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A Pharmacokinetics, Efficacy, and Safety Study of Gadoterate Meglumine in Pediatric Subjects Aged Younger Than 2 Years

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Objectives: The primary objective of this study was to investigate the pharmacokinetic profile of gadoterate meglumine in pediatric patients younger than 2 years; the secondary objectives were to document its efficacy and safety.

Material and Methods: This was a Phase IV open-label, prospective study conducted in 9 centers (4 countries). Forty-five patients younger than 2 years with normal estimated glomerular filtration rate and scheduled to undergo routine gadolinium-enhanced magnetic resonance imaging (MRI) of any organ were included and received a single intravenous injection of gadoterate meglumine (0.1 mmol/kg). To perform the population pharmacokinetics analysis, 3 blood samples per subject were drawn during 3 time windows at time points allocated by randomization.

Results: Gadoterate meglumine concentrations were best fitted using a 2-compartmental model with linear elimination from central compartment. The median total clearance adjusted to body weight was estimated at 0.06 L/h per kg and increased with estimated glomerular filtration rate according to a power model. The median volume of distribution at steady state (V_{ss}) adjusted to body weight was estimated at 0.047 L/kg. Estimated median terminal half-life ($t_{1/2\beta}$) was 1.35 h, and the median systemic exposure (area under the curve) was 1591 $\mu\text{mol h/L}$. Efficacy was assessed by comparing precontrast +postcontrast images to precontrast images in a subset of 28 subjects who underwent an MRI examination of brain, spine, and associated tissues. A total of 28 lesions were identified and analyzed in 15 subjects with precontrast images versus 30 lesions in 16 subjects with precontrast + postcontrast images. Lesion visualization was improved with a mean (SD) increase in scores at subject level of 0.7 (1.0) for lesion border delineation, 0.9 (1.6) for internal morphology, and 3.1 (3.2) for contrast enhancement. Twenty-six adverse events occurred postinjection in 13 subjects (28.9%), including 3 serious reported in 1 subject (2.2%). One subject (2.2%) experienced 1 rash of moderate intensity considered as related to gadoterate meglumine.

Conclusions: The pharmacokinetic profile of gadoterate meglumine after a single intravenous injection of 0.1 mmol/kg was appropriately described in newborns and infants younger than 2 years, for whom no dose adjustment is required. The improved efficacy of gadoterate meglumine for contrast-enhanced MRI examination of brain, spine, and associated tissues, as well as its good safety profile, was also demonstrated in this population.

Key Words: gadoterate meglumine, gadoteric acid, macrocyclic, MRI contrast agents, newborn, infants, population pharmacokinetics, GBCA

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Gadolinium-based contrast agents (GBCAs) are either linear or macrocyclic chelates of gadolinium, available as ionic or nonionic solutions. They behave as extracellular space markers and are administered by intravenous (IV) route at the usual dose of 0.1 mmol/kg of body weight (BW).¹ A GBCA was first used in 1984 in adults during magnetic resonance imaging (MRI) for diagnosis of different types of malignant or nonmalignant tumors.² Currently, in both Europe and the United States, central nervous system (CNS) imaging accounts for approximately half of all doses of contrast agents used during MRI.³ The first report of pediatric use of GBCA-enhanced MRI was published in 1988 in children older than 2 years⁴ and in 1989 in children younger than 2 years,⁵ in both cases for detection of intracranial lesions. Gadolinium-based contrast agent-enhanced MRI is now widely used in children for detection and follow-up of lesions in the CNS, that is, brain and spine, and associated tissues.^{6–10}

Gadoteric acid, meglumine salt (forming gadoterate meglumine; DOTAREM, Guerbet, Roissy CdG, France) is a macrocyclic and ionic GBCA with very high stability.¹¹ The first approved indication, contrast-enhanced MRI of the CNS, is the most widely used application. In more than 75 countries, gadoterate meglumine is approved for IV administration at a recommended dose of 0.1 mmol/kg of BW, without dose adjustment, in adult as well as in pediatric patients including the youngest younger than 2 years. In a total of 241 pediatric patients younger than 2 years included in 3 prospective clinical studies and 6 prospective postmarketing observational studies, a good level of efficacy and safety has been documented, consistent with those found for adult patients and pediatric patients older than 2 years.^{12–14} In adults, gadoterate meglumine is rapidly distributed in blood and extracellular fluid after IV injection. It is quickly renally eliminated from plasma in subjects with normal renal function^{15,16}; urinary elimination is delayed in case of renal impairment.¹⁷ In children younger than 2 years, with an ongoing maturation of renal function,^{18,19} there are no pharmacokinetics data so far obtained after gadoterate meglumine administration. The aim of the current study was to document in that fragile population the PK profile of this GBCA, as well as its safety and efficacy. This study was a company-sponsored post-marketing requirement from the US Food and Drug Administration (FDA) and was registered at www.ClinicalTrials.gov (NCT02411201).

MATERIALS AND METHODS

Study Design

This was a phase IV, open-label, prospective, multicenter, international study conducted in 4 countries: Austria, France, Hungary, and Poland. The primary objective was to evaluate pharmacokinetics profile in plasma of gadoterate meglumine after a single 0.1 mmol/kg IV administration in subjects younger than 2 years. The secondary objectives were to evaluate (a) the efficacy of gadoterate

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meglumine-enhanced MRI of CNS (brain, spine, and associated tissues) in a subgroup of subjects as assessed by on-site investigator and (b) the safety (clinical and biological) of gadoterate meglumine within 7 ± 1 days after the injection. The study was initiated after approval by the relevant Independent Ethics Committees.

Sample Size

A total of 50 subjects were to be included to ensure a minimum number of 40 evaluable subjects. Subjects were to be recruited into 3 predefined age groups to ensure age distribution across the pediatric population of the study: at least 5, 8, and 26 subjects aged 0 to 1, 1 to 3, and 3 to <24 months, respectively. Among them, at least 20 subjects who were referred for contrast-enhanced MRI of CNS were to be included to assess gadoterate meglumine-enhanced MRI efficacy in CNS.

