CLINICAL PHARMACOLOGY REVIEW

NDA Number	NDA 216986, S-9 (SDN 254)
Link to EDR	\\CDSESUB1\evsprod\NDA216986\0141
Submission Date	4-22-25
Submission Type	Efficacy Supplement
Brand Name	ELUCIREM®
Generic Name	Gadopiclenol
Dosage Form and Strength	Injection: 0.5 mmol/L gadopiclenol in single-dose vials, single-dose PFS, and pharmacy bulk packages
Route of Administration	Intravenous (IV)
Proposed Indication Change	Indicated in adult and pediatric patients ~~aged 2 years and older~~ (including term neonates) for use with MRI to detect and visualize lesions with abnormal vascularity in: ▪ the central nervous system (brain, spine, and associated tissues) ▪ the body (head and neck, thorax, abdomen, pelvis, and musculoskeletal system)
Recommended Dose	0.05 mmol/kg (proposed and currently approved)
Applicant	Guerbet LLC
OCP Review Team	Vicky Hsu, Ph.D. Yun Wang, Ph.D. Jiang Liu, Ph.D. Wentao Fu, Ph.D. Brian Booth, Ph.D.

1.1 Executive Summary

ELUCIREM® (gadopiclenol) is a macrocyclic gadolinium-based contrast agent (GBCA).

The original NDA received FDA approval (9-21-22) for the use of ELUCIREM injection as a GBCA indicated in adult and pediatric patients ≥ 2 years old for use with magnetic resonance imaging (MRI) to detect and visualize lesions with abnormal vascularity in:

- the central nervous system (brain, spine, and associated tissues)
- the body (head and neck, thorax, abdomen, pelvis, and musculoskeletal system)

In this supplemental NDA submission, the Applicant is seeking to extend the currently approved indications for ELUCIREM to cover all pediatric ages (including term neonates). The proposed recommended dose of 0.05 mmol/kg for this expanded population (pediatric population < 2 years old) is the same as the currently approved recommended dose in patients ≥ 2 years old.

The clinical pharmacology review focused on the dose selection and population PK modeling and simulation results in this expanded population.

1.1.1 Recommendations

The Office of Clinical Pharmacology reviewed the information submitted in NDA 216986 S-9. This supplemental NDA submission is approvable from a clinical pharmacology perspective.

The key review issues with specific recommendations and comments are summarized in **Table 1**.

Table 1. Recommendations and comments for NDA 216986 S-9 review issues

Review Issue	Recommendations and Comments
Pivotal and supportive evidence of effectiveness	The primary evidence of effectiveness is provided by Study **GDX-44-015** (see Section 1.3.2).
General dosing instructions	The recommended dose for gadopiclenol is 0.05 mmol/kg (equivalent to 0.1 mL/kg) administered intravenously at approximately 2 mL/s.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No updates (refer to original NDA unireview and currently approved USPI).
Drug-drug interactions	No updates (refer to original NDA unireview and currently approved USPI).
Labeling	The proposed labeling updates to Section 12.3 are acceptable upon Applicant's agreement to FDA revisions.
Bridge between the to-be-marketed and clinical trial formulations	Not applicable.

Source: FDA clinical pharmacology reviewer

Post-Marketing Requirements or Commitment

This submission fulfills post-marketing requirement (PMR) **4341-1** from the original NDA approval to evaluate ELUCIREM in pediatric patients < 2 years old.

1.2 Summary of Clinical Pharmacology Assessment

1.2.1 Pharmacology and Clinical Pharmacokinetics

Refer to the currently approved ELUCIREM USPI.

Other than the addition of new PK data from the expanded population of pediatric patients < 2 years old (Section 12.3), no other clinical pharmacology changes were made to the USPI.

1.2.2 General Dosing and Therapeutic Individualization

General Dosing

The proposed gadopiclenol dose of 0.05 mmol/kg in pediatric patients < 2 years old (down to term neonates) is approvable.

Therapeutic Individualization

N/A.

Outstanding Issues

None.

1.3 Comprehensive Clinical Pharmacology Review

1.3.1 General Pharmacology and Pharmacokinetic Characteristics

Refer to the original NDA 216986 unireview for the table overview of gadopiclenol ADME and clinical PK.

1.3.2 Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes, the Applicant used an exposure matching approach for the extrapolation of efficacy from adult and pediatric patients ≥ 2 years old to pediatric patients < 2 years old.

The data intended to support the expanded population is derived from the Applicant's pediatric Study **GDX-44-015**, which was a Phase 2, multi-center, open-label, uncontrolled study to evaluate gadopiclenol in pediatric patients aged up to 23 months who were scheduled to undergo contrast-enhanced MRI. The primary objective was to evaluate gadopiclenol PK in pediatric patients < 2 years old, while safety and efficacy were secondary objectives. All patients were administered a single-dose of 0.05 mmol/kg and contrast-enhanced MRI started shortly after the injection. PK samples were collected in all patients at each of the following post-dose time points (actual more narrow time window within each time window was randomized): 10 – 60 min, 2 – 4 h, 6 – 8 h (elimination $T_{1/2} \approx 1.5$ h).

