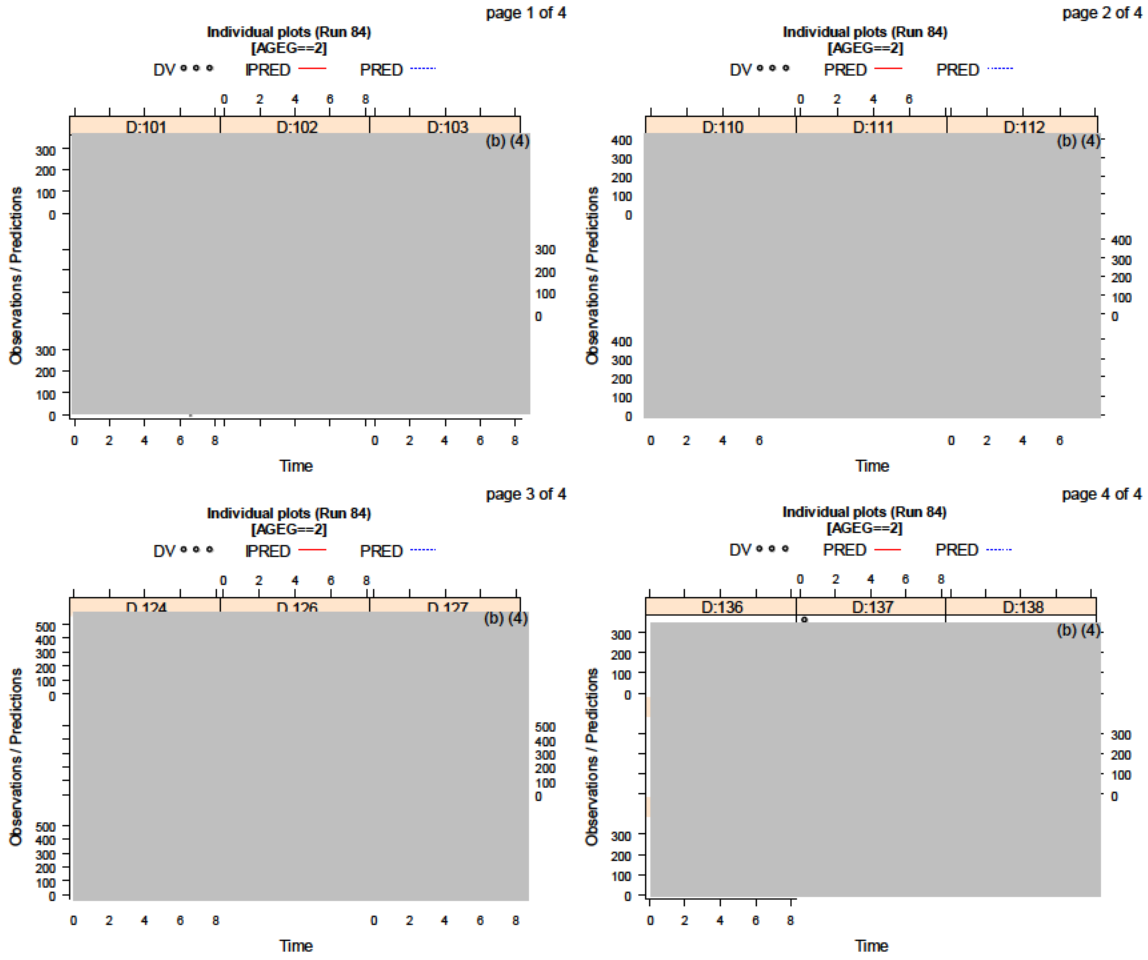

Figure 20: Individual concentration-time plots for the pediatric population aged ≥ 2 months (linear scale).

4.3.1.3 Individual PK evaluation based on the final population PK model

The individual key PK parameters were compared across all age groups in the pediatric population aged 0 – 17 years. The summary statistics of the derived exposure parameters are displayed in Table 7.