Study Population

Inclusion Criteria

Included in this study were subjects younger than 2 years (term newborn, ie, age ≥ 37 weeks of amenorrhea, to toddlers aged 23 months inclusive) scheduled to undergo routine gadolinium-enhanced MRI of any organ (eg, CNS and cardiac) at a dose of 0.1 mmol/kg BW (0.2 mL/kg BW), with normal renal function according to estimated glomerular filtration rate (eGFR) calculated by the Schwartz formula as follows: $eGFR \text{ (mL/min/1.73 m}^2\text{)} = k \times \text{height (cm)/serum creatinine (mg/dL)}$, where $k = 0.45$ for full-term infants younger than 12 months and $k = 0.55$ for children 1 year or older.²⁰

Exclusion Criteria

- History of bleeding disorder or of anaphylactoid or anaphylactic reaction to any allergen (including drugs and contrast agents), known severe liver disease;
- Change in chemotherapy within 48 hours before gadoterate meglumine injection or planned to be done up to 24 hours after this injection; administration of any other contrast agent within 72 hours before gadoterate meglumine injection or planned to be done up to 24 hours after this injection;
- Invasive procedure (eg, surgery) between the screening visit and gadoterate meglumine injection or planned to be done up to 24 hours after this injection, condition, or treatment (eg, blood loss or transfusion, diuretics) occurring before gadoterate meglumine injection or planned treatment up to 24 hours after this injection that would modify gadoterate meglumine pharmacokinetics parameters or would prevent obtaining the scheduled number of blood samples;
- Any administration of investigational product within 7 days before gadoterate meglumine injection or planned to be done during study participation.

Study Procedures

Visits

Three visits were scheduled on-site (screening visit, inclusion visit followed by nonenhanced then gadoterate meglumine-enhanced MRI, follow-up visit 24 hours later). A follow-up contact (visit or phone call) was scheduled 7 ± 1 days after the injection.

Inclusion of Subjects

Informed consent was obtained from the parents for all subjects. Once eligibility criteria were checked, subjects had to be included before injection of gadoterate meglumine. Inclusion was managed through a central web randomization system (ie, IWRS, S-Clinica, Brussels, Belgium) in order to ensure (a) a specified distribution of the 3 predefined age groups; (b) the required number of subjects

scheduled for contrast-enhanced MRI of CNS; and (c) for each subject, the random allocation of the blood sampling time points needed for the PK analysis.

Magnetic Resonance Imaging

Magnetic resonance imaging was performed before and after gadoterate meglumine administration on magnetic resonance systems (1.5 or 3 T). Preparation of subjects (warming, reassurance, sedation, etc) was left to the investigator's initiative according to local protocol. The same imaging system, planes of view, and parameters were used for both precontrast and postcontrast examinations in each subject, and care was taken to ensure that image location and angulation were identical in both cases. The imaging sequences depended on body region examined according to the site's standard imaging protocol.

Contrast Agent Dosing and Administration

The investigational product was provided in colorless vials that contained 10 mL of an aqueous solution of gadoterate meglumine, at a concentration of 0.5 mmol/mL (ie, 3.76 g of gadoterate meglumine per vial).

Gadoterate meglumine was administered as an IV injection (preferably manual bolus) at a rate of 1 to 2 mL/s, at a dose of 0.1 mmol/kg BW (0.2 mL/kg BW), followed by a saline flush at the same flow rate, through a vascular access inserted in a peripheral vein and connected to an infusion line maintained throughout the contrast-enhanced MRI.

Pharmacokinetics

A population pharmacokinetics (PopPK) approach with sparse blood sampling was chosen to minimize the volume of blood sampled in this very young population, in accordance with the current International Council for Harmonisation, FDA, and European Medicines Agency guidelines and recommendations.^{21–25} Three post-injection blood samples per subject were drawn from a catheter inserted in a peripheral vein: 1 during the 10- to 60-minute time window, 1 during the 2- to 4-hour time window, and 1 during the 6- to 8-hour time window, each time point being randomly allocated. These time windows/sampling times were defined on the basis of available pharmacokinetic data on gadoterate meglumine in adults.

Gadoteric Acid Assay

Blood samples of 1.0 mL each were collected at each time point into lithium heparin tubes. Plasma was obtained by centrifugation and aliquots of 0.5 mL stored at -20°C . The determination of gadoteric acid in plasma was performed using a validated liquid chromatography coupled with tandem mass spectrometry method in a centralized analysis center (Eurofins ADME BIOANALYSES, Vergeze, France). The lower limit of quantification was 5 $\mu\text{mol/L}$.

Efficacy of Gadoterate Meglumine-Enhanced MRI in CNS (Precontrast and Postcontrast Assessment)

Visualization of each lesion was evaluated by the on-site radiologist with a 3-point scale (scored 1, 2 and 3) for each of the following 3 co-endpoints: lesion border delineation (1, none; 2, moderate, and 3, clear and complete), internal morphology (1, poorly visible; 2, moderately visible; and 3, sufficiently visible), and contrast enhancement (1, none; 2, weak; and 3, clear and bright). At the subject level, and for each co-endpoint, a sum of scores was calculated, considering up to 5 largest lesions per subject: sum of scores = score of lesion 1 (+ score of lesion 2 + score of lesion 3 + score of lesion 4 + score of lesion 5, when applicable).

Signal Intensity (SI) was calculated on tissue of interest (TOI), healthy tissue, and background, by placing regions of interest.

- Signal-to-noise ratio (SNR) was calculated according to the following equation: $SNR_{TOI} = SI_{TOI}/Std_{BN}$, where SI_{TOI} is the SI in the TOI (suspected lesion) and Std_{BN} is the standard deviation of the background noise in the same image.
- Contrast-to-noise ratio (CNR) was calculated according to the following equation: $CNR_{TOI} = SNR_{TOI} - SNR_H$, where SNR_{TOI} is the SNR measure in the TOI and SNR_H the SNR measure in healthy tissue.

The quality of images was assessed using a 3-point scale (poor, fair, and good).

Clinical and Biological Safety

- Blood pressure and heart rate were checked at baseline (before injection) and after injection immediately after MRI, between 2 and 4 hours and at 24 ± 4 hours.
- Tolerance at the injection site was evaluated over 24 ± 4 hours after injection.
- Adverse events (AEs) were monitored from the beginning of the subject's participation in the study (ie, signature of the informed consent form) to the end of a follow-up period of 7 ± 1 days.
- Blood samples were drawn at the investigational sites at screening and 24 ± 4 hours after injection. They were shipped to a central laboratory (BARC, Ghent, Belgium) for analysis of safety variables (blood hematology and biochemistry) and eGFR. Urinalysis was performed on site at the same time points.