The breakdown of pediatric patients by age group and MRI location is shown in **Table 2**.

Table 2. Pediatric patients < 2 years old included in the full analysis set

	Patients receiving gadopiclenol injection FAS (N= 35)		
	3-23 months (N=32)	28-89 days (N=2)	0-27 days (N=1)
CNS (N=18):	17	0	1
Blood vessel (N=3):	2	1	0
Body (N=14):	13	1	0

Source: CSR GDX-44-015

PK Results

The Applicant updated their previously developed population PK model with PK data obtained in pediatric patients < 2 years old and made model adjustments (maturation of renal function based on post-menstrual age and estimated weight effect on V1) to better capture model fitness in pediatric patients < 2 years old.

Individual predictions were used to derive PK parameters, as seen summarized by age group in **Table 3**. Since the study did not have a subject < 28 days old with PK-evaluable data (PK was collected in 1 subject but the sample was improperly stored), the age group < 28 days old is based entirely on PK simulations.

Table 3. Summary of PK parameters by age group predicted from the final population PK model in patients with normal renal function receiving gadopiclenol 0.05 mmol/kg

		GM (CV%)					
Age group	N	$AUC_{0\text{-}inf}$ (h.mg/L)	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	$C_{10\ min}$ (mg/L)	$C_{20\ min}$ (mg/L)	$C_{30\ min}$ (mg/L)
Adults	9	571.5 (17.4)	0.4 (64.2)	1.7 (28.6)	350.2 (15.0)	236.2 (14.2)	154.3 (17.3)
12-17 years	18	639.8 (17.6)	0.3 (30.7)	1.8 (28.1)	396.5 (13.1)	254.5 (11.4)	160.4 (16.3)
7-11 years	19	543.4 (19.3)	0.3 (22.8)	1.6 (11.6)	341.6 (15.0)	230.5 (13.4)	148.0 (17.0)
2-6 years	19	446.1 (23.4)	0.3 (29.7)	1.7 (19.8)	285.1 (14.1)	187.1 (14.6)	117.1 (19.7)
3-23 months	33	392.3 (27.6)	0.3 (30.3)	1.5 (21.4)	226.8 (15.8)	161.5 (17.2)	109.4 (22.4)
28 days-<3 months	2	493.3 (9.9)	0.3 (30.3)	2.1 (8.4)	190.4 (16.2)	149.8 (13.4)	116.2 (13.3)

GM: geometric mean; CV: coefficient of variation

Source: PopPK analysis report, Table 9

Overall simulated values for median AUC0-∞, C10, C20, C30 (concentrations at post-dose 10, 20, 30 min; relevant time window for MRI imaging) by age group are provided in **Table 4.**

Table 4. Simulated median PK parameters based on the final population PK model in patients with normal renal function receiving gadopiclenol 0.05 mmol/kg

Age group	Median $AUC_{0-\infty}$ (mg.h/L)	Median C_{10} (mg/L)	Median C_{20} (mg/L)	Median C_{30} (mg/L)
Adults	612	362	298	243
12-17 years	560	355	286	238
7-11 years	472	308	249	205
2-6 years	406	254	214	178
3 to 23 months	396	224	188	158
28 days to <3 months	628	211	189	167
≤27 days	807	198	175	159

Source: PopPK analysis report, section 13.4

As seen above and in **Figure 4** (below), simulated median PK exposures (AUC, C10, C20, C30) showed comparability between 12 – 17 years old and adults, however pediatric exposures started to progressively decrease compared to adults from < 12 years old to the youngest age group, likely due to their higher extracellular fluid volumes and total body water per body weight (BW). In pediatric patients < 3 months old, AUC exposures were comparable to adult AUC exposures potentially due to lower clearance since renal function has not matured. These PK results are consistent with other FDA-approved GBCAs that have pediatric indications down to term neonates.

Refer to the Pharmacometrics Review in Section 1.4 for population PK modeling and simulation details.

Refer to the Clinical and Biostatistics Review of this submission for efficacy and safety details.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, refer to Section 1.3.2.

Is an alternative dosing regimen or management strategy required for sub-populations based on patient factors?

No (refer to original NDA 216986 unireview).

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

No (refer to original NDA 216986 unireview).