Body weight-normalized Vss decreased with increasing age across the entire pediatric population from age group 0 - < 2 months up to age group 12 – 17 years. The median values of $t_{1/2}$ and MRT were 3.5 – 5-fold higher in the youngest group 0 -< 2 months compared to the rest of the pediatric population. Body weight-normalized Vss, $t_{1/2}$ and MRT derived from our model are comparable to the applicant's results in pediatric population aged ≥ 2 years old, while these values were larger in age group 0-2 years than those applicant estimated. This is due to the different allometric scaling model for V1 (exponent was estimated to be 0.742) was used in our analysis compared to the applicant's model (exponent was fixed to 1).

Body weight-normalized CL decreased with increasing age from ≥ 2 months up to 17 years. AUC increased with increasing age from ≥ 2 months up to 17 years as shown in the table below.. With regard to AUC, the very young subjects aged 0 - < 2 months

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resembled the values of the oldest group aged 12 – 17 years. Overall, AUC values appear to be overlapped across the entire pediatric population aged 0 – 17 years. In Figure 18, boxplots of the estimated AUC values for the entire pediatric population evaluated are shown.

Table 7: Comparison of individual PK evaluation in pediatric population aged 0 - < 2 years (study 91741; binned by age: 0 - < 2 months and ≥ 2 - 23 months) versus pediatric population aged 2 – 17 years (study 310788, A43735; binned by age: 2 – 6 years, 7 – 11 years, and 12 – 17 years)

Parameter	All (0-<2 years) [a]	0-<2 months [a]	≥2-23 months [a]	All (2-<17 years) [a]	2-6 years [a]	7-11 years [a]	12-17 years [a]
	N=43	N=9	N=34	N=130	N=45	N=39	N=46
CL/kg [L/h/kg]	0.128 (0.0529, 0.195)	0.0639 (0.0529, 0.0778)	0.133 (0.0803, 0.195)	0.0983 (0.0433, 0.215)	0.119 (0.0801, 0.215)	0.0994 (0.0433, 0.165)	0.0808 (0.0455, 0.103)
Vss/kg [L/kg]	0.524 (0.363, 1.04)	0.741 (0.659, 1.04)	0.479 (0.363, 0.804)	0.244 (0.109, 0.414)	0.332 (0.189, 0.414)	0.240 (0.158, 0.303)	0.196 (0.109, 0.285)
AUC [µmol*h/L]	781 (513, 1891)	1597 (1285, 1891)	757 (513, 1229)	1055 (412, 2285)	846 (412, 1331)	1025 (623, 2285)	1237 (946, 2211)
$t_{1/2}$ [h]	2.91 (1.60, 12.4)	8.62 (6.60, 12.4)	2.45 (1.60, 4.44)	1.73 (0.905, 2.71)	1.91 (1.04, 2.70)	1.66 (0.905, 2.71)	1.68 (1.31, 2.48)
MRT [h]	4.20 (2.30, 17.9)	12.4 (9.52, 17.9)	3.54 (2.30, 6.41)	2.49 (1.31, 3.90)	2.76 (1.51, 3.89)	2.39 (1.31, 3.90)	2.42 (1.89, 3.57)

[a] Median (Minimum, Maximum)

4.3.1.4 Simulations based on the final population pharmacokinetic model

The median values and the 5th/95th percentile ranges of simulated C20 and C30 concentrations after i.v. bolus dose of 0.1 mmol/kg gadobutrol in pediatric population across all age groups were presented in Table 8. Figure 18 shows the AUC of gadobutrol for the pediatric population aged 0 - 17 years plotted against age based on simulation results in 200 virtual subjects for each age group. AUC values tend to slightly increase with increasing age except for in the very young subjects (aged 0 - 2 months), and AUC values in pediatric population aged 0 – 2 months appear to be comparable to those in population aged 12 – 17 years. Overall, AUC values widely overlapped across the entire pediatric population aged 0 – 17 years, which was consistent with the applicant's results.
Simulated C20 (Figure 19) and C30 (Figure 20) concentrations increased with increasing age across the entire pediatric population from age group 0 - < 2 months up to age group 12 - 17 years by approximately 75%. Nevertheless, the 5th/95th percentile range of the two youngest age groups 0 - < 2 months and ≥ 2 - 23 months overlapped to a large extent with the 5th/95th percentile range of the older age groups 2 - 17 years. These results are consistent with the applicant's finding.