Statistical Analysis

The results were reported by using descriptive statistics (Statistical Analysis System version 9.2, SAS Institute Inc, Cary, NC). Descriptive statistics were provided according to the nature of variables:

- Sample size, mean, standard deviation, minimum, and maximum for quantitative variables
- Sample size, mean, standard deviation, median, minimum, and maximum for ordinal variables
- Sample size and frequencies converted into percentages for qualitative (nominal or ordinal) variables

Analysis Dataset Definition

- The Pharmacokinetic Set included all subjects receiving 1 injection of gadoterate meglumine, regardless of the dosage, and for whom at least 1 blood sample for pharmacokinetics was available.
- The Evaluable Efficacy Set included all subjects undergoing a gadoterate meglumine-enhanced MRI examination of CNS with images assessed by the on-site radiologist.
- The Safety Set included all subjects receiving 1 injection of gadoterate meglumine, regardless of the dosage.

Pharmacokinetics Analysis (PhinC Development, Massy, France)

Population pharmacokinetic parameters were estimated by nonlinear mixed effect modeling using NONMEM version 7.2 (Icon Development Solutions, Ellicott City, MD). The population model was defined by 4 components: (1) the structural model component, which predicts the dependent variable (plasma concentrations) as a function of time, dose, and parameters; (2) the between-subject variance component; (3) the covariate model component; and (4) the residual error model component. To calculate pharmacokinetic parameters, concentrations below the limit of quantification (4% of the total

concentration) were considered as missing for the analysis, which is referred as the M1 method described by Beal.²⁶

The following pharmacokinetic parameters from plasma samples were determined from typical and individual gadoteric acid concentration-time profiles: area under the curve (AUC), rate constant of the terminal phase (β), elimination half-life ($t_{1/2\beta}$), total clearance (CL; per subject and normalized for BW), and volume of distribution (Vd; per subject and normalized for BW). For CL and Vd, the significant covariables responsible for the variations of the parameters were studied. In addition, a simulation of plasma concentration at 10, 20, and 30 minutes postinjection (C_{10} , C_{20} , and C_{30}) was done, and those values were compared to the same values in adults (derived from historical data in adult subjects). A PopPK analysis was performed based on the PK data collected in a previous study conducted in 2003 in 32 healthy adult subjects. Exposure to gadoteric acid in adults was then compared, through simulations, with that of pediatric subjects younger than 2 years at the standard dose of 0.1 mmol/kg. Results were summarized using descriptive statistics and represented graphically using box plots. For quantitative comparison with pediatric population, the proportion of pediatric subjects falling outside the adult 95% percentile interval was computed for distribution of concentrations and AUC. It must be noted that the adult and the pediatric models were built with nonstrictly comparable absolute values of circulating compound model: total gadolinium concentrations (obtained by inductively coupled plasma optical emission spectrometry) for adults and gadoteric acid concentrations (obtained by liquid chromatography coupled with tandem mass spectrometry) for pediatrics. However, as gadoteric acid is a gadolinium macrocyclic chelate that is not metabolized in vivo, the concentrations of total gadolinium accurately represent that of gadoteric acid.

RESULTS

Subject Disposition, Baseline Characteristics, and Indications for Contrast-enhanced MRI

From March 3, 2015, to October 19, 2015, a total of 51 subjects were enrolled in 9 centers from 4 countries: 32 (62.7%) from 2 centers in Poland, 11 (21.6%) from 3 centers in Hungary, 5 (9.8%) from 3 centers in France, and 3 (5.9%) from 1 center in Austria. Among them, 6 subjects did not receive the study product and were not analyzed: 2 because of parent consent withdrawal, 2 because of AEs (unrelated to the study drug), and 2 because of planned number of subjects already reached in the age group.

Finally, 45 subjects were included, received the planned injection of gadoterate meglumine, and completed the study. Among the 45 subjects, 11 (24.4%) received sedation before MRI procedure. No major deviations were observed. All were included in the Safety Set and the Pharmacokinetic Set. The age ranged from younger than 1 week to 23.8 months, with a mean (SD) of 9.9 (7.4) months. Five subjects were aged 0 to 1 month, 9 subjects were aged 1 to 3 months, and 31 subjects were aged 3 to younger than 24 months. Baseline characteristics are shown in Table 1, and indications for GBCE-enhanced MRI, in Table 2. Mean (SD) baseline eGFR ($\text{mL}/\text{min}/1.73 \text{ m}^2$) was 129.7 ± 41.5 and varied between 52 and 217; 11 subjects (age range, 0.5–46 weeks; BW, 3–9 kg) had an eGFR value between 52 and $100 \text{ mL}/\text{min}/1.73 \text{ m}^2$.

A total of 28 subjects underwent a gadoterate meglumine-enhanced MRI examination of CNS, with images assessed by the on-site radiologist and were included in the Evaluable Efficacy Set.

Pharmacokinetics Results

Gadoterate meglumine concentrations were best fitted using a 2-compartmental model with linear elimination from central compartment, parameterized in terms of CL, central volume of distribution (V_1), intercompartment clearance (Q), and volume of distribution at steady state (V_{ss}). Standard allometric scales^{27,28} according to BW were

TABLE 1. Demographic Characteristics at Screening—Safety Set/Pharmacokinetic Set and Evaluable Efficacy Set

	Safety Set/Pharmacokinetic Set (n = 45)	Evaluable Efficacy set (n = 28)
	N (%)	
Male	22 (48.9%)	15 (53.6%)
Female	23 (51.1%)	13 (46.4%)
Age (categories)		
≤30 d	5 (11.1%)	5 (17.9%)
≥31 d–≤90 d	9 (20.0%)	6 (21.4%)
≥91 d–<2 y	31 (68.9%)	17 (60.7%)
	Mean ± SD (Minimum-Maximum)	
Age, mo	9.9 ± 7.4 (0–23.8)	8.2 ± 7.2 (0–23.8)
Weight, kg	8.1 ± 3.1 (3.0–15.0)	7.6 ± 3.5 (3.0–15.0)
Height, cm	68.8 ± 11.5 (47–87)	66.8 ± 12.3 (47–87)
eGFR, mL/min/1.73 m ²	129.7 ± 41.5 (52–217)*	119.5 ± 42.5 (52–192)*

*For 2 subjects, eGFR at baseline was not calculated because their serum creatinine values were below the lower limit of quantification and thus their renal function was considered as normal.

applied on CL and V_1 with exponents of 0.75 and 1, respectively, and a reference BW of 70 kg. The best model for residual error was the proportional model. All fixed parameters were correctly estimated, and the model did not exhibit any relevant bias. They were estimated at 2.51 L/h for CL, 0.161 L for V_1 , 0.335 L/h for Q, and 0.408 L for V_{ss} . Typical CL and V_1 were provided for a 70 kg adult and for typical CL for an eGFR of 138 mL/min/1.73 m². Moreover, CL was increased with eGFR according to a power model. As gadoterate meglumine was administered in mmol/kg, estimated CL and V_{ss} in the population were normalized to unit per kilograms by dividing the individual parameter by the individual BW of the subject. The median CL adjusted to BW was estimated at 0.06 L/h per kg and increased with eGFR. The median V_{ss} adjusted to BW was estimated at 0.047 L/kg. Estimated median $t_{1/2\beta}$ was 1.35 h, and the median systemic exposure (AUC) was 1591 $\mu\text{mol h/L}$ (Table 3). The interindividual variability on CL and V_{ss} was moderate (17% to 26% coefficient of variation) as well as the residual variability (16%).