1.4 Pharmacometrics Review

1.4.1 Population PK analysis

1.4.1.1 Review Summary

In general, the applicant's population PK (PopPK) analysis is considered acceptable for the purpose of characterizing the PK profile of gadopiclenol in pediatric patients less than 2 years of old undergoing contrast-enhanced MRI. The PopPK results are acceptable**.**

Table 5. Specific Comments on Applicant's Final Population PK model

Utility of the final model			Reviewer's Comments
Support applicant's proposed labeling statements about intrinsic and extrinsic factors	**Intrinsic factor**	Change in current supplement: [redacted] (b) (4)	No change was proposed regarding to statements related to intrinsic factor. The reviewer verified the PK exposure listed in proposed labeling Table 4, which is calculated based on PopPK model simulation. The applicant [redacted] (b) (4) the age group (<2 years) in the table.
	Extrinsic factor	N/A	N/A

1.4.1.2 Introduction

The primary objectives of applicant's analysis were to:

1. To assess whether the PopPK model previously developed for adults and children of 2-17 years of age for gadopiclenol is predictive of exposure for the pediatric population aged up to 23 months (inclusive);
2. To update the PopPK model previously developed for adults and children of 2-17 years of age with data obtained in pediatric population <2 years from the GDX-44-015 study;
3. To search population specific covariates that can explain any difference between pediatric patients < 2 years and older patients;
4. To predict PK parameters and exposure in pediatric patients <2 years receiving IV injection of gadopiclenol for contrast-enhanced MRI;
5. To simulate PK parameters and exposure in pediatric patients <2 years receiving IV injection of other doses of gadopiclenol (0.025 mmol/kg, 0.1mmol/kg).

1.4.1.3 Model development

Data

PopPK analysis was performed using 35 pediatric subjects (Age: N=33 3-23 months, N=2 28-89 days) who received one injection of gadopiclenol (Region imaging cohort: N=18 CNS, N=3 blood vessel, N=14 body). The only patient between 0-27 days was excluded due to blood/plasma PK sample storage temperature excursion. In addition, 134 subjects were included

in the reference population from study Nos. GDX-44-003, GDX-44-005, GDX-44-007. Brief descriptions of the studies included are presented in **Table 6**.

Table 6. Summary of Studies with PK Sampling Included in Population PK Analysis

Study Number	Study Title and Design	Number of Participants	Dosing Regimen	PK Assessments
GDX-44-015, Phase II	Gadopiclenol Pharmacokinetics, Safety and Efficacy in Pediatric Patients < 2 Years of Age Undergoing Contrast-enhanced MRI	• Enrolled (All enrolled Patients Set): 41 • Analyzed for safety (Safety Set): 36 • Analyzed for Pharmacokinetics (Per Protocol Set): 35 • Analyzed for Efficacy (Full Analysis Set, FAS): 35 Patients were recruited into 3 predefined age groups: 3 to 23 months (inclusive), 28 days to less than 3 months, from birth to 27 days (term newborns). 11 investigational centers: six centers in Poland, three centers in Hungary and two centers in the USA.	Single intravenous injection of 0.05 mmol/kg body weight (BW)	A total of 3 blood samples per patient were taken post-injection for PK analysis, one within each window (10-60 minutes, 2-4 hours, 6-8 hours). Each time window contained 4 time points for blood collection. One of the time points within each time window was randomly allocated to the patients by Interactive Web Response System (IWRS).
GDX-44-003, Phase I/IIa	Assessment of Pharmacokinetics, Pharmacodynamics Profile and Tolerance of gadopiclenol in Healthy Subjects and Patients with Brain Lesions.	• Phase I: N =54 healthy male and female, 18-45 years old • Phase IIa: N=12 patients with brain lesions, 3 per dose group	Phase I: 0.025, 0.05, 0.075, 0.1, 0.2, and 0.3 mmol/kg Phase IIa: 0.05, 0.075, 0.1 and 0.2 mmol/kg	Concentrations were measured in plasma samples collected before administration and over a 24-hour period post-administration and in urine specimens (phase I) collected until 7 days after administration.
GDX-44-005, Phase I	Pharmacokinetics, dialysability and safety of gadopiclenol, a new gadolinium-based contrast agent, in healthy volunteers and in patients with impaired renal function	N=40 (8 subjects for 5 cohorts, healthy, mild, moderate, severe renal impairment or ESRD)	0.1 mmol/kg	Blood samples were collected at different time points in cohorts 1 to 4, and blood and dialysate samples were collected at each hemodialysis session (4-hour session on day 1, day 3, and day 5) in cohort 5. Gadopiclenol elimination and safety were assessed for up to 6 months.
GDX-44-007	Pharmacokinetics, safety and efficacy of a new gadolinium-based contrast agent, gadopiclenol, in pediatric patients from 2 to 17 years of age undergoing	N=59, age 2-17 years old.	0.05 mmol/kg	Blood sampling was performed following an optimized flexible design with 4 sampling windows (1-20 minutes, 30-45 minutes, 2-3 hours, 7-8 hours) covering the first 8 hours (at least

	contrast-enhanced MRI			4 elimination half-lives of gadopiclenol)

Source: Reviewer summarized from Section 2.7.2 Clinical Summary

PopPK modeling and simulation was conducted via nonlinear mixed effects modelling with nonlinear mixed effects modelling (NONMEM) software, (Version 7.2) (ICON plc, Ellicott City, MD). First-order conditional estimation with interaction (FOCEI) was used as estimation method. SAS V9.4 was used for structuring the analysis dataset, producing graph and summary tables.