Table 8: Comparison of simulated gadolinium plasma concentrations at 20 min (C20) and 30 min (C30) after i.v. bolus dose of 0.1 mmol/kg gadobutrol in pediatric population aged 0 - < 2 years versus pediatric population aged 2 – 17 years.

Parameter	All (0-<2 years) [a,b]	0-<2 months [a,b]	≥2-23 months [a,b]	All (2-<17 years) [a,b]	2-6 years [a,b]	7-11 years [a,b]	12-17 years [a,b]
	N=400	N=200	N=200	N=600	N=200	N=200	N=200
C_{20} [µmol/L]	290 (137, 461)	268 (133, 446)	300 (164, 509)	442 (221, 786)	362 (195, 628)	452 (255, 750)	518 (276, 867)
C_{30} [µmol/L]	249 (125, 380)	243 (122, 369)	254 (133, 392)	361 (200, 597)	309 (182, 479)	367 (211, 367)	436 (215, 681)

[a] Median (5th, 95th percentile)

[b] Statistics of 1000 simulations based on 5 different median weights and different typical CL values scaled to body weight corresponding to age group 0 - < 2 months (median age: 0.9 months, median body weight: 4.4 kg), age group 2 - 23 months (median age: 10.2 months, median body weight: 8.2 kg), age group 2 – 6 years (median age: 4 years, median body weight: 16 kg) , age group 7 – 11 years (median age: 9 years, median body weight: 31.1 kg) and age group 12 – 17 years (median age: 15 years, median body weight: 55.1 kg) with 200 virtual subjects per group.

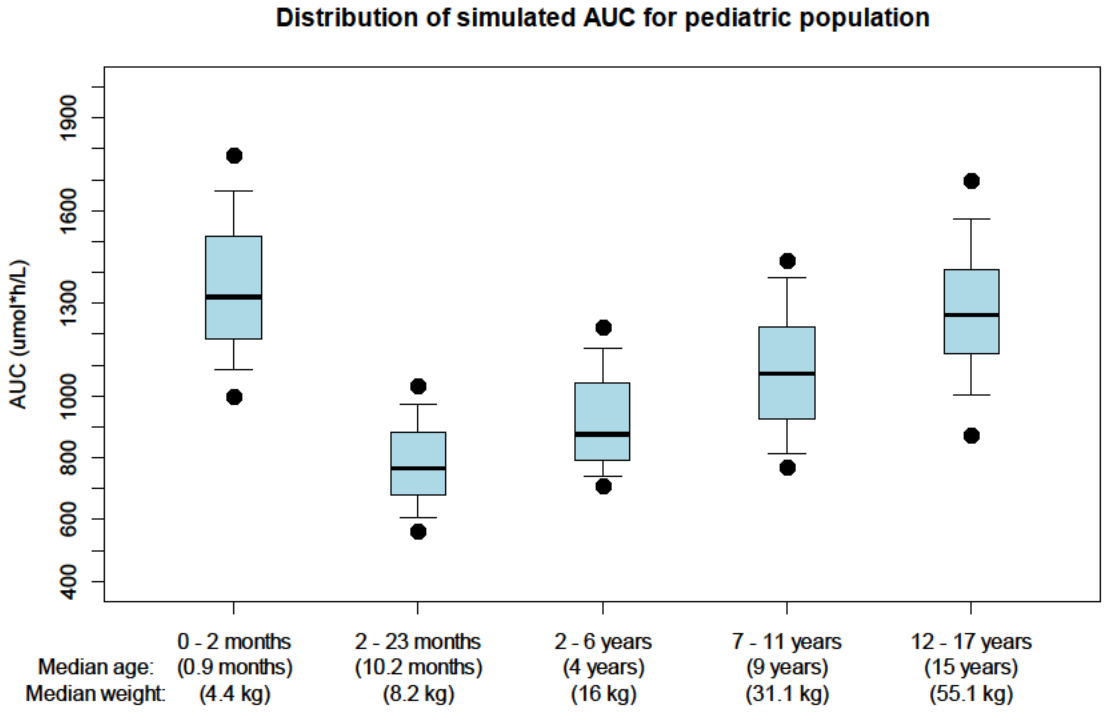

Figure 21: Distribution of simulated AUC values for the pediatric populations aged 0 - < 2 months, 2 - 23 months, 2 – 6 years, 7 – 11 years and 12 - 17 years based on the final population PK, respectively (n = 200).