Predictive checks performed on the final model were consistent with the previous findings and confirmed that the population PK model captured correctly the central tendency and the variability of gadoterate meglumine concentrations over time (Fig. 1). According to simulations

TABLE 2. Indication of the MRI Examination at Inclusion Visit—Safety Set/Pharmacokinetic Set (N = 45)

Indications*	n (%)
CNS	28 (62.2%)
Brain	24
Spine	7
Associated tissue (head and neck)	4
Abdomen	7 (15.6%)
Musculoskeletal	5 (11.1%)
Whole body	4 (8.9%)
Other	7 (15.6%)

*Several indications could be reported for the same subject.
CNS indicates central nervous system.

TABLE 3. Plasma Pharmacokinetics of Gadoterate Meglumine Based on Final Population PK Model in Pediatric Subjects Younger Than 2 Years: Individual (Conditional) Parameters Estimate and Derived PK Parameters

Parameter	Median	Minimum	Maximum
AUC, h $\mu\text{mol/L}$	1591.1	981.43	2841
CL/kg, L/h per kg*	0.0602	0.0352	0.1019
V_{ss} /kg, L/kg*	0.0473	0.0273	0.1597
$t_{1/2\beta}$, h	1.3545	0.8859	3.0291

*Body weight normalized parameters.

AUC indicates area under the curve; CL/kg, total clearance normalized for body weight; V_{ss} /kg, volume of distribution at steady state normalized for body weight; $t_{1/2\beta}$, elimination half-life.

performed using the final model, median simulated plasma concentration at 10, 20, and 30 minutes postinjection (C_{10} , C_{20} , and C_{30}) were 320.8, 274.1, and 251.9 $\mu\text{mol/L}$, respectively (Table 4). Overall, the simulations showed that concentrations at 10, 20, and 30 minutes (Table 4 and Fig. 2) and AUC (Table 4 and Fig. 3) were roughly similar between age groups in children.

The PopPK model in adults showed a median AUC estimated at 962 $\mu\text{mol h/L}$ (5th–95th percentiles, 765–1403 $\mu\text{mol h/L}$) and BW normalized CL and V_{dtotal} of 0.10 L/h per kg (0.08–0.13 L/h) and 0.20 L/kg (0.16–0.25 L/kg), respectively. Therefore, a slightly lower BW normalized CL was observed in children than in adults (0.06 vs 0.10 L/h/kg). Volumes of distribution of both PopPK models could not be formally compared since the PopPK model for children was parameterized with V_{ss} , while it was parameterized with V_{dtotal} for adults. Nevertheless, the V_{ss} in children could be compared with the V_{ss} obtained in adults by noncompartmental analysis and was found also to be different (0.047 L/kg for children and ca. 0.200 L/kg for adults). Overall, simulated concentrations at 10, 20, and 30 minutes were lower than that of adults, with ratios between geometric means (adults/children) varying from 1.8 (C_{10}) to 1.5 (C_{30}) (Fig. 2), whereas simulated AUC was higher than that of adults with a ratio between geometric means (adults/children) of 0.62 (Fig. 3). This difference can be explained by the difference in CL and the fact that renal function maturation was not completely achieved in children younger than 2 years.²⁹ The

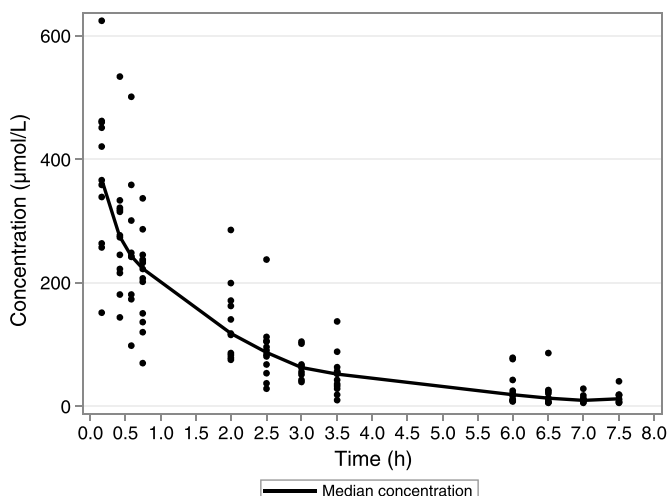
**FIGURE 1.** Individual concentrations and median concentration of gadoterate meglumine over time in 45 pediatric subjects younger than 2 years after IV administration of gadoterate meglumine (0.1 mmol/kg BW).

TABLE 4. Simulated Concentrations at 10 Minutes (C_{10}), 20 Minutes (C_{20}), and 30 Minutes (C_{30}) Postinjection and Simulated AUC in Pediatric Subjects Younger Than 2 Years and in Healthy Adults After Intravenous Administration of Gadoterate Meglumine at the Dose of 0.1 mmol/kg BW Based on Final Population PK Model

Endpoint	Age Group	No. Subjects	N*	2.5th Percentile	Median	97.5th Percentile
C_{10}	0-<2 mo	8	8,000	144.19	282.72	525.06
	2-<6 mo	9	9,000	145.15	309.92	604.63
	6-<12 mo	9	9,000	150.24	351.3	815.38
	12-<24 mo	19	19,000	123.28	336.84	917.98
	All children <2 y	45	45,000	135.65	320.75	806.41
	Adults	32	32,000	416.78	584.75	786.38
C_{20}	0-<2 mo	8	8,000	135.61	266.43	485.9
	2-<6 mo	9	9,000	133.87	284.62	543.82
	6-<12 mo	9	9,000	136.67	299.26	612.94
	12-<24 mo	19	19,000	108.98	261.09	573.06
	All children <2 y	45	45,000	121.16	274.06	564.26
	Adults	32	32,000	333.71	450.18	600.52
C_{30}	0-<2 mo	8	8,000	128.13	249.69	460.69
	2-<6 mo	9	9,000	124.2	262.74	505.45
	6-<12 mo	9	9,000	125.19	275.6	565.13
	12-<24 mo	19	19,000	97.498	236.36	515.27
	All children <2 y	45	45,000	110.57	251.93	516.65
	Adults	32	32,000	281.33	378.72	513.23
AUC (h μ mol/L)	0-<2 mo	8	8,000	911.45	1500.5	2434.9
	2-<6 mo	9	9,000	961.31	1567.2	2591
	6-<12 mo	9	9,000	1045.6	1698.2	2829.3
	12-<24 mo	19	19,000	928.43	1611.8	2679.6
	All children <2 y	45	45,000	949.56	1597.4	2664.7
	Adults	32	32,000	744.91	986.9	1301.8

*The original dataset was used for the simulations, and 1000 replicates of this dataset were obtained to determine the distribution of C_{10} , C_{20} , C_{30} , and AUC. AUC indicates area under the curve; BW, body weight.