Table 7 provides summary statistics of the baseline demographic covariates in the analysis dataset.

Table 7. Summary of Baseline Demographic Covariates for Analysis
Pediatrics from No. GDX-44-015

Covariate	Category	Statistics	GDX-44-015	3-23 months	28 days-<3 months
Gender	Female	n (%)	18 (51.4)	17 (51.5)	1 (50.0)
	Male	n (%)	17 (48.6)	16 (48.5)	1 (50.0)
Age(*)		N/Nmiss	35/0	33/0	2/0
		Mean (SD)	12.1 (6.6)	12.7 (6.3)	1.5 (0.7)
		Min/Median/Max	1/12.0/23	2/12.0/23	1/1.5/2
Height (cm)		N/Nmiss	35/0	33/0	2/0
		Mean (SD)	74.7 (8.7)	75.8 (7.8)	57.0 (1.4)
		Min/Median/Max	54/74.0/87	54/75.0/87	56/57.0/58
Weight (kg)		N/Nmiss	35/0	33/0	2/0
		Mean (SD)	9.16 (2.35)	9.40 (2.18)	5.10 (0.28)
		Min/Median/Max	4.2/9.10/13.7	4.2/9.20/13.7	4.9/5.10/5.3
BMI (kg/m^2)		N/Nmiss	35/0	33/0	2/0
		Mean (SD)	16.23 (2.54)	16.26 (2.62)	15.70 (0.14)
		Min/Median/Max	12.0/15.90/22.6	12.0/15.90/22.6	15.6/15.70/15.8
eGFR (mL/min/1.73 m^2)		N/Nmiss	35/0	33/0	2/0
		Mean (SD)	142.5 (48.2)	145.9 (47.2)	87.5 (31.8)
		Min/Median/Max	65/135.0/345	77/138.0/345	65/87.5/110
Serum Creatinine (µmol/L)		N/Nmiss	35/0	33/0	2/0
		Mean (SD)	20.48 (4.98)	20.17 (4.63)	25.65 (9.97)
		Min/Median/Max	9.0/20.00/33.0	9.0/20.00/33.0	18.6/25.65/32.7
(*): Age is expressed in months					

Baseline Covariates for All Patients

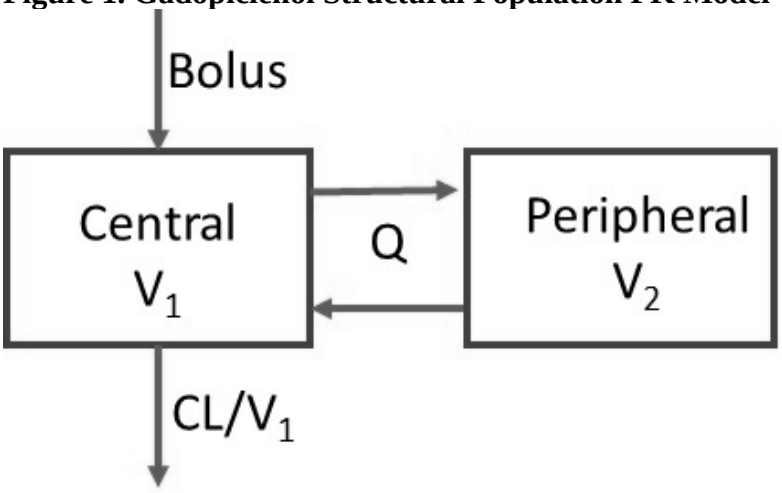
Covariate	Category	Statistics	All	Adults
Gender	Female	n (%)	84 (49.7)	41 (52.6)
	Male	n (%)	85 (50.3)	37 (47.4)
Age (years)		N/Nmiss	169/0	78/0
		Mean (SD)	21.7 (20.9)	40.3 (16.3)
		Min/Median/Max	0/16.0/71	18/37.5/71
Height (cm)		N/Nmiss	169/0	78/0
		Mean (SD)	138.6 (39.5)	169.1 (9.5)
		Min/Median/Max	54/158.0/188	147/168.4/188
Weight (kg)		N/Nmiss	169/0	78/0
		Mean (SD)	49.34 (29.85)	74.86 (11.92)
		Min/Median/Max	4.2/56.80/100.2	51.0/73.95/100.2
BMI (kg/m^2)		N/Nmiss	169/0	78/0
		Mean (SD)	21.82 (5.80)	26.21 (3.84)
		Min/Median/Max	11.9/22.00/36.1	18.7/26.35/36.1
eGFR ($mL/min/1.73 m^2$)		N/Nmiss	169/0	78/0
		Mean (SD)	107.4 (39.8)	88.7 (33.7)
		Min/Median/Max	14/108.0/345	14/98.0/133
Serum Creatinine (µmol/L)		N/Nmiss	169/0	78/0
		Mean (SD)	67.40 (60.98)	102.95 (73.13)
		Min/Median/Max	9.0/61.00/361.8	53.0/76.00/361.8

Source: Table 4 and 5 in PopPK analysis report: "Population pharmacokinetic analysis of the following study: Gadopiclenol Pharmacokinetics, Safety and Efficacy in Pediatric Patients < 2 Years of Age Undergoing Contrast-enhanced MRI Phase II Clinical Study".