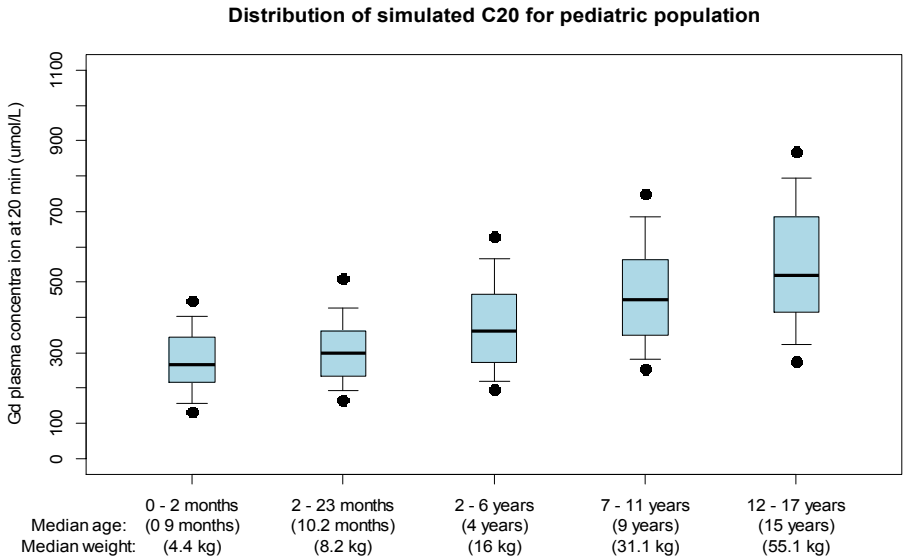

Figure 22: Distribution of simulated gadobutrol plasma concentrations [µmol/L] at 20 minutes (C20) after i.v. bolus dose of 0.1 mmol/kg gadobutrol for the pediatric populations aged 0 - < 2 months, 2 - 23 months, 2 – 6 years, 7 – 11 years and 12 - 17 years based on the final population PK, respectively (n = 200).

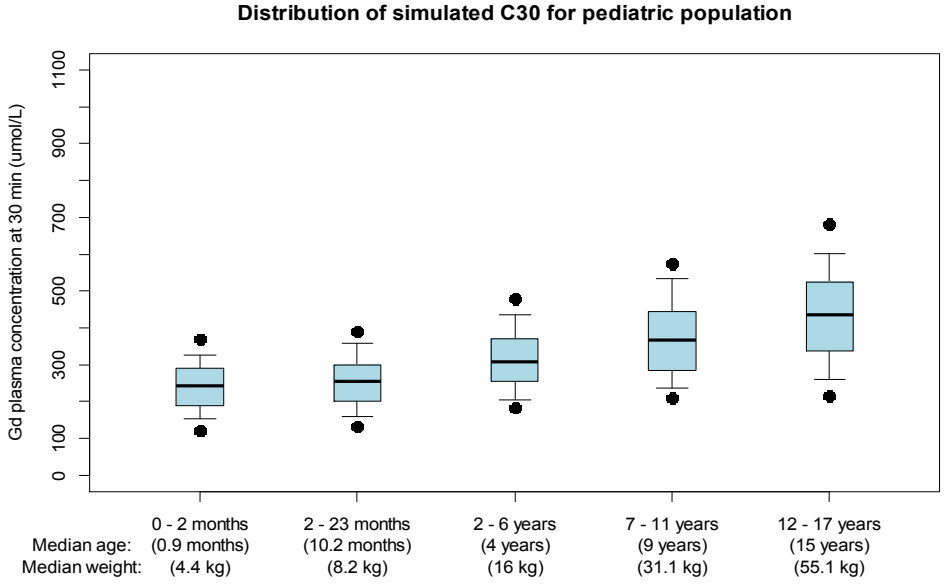

Figure 23: Distribution of simulated gadobutrol plasma concentrations [µmol/L] at 30 minutes (C30) after i.v. bolus dose of 0.1 mmol/kg gadobutrol for the pediatric populations aged 0 - < 2 months, 2 - 23 months, 2 – 6 years, 7 – 11 years and 12 - 17 years based on the final population PK, respectively (n = 200).