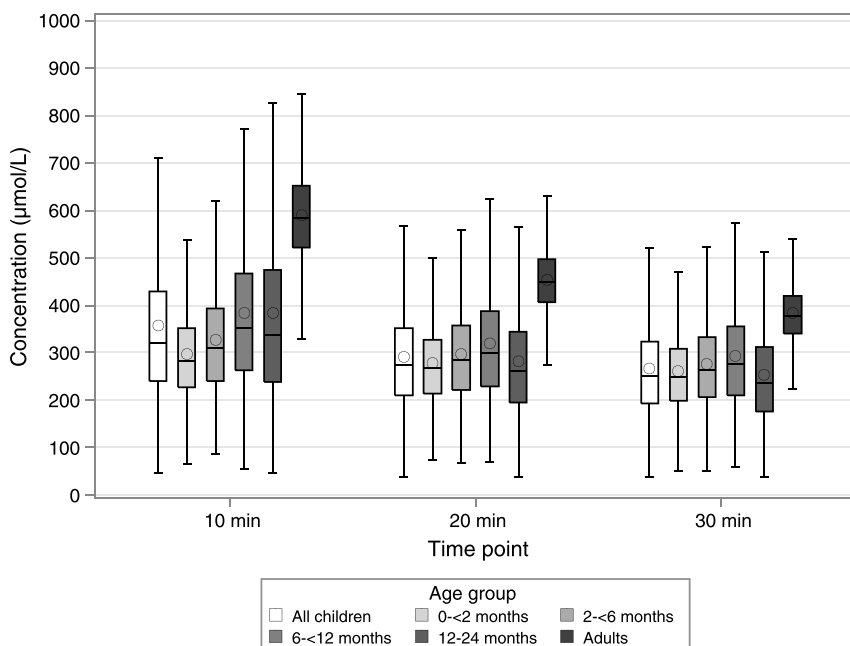


FIGURE 2. Simulated concentrations in 45 pediatric subjects younger than 2 years and in 32 healthy adults at 10, 20, and 30 minutes after IV administration of gadoterate meglumine (0.1 mmol/kg BW).

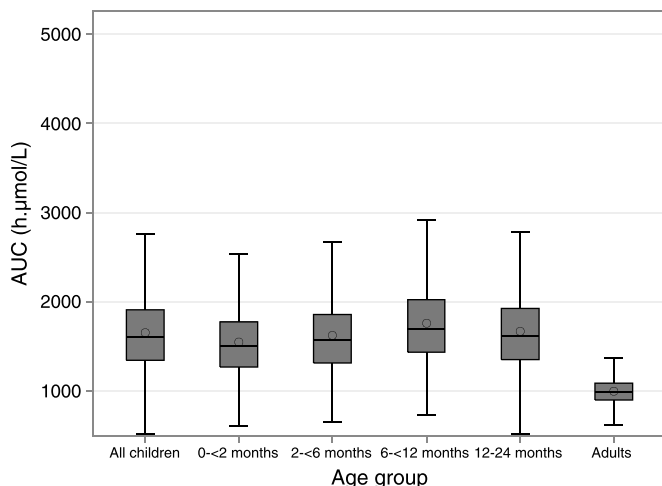


FIGURE 3. Simulated AUC in 45 pediatric subjects younger than 2 years and in 32 healthy adults after IV administration of gadoterate meglumine (0.1 mmol/kg BW).

proportion of children's values outside adults' 95% percentile interval was 64% to 76% for concentrations and 79% for AUC.

Efficacy Results

Among the 28 subjects who underwent contrast-enhanced MRI for CNS indication, the overall quality of images was considered "good" for 26 subjects (92.9%) and "fair" for 2 subjects (7.1%) with precontrast images, whereas it was "good" for all subjects with precontrast + postcontrast images.

The number of lesions detected per subject ranged from 0 to 11, with a median of 1 lesion per subject, in precontrast images as well as in precontrast + postcontrast images. The same number of lesions was detected with precontrast and precontrast + postcontrast images for 27 subjects, whereas for 1 subject, 2 lesions were identified only with precontrast + postcontrast images (no lesion identified with precontrast images by the on-site reader) (Table 5). These 2 lesions were localized in the right hemisphere (temporal, frontal, parietal, and occipital lobes) and the right eye in a 15-month-old boy with Sturge-Weber syndrome (Fig. 4).

Only the 5 largest lesions were analyzed for the 1 subject with 11 lesions. Finally, a total of 28 of 34 lesions detected in 15 subjects with precontrast images were analyzed, and a total of 30 of 36 lesions detected in 16 subjects with precontrast + postcontrast images were analyzed (Tables 5 and 6).

Lesion visualization was improved with precontrast + postcontrast images compared to precontrast images, with more lesions having the highest score: clear and complete lesion border delineation for 73.3% of the lesions versus 39.3%; sufficiently visible internal morphology for 76.7% versus 50.0%. With precontrast + postcontrast images, contrast enhancement was clear and bright for 23 lesions (76.7%) and weak for 4 lesions (13.3%) and remained null for 3 lesions (10.0%) owing to the nature of lesions (cyst, postsurgery changes, or hemorrhage) that do not capture contrast agent (Table 6).

At subject level (Table 6), the mean sum of scores was higher with precontrast + postcontrast images compared with precontrast images for the 3 co-endpoints of lesion visualization, but with a large variability between subjects. The mean (SD) increase was 0.7 (1.0) for lesion border delineation, 0.9 (1.6) for internal morphology, and 3.1 (3.2) for contrast enhancement.