Base model

The previous developed PopPK model for gadopiclenol was used as the starting point for model development (***Figure 1***). The model was parameterized in terms of clearance (CL), central volume of distribution (V_1), inter-compartment clearance (Q) and peripheral volume of distribution (V_2). All parameters were scaled to body weight using fixed allometric rules. The CL was also scaled to eGFR with a power model for pediatric population and a Gompertz function for adult population (see below). Exponential models were used to describe the interindividual variability on CL, V_1 and V_2 and a proportional model was considered as error.

Figure 1. Gadopiclenol Structural Population PK Model



$$CL_i = \theta \times (1 - A \times \exp(-\exp(-B \times (Screat - C)))) \times \exp(\eta)$$

A=asymptote value, B=growth rate, C=inflexion point, Screat = serum creatinine, η: CL IIV (interindividual variation).

Source: Figure 1 and Page 24/68 in PopPK analysis report: "Population pharmacokinetic analysis of the following study: Gadopiclenol Pharmacokinetics, Safety and Efficacy in Pediatric Patients < 2 Years of Age Undergoing Contrast-enhanced MRI Phase II Clinical Study".

Covariate analysis

No additional covariate was included in the model on top of the *Screat*. However, the preliminary check based on base model discussed above shows the overall elimination of gadopiclenol in the children from the study No. GDX-44-015 is slower than what the model can predict, which suggests that the maturation of renal function was not sufficiently considered in the reference model. The applicant used the model proposed by Rhodin et al (see below)[1] to add on the clearance of base model to describe the maturation of renal function in neonates and young children.

$$MF_{renal} = \frac{PMA^s}{PMA_{50}^S + PMA^S}$$

$$CL = \theta_1 \times \left(\frac{Weight}{70}\right)^{0.75} \times \frac{PMA^{3.4}}{47.7^{3.4} + PMA^{3.4}}$$

Where:

- PMA is the post-menstrual age, calculated as the sum of 37 weeks gestational age (assuming a standard gestational age), plus post-natal age;

- s is the sigmoidicity factor (s=3.4);

[1] Rhodin, M.M., Anderson, B.J., Peters, A.M., Coulthard, M.G., Wilkins, B., Cole, M., Chatelut, E., Grubb, A., Veal, G.J., Keir, M.J., Holford, N.H.G., 2009. Human renal function maturation: a quantitative description using weight and postmenstrual age. Pediatr Nephrol 24, 67–76.

- PMA_{50} is the PMA at which MFrenal reaches 0.5 (47.7 weeks).

Source: Page 33/68 in PopPK analysis report: "Population pharmacokinetic analysis of the following study: Gadopiclenol Pharmacokinetics, Safety and Efficacy in Pediatric Patients < 2 Years of Age Undergoing Contrast-enhanced MRI Phase II Clinical Study".

1.4.1.4 Final Model

The parameter estimates for the final covariate model are listed in **Table 8**. The model described the observed data adequately, as seen in the goodness-of fit plots (**Figure 2**). Prediction-corrected visual predictive check (pcVPCs) plots also show that the final PopPK model adequately captured the central tendency and variability of the data (