4.4 Conclusion

Based on the independent analysis conducted by the reviewer, we agree with the applicant's proposed dose 0.1 mmol/kg gadobutrol for pediatric population aged 0 – 2 years.

5 Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
Run84 mod	Final PK Model Control Stream	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Gadobutorol_201277_LL\PPK Analyses\Final Model
Run84.lst	Final PK Model Output	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Gadobutorol_201277_LL\PPK Analyses\Final Model
Run84sim.mod	Simulation of Final PK Model Control Stream	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Gadobutorol_201277_LL\PPK Analyses\Final Model
Run84sim.lst	Simulation of Final PK Model Output	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Gadobutorol_201277_LL\PPK Analyses\Final Model
Model evaluation.R	R code for Figure 11, 12 and 13	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Gadobutorol_201277_LL\PPK Analyses\Graphs of final model
Model prediction.R	R code for Table 8	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Gadobutorol_201277_LL\PPK Analyses\Graphs of final model
VPC plot for final model.R	R code for Figure 14 and 15	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Gadobutorol_201277_LL\PPK Analyses\Graphs of final model
Individual plot for final model.R	R code for Figure 16 and 17	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Gadobutorol_201277_LL\PPK Analyses\Graphs of final model
Simulation results.R	R code for Figure 18, 19 and 20	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Gadobutorol_201277_LL\PPK Analyses\Graphs of final model

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4.2 Coversheet and OCP filing review form

Office of Clinical Pharmacology and Biopharmaceutics *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		Information
NDA Number	201-277	**Brand Name**	Gadavist Injection
OCPB Division (I, II, III, IV, V)	V	**Generic Name**	Gadavist Injection
Medical Division	Medical Imaging Products (DMIP)	**Drug Class**	Imaging
OCP Reviewer	Christy S. John, Ph.D.	**Indication(s)**	Gadavist is a gadolinium-based contrast agent indicated for intravenous use: In diagnostic magnetic resonance imaging (MRI) in adults and children of all ages (including term neonates) to detect and visualize areas with disrupted blood brain barrier (BBB) and/or abnormal vascularity of the central nervous system. For MRI of the breast to assess the presence and extent of malignant breast disease.
OCP Team Leader	Gene Williams, Ph.D.	**Dosage Form**	Gadavist injection contains 1 mmol gadobutrol/mL (equivalent to 604.72 mg gadobutrol/mL) and is available in vials and prefilled syringes.
		Dosing Regimen	The recommended dose of Gadavist for adults and children of all ages (including term neonates) is 0.1 mL/kg body weight (0.1 mmol/kg).
Date of Submission	6/30/2014	**Route of Administration**	Intravenous

Estimated Due Date of OCPB Review	11/21/14	**Sponsor**	Bayer HealthCare Pharmaceuticals, Inc.
PDUFA Due Date	12/30/14	**Priority Classification**	S
Division Due Date	1/15/2015		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	X	1		
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				

Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	X	1		
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		1		

Filability and QBR comments		
	"X" if yes	Comments
Application fileable ?	**X**	This sNDA is supported by a single pharmacokinetic (PK) and safety study #91741 of gadavist in children 0-<2 years of age. This pediatric study was designed to provide sufficient PK and safety data to support extrapolation of efficacy from adults to children 0-< 2 years of age and to establish a dose recommendation for this young pediatric population. The application is fillable from a clinical pharmacology perspective.
Comments sent to firm ?		
QBR questions (key issues to be considered)	The key question for the review is to compare the pharmacokinetics and exposure of gadavist in children 0 - <2 years of age to that of children over 2 years of age. The PK parameters to be compared include simulation of C20 (20 min post-injection).	

Other comments or information not included above	
Primary reviewer	**Christy S. John, Ph.D**
Secondary reviewer, Team Leader	**Gene Williams, Ph.D.**

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

/s/

CHRISTY S JOHN
11/20/2014

NITIN MEHROTRA
11/20/2014

NAM ATIQUR RAHMAN
11/20/2014