Regarding quantitative assessments, a mean increase in CNR and SNR was reported in precontrast + postcontrast images compared with precontrast images. At lesion level, mean (SD) SNR increased

from 112.3 (57.8) in precontrast images to 212.6 (198.3) in precontrast + postcontrast images, and mean CNR increased from 9.3 (27.8) to 79.4 (109.9) (Table 7).

Safety Results

Extent of Exposure

The mean (SD) dosage of gadoterate meglumine was 1.6 (0.6) mL for both theoretical dose and actual dose administered. The estimated injection rate was 1 to 2 mL/s, with a mean (SD) of 1.1 (0.4) mL/s.

Vital Signs

Vital signs remained mostly stable overall. However, there was a great variability between subjects, with a large range of values for change from baseline: -30 to $+59$ mm Hg for systolic blood pressure, -43 to $+57$ mm Hg for diastolic blood pressure, and -49 to $+50$ beats/min for heart rate. These changes may be explained by either spontaneous sleepiness or sedation received just before MRI (baseline) and return to normal state after MRI.

Adverse Events

Among the 45 subjects of the Safety Set, 19 (42.2%) experienced at least 1 AE, for a total of 43 AEs. Of these 43 AEs, 26 were postinjection [subsequently referred as "treatment emergent AEs" (TEAEs)], reported in 13 subjects (28.9%). The most frequently reported TEAEs were pyrexia (6 subjects, 13.3%) and leukopenia (2 subjects, 4.4%). All other TEAEs were reported for 1 subject each and were mainly reported in the System Organ Class "Infections and infestations" (6 subjects, 13.3%) and "Gastrointestinal disorders" (3 subjects, 6.7%).

Most TEAEs (16/26, 61.5%) were of mild intensity, 38.5% were of moderate intensity, and none was severe. All TEAEs resolved, with medication for 14 of them (in 9 subjects). Only 1 subject (2.2%) experienced 1 TEAE considered related to gadoterate meglumine by the investigator: rash of moderate intensity, occurring 8 hours after contrast agent administration and resolving within 5 days with IV administration of an antihistaminic drug (clemastine) and of hydrocortisone.

The TEAEs were considered serious for 1 subject (2.2%). This 1-year-old girl (10.3 kg, 81 cm) experienced 3 serious AEs on the day after gadoterate meglumine administration: anemia, pyrexia, and upper respiratory tract infection. The patient recovered, and these events were not considered as related to gadoterate meglumine administration. No TEAE led to stop the ongoing injection of gadoterate meglumine. No death was reported during the study.

Laboratory Parameters

No abnormal results in urinalysis were reported at the safety visit after gadoterate meglumine administration. For hematology

TABLE 5. Number of Subjects According to the Number of Detected Lesions—Evaluable Efficacy Set

	Precontrast (n = 28 Subjects)	Precontrast + Postcontrast (n = 28 Subjects)
No. subjects without lesions	13 (46.4%)	12 (42.9%)
No. subjects with lesions	15 (53.6%)	16 (57.2%)
–1 lesion	10	10
–2 lesions	1	2
–3 lesions	2	2
>3 lesions	2*	2*

*5 lesions in 1 subject, 11 lesions in 1 subject.

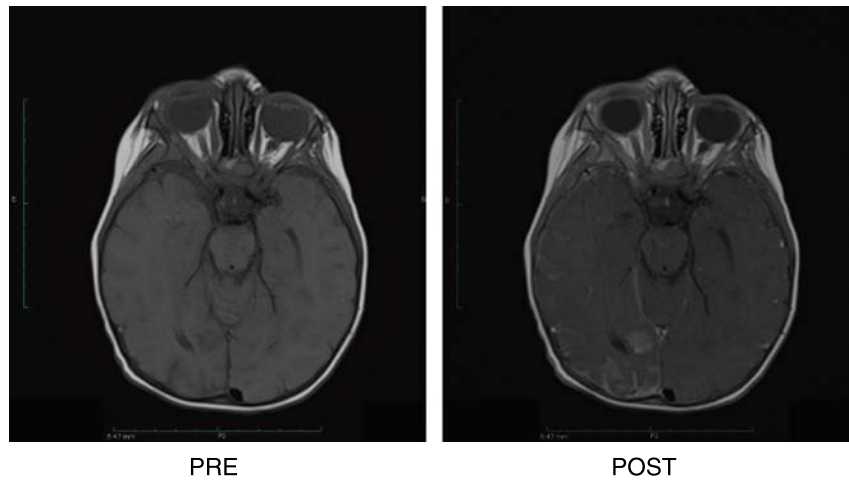


FIGURE 4. Brain MRI (at 1.5 T) in a 15-month-old boy with Sturge-Weber syndrome preintravenous and postintravenous administration of gadoterate meglumine (0.1 mmol/kg BW), showing better outlining of diffuse lesions on post-T1-weighted spin echo image.

and biochemistry parameters, the main changes observed overall were nonclinically significant decreases in mean values of erythrocytes, hemoglobin, leukocytes, lymphocytes, platelets, blood urea nitrogen, aspartate transaminases, alanine transaminases, alkaline phosphatase, and lactate dehydrogenase. At screening visit, eGFR (mL/min/1.73 m²) ranged from 52 to 217, with a mean (SD) of 129.7 (41.5). At safety visit, mean (SD) eGFR was 135.9 (51.0), with a mean (SD) change from baseline of 3.3 (27.6). Changes from baseline varied between subjects, ranging from -89 to +92. Mean (SD) blood creatinine level (μmol/L)

was 23.51 (6.03) at screening visit and 23.95 (5.43) at safety visit, with a mean (SD) change of 0.35 (4.35).

DISCUSSION

This study was primarily designed to document the pharmacokinetics of gadoterate meglumine in children younger than 2 years. A population pharmacokinetic approach was chosen to minimize the volume of blood sampled, in accordance with FDA and European

TABLE 6. Visualization Scores for Detected and Analyzed Lesions at Lesion Level and at Subject Level—Evaluable Efficacy Set

Lesions Detected and Analyzed*	Lesion Visualization at Lesion Level		Lesion visualization at subject level	
	N (%) Lesions		N (%) Lesions	
	Precontrast (n = 28)	Precontrast + Postcontrast (n = 30)†	Pre-contrast (n = 28)	Precontrast + Postcontrast (n = 28)
Lesion border delineation score			Mean (SD)	Median (Min;Max)
1—None	2 (7.1)	0	4.3 (3.7)	3 (2;15)
2—Moderate	15 (53.6)	8 (26.7)	4.3 (3.9)	3 (1;15)
3—Clear and complete	11 (39.3)	22 (73.3)	1.9 (1.5)	1 (1;5)
Internal morphology score			Mean (SD)	Median (Min;Max)
1—Poorly visible	5 (17.9)	0	5.1 (4.0)	3 (2;15)
2—Moderately visible	9 (32.1)	7 (23.3)	5.2 (4.3)	3 (2;15)
3—Sufficiently visible	14 (50.0)	23 (76.7)	5.0 (4–5)	3 (1;15)
Contrast enhancement score				
1—None	NA	3 (10)		
2—Weak	NA	4 (13.3)		
3—Clear and bright	NA	23 (76.7)		

*1 to 5 lesions per patient.