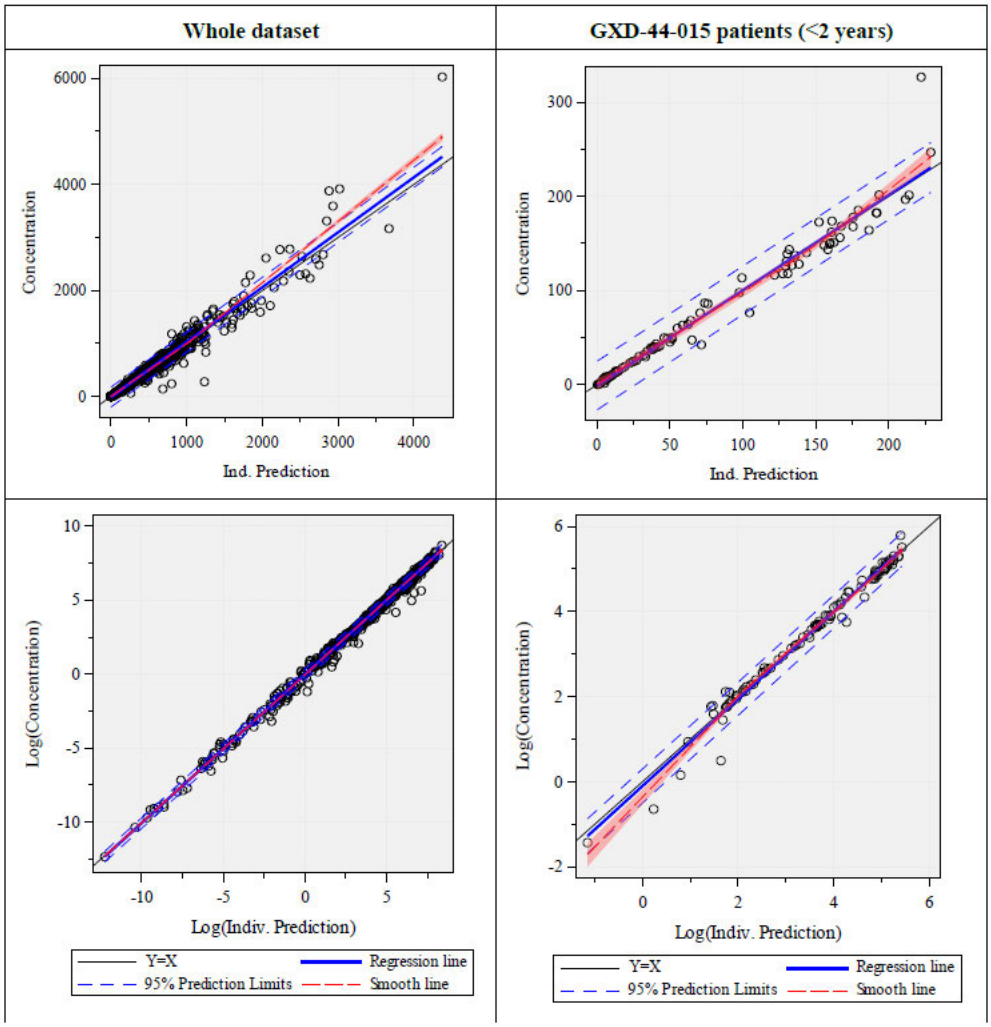
Figure 3).

Table 8. Parameter estimates of the final PopPK model

Parameter	Estimate (%RSE)	95% CI	Variability (CV%) Correlation (R%)
CL(L/h) =θ_1(Weight/70)$^{0.75}$*MF_{renal} * (1-θ_5*EXP(- EXP(- θ_6*(Screat - θ_7))))*EXP(η_1) MF_{renal}=$PMA^{3.4}$/(47.7$^{3.4}$+$PMA^{3.4}$)**			
θ_1: CL typical value	5.95 (2.79)	(5.62;6.28)	
θ_5: Asymptotic (maximal) effect of Screat on CL	0.877 (1.29)	(0.855;0.899)	
θ_6: growth rate of CL	0.0298 (14.2)	(0.0215;0.0381)	
θ_7: inflexion point of adults CL	103 (3.46)	(96;110)	
η_1 (IIV CL)	0.0509 (10.8)	(0.0402;0.0616)	CV=22.6%
Q (L/h) =θ_2(Weight/70)$^{0.75}$*EXP(η_2)			
θ_2: Q typical value	4.07 (8.48)	(3.39;4.75)	
η_2 (IIV Q)	0.329 (29.9)	(0.136;0.522)	CV=57.4%
$\eta_{2,1}$ (cov CL, Q)	0.0176 (114)	(-0.0216; 0.0568)	R=13.6%
V_1 (L)=θ_3(Weight/70)$^{\theta 8}$*EXP(η_3)			
θ_3: V_1 typical value	7.27 (3.05)	(6.83;7.71)	
θ_8: Effect of weight	0.763 (3.62)	(0.709; 0.817)	
η_3 (IIV V_1)	0.0769 (15.7)	(0.0532; 0.101)	CV=27.7%
$\eta_{3,1}$ (cov CL, V_1)	0.0175 (49.0)	(0.000703; 0.0343)	R=28.0%
$\eta_{3,2}$ (cov Q, V_1)	-0.130 (22.0)	(-0.186; -0.0739)	R=-81.7%
V_2 (L)=θ_4(Weight/70)*EXP(η_4)			
θ_4: V_2 typical value	4.73 (6.74)	(4.10;5.36)	
η_4 (IIV V_2)	0.223 (23.6)	(0.120;0.326)	CV=47.2%
$\eta_{4,1}$ (cov CL, V_2)	-0.00961 (127)	(-0.0335; 0.0143)	R=-9.02%
$\eta_{4,2}$ (cov Q, V_2)	0.0821 (65.7)	(-0.0235; 0.188)	R=30.3%
$\eta_{4,3}$ (cov V_1, V_2)	-0.0470 (41.3)	(-0.0850; -0.00898)	R=-35.9%
Residual error			
ε_1: proportional component	0.0205 (3.37)	(0.0191 ;0.0219)	CV=14.3%
OFV: 9993.817/AIC: 10031.8 - Run number R011 Condition Number: 199.5			

Source: Table 8 in PopPK analysis report: "Population pharmacokinetic analysis of the following study: Gadopiclenol Pharmacokinetics, Safety and Efficacy in Pediatric Patients < 2 Years of Age Undergoing Contrast-enhanced MRI Phase II Clinical Study".