†Lesions identified in pre and post contrast images could be different.

NA indicates not applicable; min: minimum; max: maximum.

TABLE 7. Signal Intensity Measurements (CNR, SNR) at Lesion Level and at Subject Level—Evaluable Efficacy Set

Signal Intensity Measurement at Lesion Level				
Lesions Detected and Analyzed	Precontrast (n = 28)		Precontrast + Postcontrast (n = 29)*	
	Mean (SD)	Median (Min;max)	Mean (SD)	Median (Min;max)
SNR	112.3 (57.8)	108 (27;268)	212.6 (198.3)	144 (51;1061)
CNR	9.3 (27.8)	11 (−53;89)	79.4 (109.9)	51 (−25;561)
Signal Intensity Measurement at Subject Level				
Subjects Analyzed	Pre-contrast (n = 28)		Precontrast + Postcontrast (n = 28)	
	Mean (SD)	Median (Min;Max)	Mean (SD)	Median (Min;Max)
SNR	93.1 (56.0)	82 (27;225)	214.3 (244.4)	134 (51;1061)
CNR	6.9 (23.3)	6 (−25;54)	78.3 (135.4)	47 (−25;561)

*For 1 subject, a lesion was detected but no signal intensity was reported (missing data).
CNR indicates contrast-to-noise ratio; SNR, signal-to-noise ratio; min, minimum; max, maximum.

Medicines Agency recommendations for pediatric subjects.^{23–25} The age of these young patients ranged from younger than 1 week to 23.8 months, and their distribution according to age groups was consistent with what was planned in the protocol. Glomerular filtration was estimated by the Schwartz formula calculated from serum creatinine and height.²⁰ Although this formula is known to overestimate true renal clearance (eg, inulin clearance),³⁰ it provides an estimate that is accurate enough for most clinical purpose.³¹ Keeping that in mind, and compared with the range of GFR measured using infusion of inulin or mannitol,^{19,20,32} the eGFR values observed in our pediatric population were consistent with the normal values reported by Schwartz and Furth³² for newborns and infants up to 2 years of age: mean \pm SD of 20.8 ± 5.0 mL/min/1.73 m² for 1- to 3-day-old babies to 105.2 ± 17.3 mL/min/1.73 m² for 1- to 2-year-old children.

The PopPK consisted of a 2-compartment model with a linear elimination from central compartment, which proved appropriate to describe pharmacokinetics of gadoterate meglumine.¹⁵ It led to an accurate description of its PK profile in this population of children younger than 2 years. All checks and validations supported the appropriateness of this model. As anticipated, CL was found to increase with eGFR value. Overall interindividual variability was limited, regardless of the parameters, and the residual variability was also limited.

Median BW adjusted PopPK estimated CL value was 0.06 L/h/kg whereas it was determined to be around 0.10 L/h/kg in healthy adults after gadoterate meglumine injection.¹⁶ This lack of marked difference between typical values of CL between the study population and adults, although the level of eGFR was found to impact drug elimination, was ascribed to the fact that only a fraction of the study population (11/45, 24.4%) had an eGFR level of 100 mL/min/1.73 m² or lower. However, the inclusion of eGFR as a covariate in the determination of CL in the PopPK model allows an accurate estimation of all individual PK parameters from younger than 1 week to 23 months.

The small volume of distribution V_{dss} estimated in the study (0.0473 L/kg) may confirm the limited distribution of gadolinium to vascular compartment.

From this PK model, the median estimated $t_{1/2\beta}$ was 1.35 hours. It is similar to the values of 1.5 to 1.6 hours that were reported in adults after gadoterate meglumine injection^{15,16} and 1.6 hours reported in children aged 0 to younger than 2 years who received gadobutrol.³³ These values were also close to those obtained in older pediatric patients who received either gadobutrol,³⁴ or the linear GBCA gadoversetamide,³⁵ and in healthy pediatric subjects after administration of gadoversetamide.³⁶

Similarly, at a given dose of 0.1 mmol/kg, the median (range) AUC (μ mol h/L) calculated in our study (1591 [981;2841]) was roughly

in the same order of magnitude than the values reported after administration of gadoterate meglumine in adults (median not reported, mean \pm SD, 974 ± 76)¹⁶ and after administration of gadobutrol in infants younger than 2 years [776 (544–1470)],³³ children aged 2 to 17 years [999 (397, 2163)],³⁴ and in adults [1110 (724, 1956)].³³

Concentrations of and exposures to gadoterate meglumine of children younger than 2 years were compared (a) between the different age groups of children and (b) with the concentrations and exposures of adults through simulations for a dose of 0.1 mmol/kg using the PopPK models.

The comparison of values of concentrations and of AUC between age groups in children did not show any clear differences, a result roughly in keeping with those published by Kunze et al³³ with gadobutrol in children aged 0 to younger than 2 years, the only difference in this publication being a slightly higher mean AUC in subjects aged 0 to 2 months compared with the AUC of subjects aged 2 months to younger than 2 years.

Body weight normalized CL and V_{dtotal} estimated for adults were higher than the estimations for children. These simulations showed that concentrations in children at 10, 20, and 30 minutes after the injection were lower than those in adults, with ratios between adults and children varying from 1.8 to 1.5. Moreover, AUC in children were shown higher than those of adults, as a consequence of the lower clearance. These results were quite well related to the difference of renal activity, as expressed by GFR or cystatin C, for example, observed between children younger than 2 years and older children and adults.²⁹ Considering that gadoterate meglumine is almost exclusively excreted unchanged in urine and that urinary excretion essentially consists in filtration, renal activity is the pivotal process of elimination of gadoterate meglumine and, thus, of its clearance. Renal activity is directly age related; therefore, the present results appeared in very good agreement with expected results based on PK characteristics of gadoterate meglumine. No dose adjustment appears to be needed in pediatric patients.