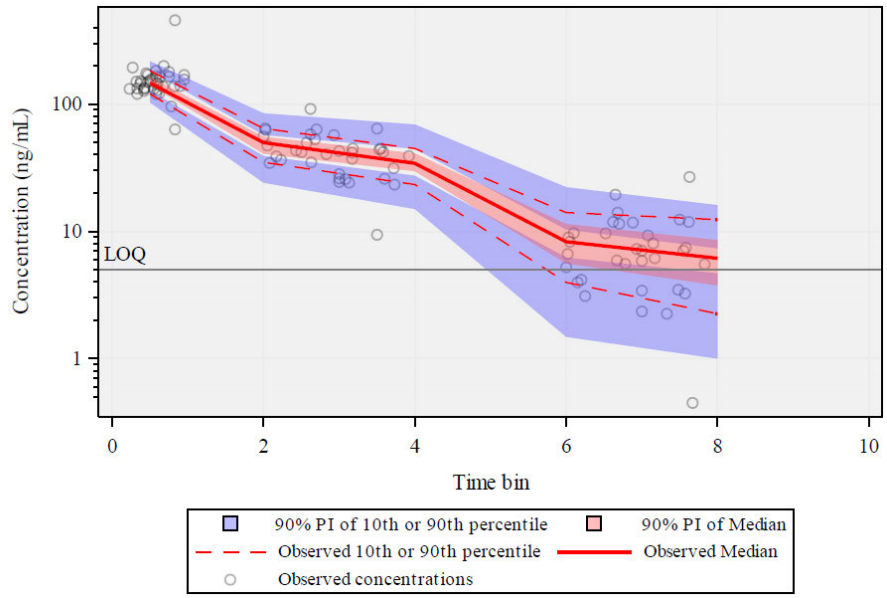
Figure 2. Goodness-of-Fit Plots for final PopPK model
Upper: natural scale; lower: log scale



Source: Figure 4 in PopPK analysis report: "Population pharmacokinetic analysis of the following study: Gadopiclenol Pharmacokinetics, Safety and Efficacy in Pediatric Patients < 2 Years of Age Undergoing Contrast-enhanced MRI Phase II Clinical Study".

Figure 3. pcVPC Plots for final PopPK model

Study No. GDX-44-015 Pediatric Patients



Source: Figure 5 in PopPK analysis report: "Population pharmacokinetic analysis of the following study: Gadopiclenol Pharmacokinetics, Safety and Efficacy in Pediatric Patients < 2 Years of Age Undergoing Contrast-enhanced MRI Phase II Clinical Study".

Based on final PopPK model, individual predictions (EBE) were used to derive PK exposure parameters (AUC, $t_{1/2}$, concentrations at 10, 20 min) (**Table 9**).

Table 9. Summary of exposure parameters by age group predicted from PopPK for subjects receiving gadopiclenol 0.05 mmol/kg

Age group	N	$AUC_{0\text{-}inf}$ (h.mg/L)*	$t_{1/2}$ (hr)*	$C_{10\ min}$ (µg/mL)*	$C_{20\ min}$ (µg/mL)*
Adults	9	571.97 [408.6, 695.0]	1.62 [1.2, 3.0]	364.09 [241.2, 390.1]	241.43 [190.8, 280.8]
12-17 years	18	637.57 [462.0, 1039.9]	1.78 [1.4, 5.0]	406.54 [307.3, 499.0]	256.24 [209.5, 302.4]
7-11 years	19	575.36 [369.7, 792.0]	1.61 [1.3, 2.2]	327.78 [280.5, 439.2]	234.03 [179.9, 289.5]
2-6 years	19	465.07 [281.5, 764.4]	1.75 [1.2, 2.5]	280.15 [228.7, 374.3]	195.28 [139.2, 250.4]
3-23 months	33	375.48 [185.7, 777.3]	1.45 [0.9, 2.5]	225.80 [141.5, 367.3]	161.63 [100.6, 269.1]
28 days -< 3 months	2	494.52 [460.1, 528.9]	2.10 [2.0, 2.2]	191.61 [169.9, 213.3]	150.42 [136.3, 164.6]