Efficacy

The efficacy of gadoterate meglumine was evaluated by the on-site radiologist in 28 subjects who underwent gadoterate meglumine-enhanced MRI examination of CNS. Precontrast + postcontrast images allowed improvement from precontrast images for lesion visualization (border delineation, internal morphology, and contrast enhancement) in this population. Precontrast + postcontrast images allowed to identify 2 lesions in 1 patient, which were not detected by precontrast images. The overall quality of images was considered “good” for all 28

subjects with precontrast + postcontrast images. This is consistent with results reported with gadoterate meglumine in 1631 children aged 0 to 17 years enrolled in SECURE, a prospective observational study: good to very good image quality was obtained for more than 98% of the pediatric patients and diagnosis could be established for 99.6% of the cases.³⁷ These results are also in keeping with the efficacy results obtained with gadobutrol in a similar population,³³ where contrast enhancement of lesions was assessed as good or excellent in 93.2% of the subjects, and border delineation and internal morphology of lesions were both rated good or excellent in 97.7% of the subjects in the combined MRI, compared with 75% and 61.4% of the subjects, respectively, in unenhanced MRI.

Safety

In the present prospective study, 13 of 45 subjects (28.9%) experienced postinjection AEs, but only 1 subject (2.2%) experienced 1 AE considered related to gadoterate meglumine by the investigator (rash of moderate intensity, occurring on the day of administration). No AE was severe in intensity and all resolved. Serious postinjection AEs were reported for only 1 subject and were not considered related to gadoterate meglumine administration. This is comparable with what was observed in a similar population after administration of gadobutrol,³³ where 18 of 44 subjects (40.9%) experienced an AE, serious in 3 subjects but not study drug related, and 1 subject experienced an AE assessed as study drug related, of mild intensity. These figures are also consistent with the good safety profile of gadoterate meglumine in pediatric subjects reported from clinical studies, where 140 children aged 0 to 17 years were included^{12,14}: 9 patients (6.4%) experienced AEs, related to gadoterate meglumine for 6 patients (4.3%) and 1 patient experienced 2 severe AEs assessed as not related to gadoterate meglumine. More generally, as concerns immediate reactions, GBCAs are well tolerated by children, even better than by adults: in a retrospective study of 65,009 adults and 13,344 pediatric patients conducted over a 7-year period (2001–2006), acute allergic-like reactions rates were documented in 52 patients after 54 injections: 48 reactions (0.07%) in 46 adult patients and 6 reactions (0.04%) in 6 pediatric patients.³⁸

As regard to laboratory tests, no clinically significant changes were observed in mean values of measured blood parameters. This also holds true for mean values of eGFR, which remained globally stable throughout the study, but with a wide interindividual variability.

Although not addressed, because of the short-term follow-up of the present study primarily aimed at documenting PK profile of gadoterate meglumine, long-term safety is a growing concern not only in adults but also in children, especially the youngest ones. Two long-term complications, nephrogenic systemic fibrosis (NSF) and brain retention of gadolinium, have been linked to repeated administration of some GBCAs. Nephrogenic systemic fibrosis is a rare, but severe and occasionally fatal, condition with rapidly progressive skin thickening, flexion contractures of joints, and sometimes fibrosis of internal organs.³⁹ The prolonged exposure to gadolinium in adult patients with moderate or severe chronic kidney disease after administration of GBCAs with a linear structure is currently considered as a significant, although probably not exclusive, factor leading to the occurrence of NSF months to years later.^{39,40} Exceptional occurrences of NSF have been identified in children. When the type of GBCAs was recorded, none of these cases was observed after administration of a macrocyclic GBCA, but only after repeated injection of linear GBCA. When noted, their renal function was substantially altered.

The European Society of Urogenital Radiology made recommendations aimed at preventing NSF, including in the pediatric population.^{41–43} In neonates, high-risk linear GBCAs (gadodiamide, gadopentetate dimeglumine, and gadoversetamide) are contraindicated, and in infants younger than 1 year, they should be used with caution; in both populations, medium-risk linear GBCAs (gadobenate dimeglumine, gadofosveset trisodium, and gadoxetatic acid) and low-risk macrocyclic

GBCAs (gadobutrol, gadoterate meglumine, and gadoteridol) should be administered at the lowest possible dose in a single injection, with a washout period of 7 days between 2 GBCA-enhanced procedures. Some authors clearly advocate the use of macrocyclic GBCAs only in this fragile population.⁴⁴

Similar to findings in adults, 2 pediatric case records^{45,46} then 3 publications of pediatric series (including few infants <2 years)^{47–49} have recently shown on unenhanced MRIs an increased brain SI after repeated administration of the linear GBCA gadopentetate dimeglumine. A recent retrospective study⁵⁰ conducted on 41 pediatric patients (3–17 years) showed no increase in brain SI after serial injections of gadoterate meglumine, confirming in pediatric patients the findings reported after serial injections of macrocyclic GBCAs in adults. If multiple enhanced magnetic resonance examinations are nevertheless indicated, current knowledge suggests that it is safe to perform them with all 3 macrocyclic agents,^{51,52} while awaiting the results of long-term research on this topic.

In NSF and brain retention of gadolinium, the progressive release of free gadolinium ion is considered as a key pathophysiological factor.^{40,53–55} This phenomenon depends on the stability of GBCAs, determined by the molecular structure of their chelates: the weaker the stability, the higher the risk of release of gadolinium ion.^{1,11} Macrocyclic chelates such as gadoterate meglumine offer a strong binding to gadolinium ion and have a higher stability than the flexible, open chains of linear chelates.

Regarding the pharmacokinetics analysis, the limitation of the study could be the relatively small sample size and the sparse sample collection. However, using the modeling techniques, it was possible to draw robust estimates of gadoterate meglumine PK parameters in neonates. Another limitation is the use of only 1 reader for the images evaluation, but this was considered acceptable, the efficacy assessment being a secondary endpoint.

CONCLUSION

Using a PopPK approach, this study appropriately described the pharmacokinetic profile of gadoterate meglumine in newborns and infants younger than 2 years, with values of PK parameters close to those already observed in adults with the same dose of 0.1 mmol/kg BW, without the need for dose adjustment. The present study also demonstrated the good tolerance and safety of gadoterate meglumine, as well as its efficacy for contrast-enhanced MRI examination of CNS, in this population. Given the current data concerning GBCAs involved in the pathophysiology of NSF and gadolinium brain retention, and taking into account the high stability of its macrocyclic structure, gadoterate meglumine appears as one of the preferred GBCAs to be administered in this very young pediatric population for contrast-enhanced MRI.

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