** Each PK metrics is expressed as Median (range).*

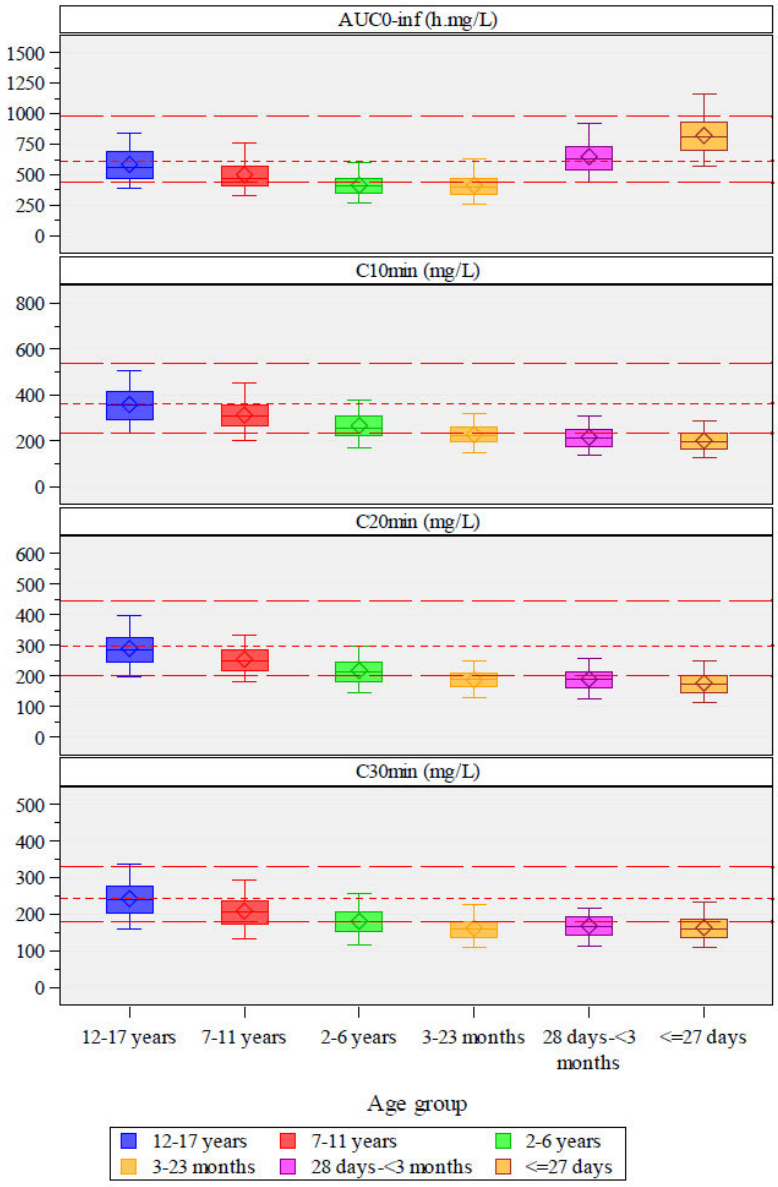
Source: Table 15.4.1-1, 15.4.1-2 in PopPK analysis report: "Population pharmacokinetic analysis of the following study: Gadopiclenol Pharmacokinetics, Safety and Efficacy in Pediatric Patients < 2 Years of Age Undergoing Contrast-enhanced MRI Phase II Clinical Study".

1.4.1.5 PK simulation based on PopPK model

Because the recruitment of study GDX-44-015 could not be completed, with only 2 patients in group of patients aged from 28 days to <3 months and none in group of patients <28 days, the exposure in these groups was obtained by simulation. Two hundred individuals (100 male and 100 female) were sampled with replication, from DGD-44-063 dataset[2]. The simulation result is shown in **Figure 4**. The simulation results suggest the early plasma concentrations 10, 20 and 30 minutes following a single administration in children between 12 and 17 years were comparable to those of adults, but lower than adults for below 12 years age group. The lower concentration is potentially due to the higher volumes of extracellular fluid and total body water (per body weight) in children than adult. The decrease was progressive for 7-11 and 2-6 years age groups. However, the concentration below 2 years remained in the same range as for the 2-6 years group, which was approved to use previously. For $AUC_{0-\infty}$, an age dependent decrease in exposure was also observed up to the 2-6 years group, but for the 3-23 months the AUC was similar to 2-6 years and then, below 3 months, increased to become comparable to adult values as a consequence of lower CL for those children whose renal function is not mature. Overall, the reviewer concludes the gadopiclenol exposure is comparable between previously approved age (2 and above) and 2 years below.

[2] Scala M, Koob M, de Buttet S, Bourrinet P, Felices M, Jurkiewicz E. A. Pharmacokinetics, Efficacy, and Safety Study of Gadoterate Meglumine in Pediatric Subjects Aged Younger Than 2 Years. Invest Radiol.2017. DOI: 10.1097/RLI.0000000000000412

Figure 4. Simulated exposure parameters from the final model at the dose 0.05 mmol/kg in participants with normal renal function (Dose: 0.05 mmol/kg)



Source: Figure 6 in PopPK analysis report: "Population pharmacokinetic analysis of the following study: Gadopiclenol Pharmacokinetics, Safety and Efficacy in Pediatric Patients < 2 Years of Age Undergoing Contrast-enhanced MRI Phase II Clinical Study".

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