Clinical Pharmacology Review

NDA (SDN)	204781 (SDN113)
Submission Date:	October 27, 2016
Brand Name:	Dotarem
Generic Name:	Gadoterate meglumine injection
Formulation:	DOTAREM Injection is a clear, colorless to yellow solution containing 0.5 mmol/mL of gadoterate meglumine.
Pharmacometrics Primary Reviewer:	Lian Ma, PhD
Pharmacometrics Secondary Reviewer	Yaning Wang, PhD
OCP Division:	Division of Pharmacometrics Division of Clinical Pharmacology V
ORM Division:	Division of Medical Imaging Products
Applicant:	Guerbet LLC
Dosing regimen:	0.1 mmol/kg
Indication:	DOTAREM is a gadolinium-based contrast agent indicated: for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissues in adult and pediatric patients (including term neonates) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity.

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1. Executive Summary

Dotarem® is a macrocyclic, ionic, gadolinium-based contrast agent (GBCA), an injectable solution administered by intravenous route and intended for diagnostic examinations carried out by magnetic resonance imaging (MRI).

Dotarem (gadoterate meglumine) has been approved by the FDA on 20th March 2013 (NDA 204-781) to be used in the MRI in brain (intracranial), spine and associated tissues in adult and pediatric patients (2 years of age and older) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity. In the current submission, the applicant is seeking to expand the indication to pediatric patients 0-2 years of age.

The proposed dose for the additional population targeted (pediatric population < 2 years of age) is the same dose currently recommended, 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 for adults and 1-2 mL/second for children.

The pivotal study supporting the expansion of indication was an open-label, single-arm, non-randomized study in pediatric patients (term newborn infant to 23 months of age) undergoing a contrast-enhanced MRI with an intravenous injection of 0.1 mmol/kg Dotarem (DGD-44-063). Forty-five patients were evaluated for PK and safety, and 28 were evaluated for efficacy. This study and additional post-marketing data suggest the safety and efficacy of Dotarem in pediatric patients aged 0-2 years is similar to the approved age range of uggest the

The proposed dosing regimen (0.1 mmol/kg) for Dotarem is supported by the overall PK, safety and efficacy data in pediatric study DGD-44-063. Based on population PK analysis, the predicted AUC following 0.1 mmol/kg dose appear to be comparable in pediatric patients aged birth (term neonates) to 23 months to those in adults with approved dosing regimen. However, there is a trend of lower AUC values with older age (**Figure 2**). As indicators for imaging efficiency, the early plasma concentrations at 20 and 30 min (C20 and C30) following a single dose administration of 0.1 mmol/kg in pediatrics are predicted to be 25-35% lower than that in adults, potentially due to the higher volumes of extracellular fluid and total body water (per body weight) in neonates and infants. However, the efficacy is not expected to be affected because the predicted plasma levels are consistent with the exposure associated with Gadavist®, an approved GBCA product in the same patient population (< 2 years old).

1.1. Recommendations

The Office of Clinical Pharmacology has determined that there is sufficient clinical pharmacology information provided in this sNDA to support the approval of Dotarem in pediatrics 0-2 years of age. The proposed dose of 0.1 mmol/kg is acceptable. This submission fulfills a Post Marketing Requirement (PMR 2021-2) from the original approval of March 20, 2013 to study the product in pediatric patients 0-2 years of age.

1.2. Summary of Clinical Pharmacology Findings

Details on the Clinical pharmacology of Dotarem in adults and children (2 years of age and older) are available in the Clinical Pharmacology Review by Dr. John dated 20th February 2013. Highlights of clinical pharmacology for Dotarem are provided in Section 4.2.

Overall, the proposed dosing regimen (0.1 mmol/kg) of Dotarem for pediatric patients < 2 years of age is supported by the following observations:

- The pivotal study DGD-44-063 and additional post-marketing data suggest that the safety and efficacy is similar to the approved age range of ≥ 2 years.
- Predicted AUC is comparable to that in adults with the approved (same) dosing regimen.
- The predicted early plasma concentration levels (C20 and C30) are consistent with the reported exposure associated with Gadavist®, an approved GBCA product in the same patient population (< 2 years old).

The dializability of Dotarem was evaluated in 10 patients with chronic renal failure who require hemodialysis treatment (DGD-44-054). Dotarem was shown to be dialyzable after an IV injection of 0.1 mmol/kg in 10 patients with end-stage renal failure who required hemodialysis treatment. Dotarem serum concentration decreased over time by 88%, 93% and 97% at 0.5 hr, 1.5 hr, and 4 hrs after start of dialysis, respectively. A second and third hemodialysis session allowed further removal of Dotarem from the body, with a 99.7% of Gd serum concentration decrease after the third dialysis.

1.3. Signatures

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2. Question Based Review

2.1. What are the design features of the clinical studies used to support the dosing or claims?

To support the proposed indication, the applicant conducted a PK study in pediatric patients from term neonates to 2 years of age who received a 0.1 mmol/kg IV dose (Study DGD-44-063). Safety and efficacy of Dotarem were also evaluated as secondary objectives. Of 51 subjects enrolled in the study, 45 subjects received Dotarem and were included for PK and safety evaluation. The efficacy was evaluated in a subset of 28 subjects who were referred for a central nervous system (CNS) imaging. The number of blood sampling was limited to 3 per subject, 1 during each time window (10 min to 60 min, 2.0 hours to 4.0 hours and 6.0 hours to 8.0 hours post-injection). The time points were allocated by randomization. Primary study endpoints were PK parameters estimated from Dotarem concentration time profiles: Area under the curve (AUC), rate constant of the terminal phase (β), elimination half-life ($t_{½\beta}$), total clearance (CL), volume of distribution at steady state (Vss). The evaluation of efficacy was based on qualitative assessment of image quality and lesion visualization (border delineation, internal morphology, contrast enhancement) based on pre + post-contrast images compared to pre-contrast images. Safety monitoring data was also evaluated.

The applicant also summited a study of the dializability of Dotarem in dialyzed patients (DGD-44-054). This was a single center, non-comparative, non-randomized, open-label study. The primary objective was to evaluate the dialysability of Dotarem, after an intravenous injection of 0.1 mmol/kg in patients with chronic renal failure who require hemodialysis treatment. A total of 10 patients (5 male/5 female) received Dotarem at 0.1 mmol/kg injected intravenously. After administration, 3 sessions of hemodialysis were performed as follows:

- first hemodialysis session started between 1 to 2 h after the injection;
- second hemodialysis session occurred 2 days (i.e., 48 ± 2 h) after the Dotarem injection;
- third hemodialysis session occurred 4 days (i.e., 96 ± 4 h) after the Dotarem injection.

The decrease in serum Dotarem concentration was assessed after each hemodialysis session. Safety assessments included AEs, vital signs, injection-site tolerance, and laboratory assessments.

2.2. What are the pharmacokinetics characteristics of Dotarem in pediatric patients aged birth (term neonates) to 23 months?

Dotarem concentration profiles in study DGD-44-063 (**Figure 1**) were best fitted using a two-compartmental model with linear elimination from central compartment, parameterized in terms of total clearance (CL), central volume of distribution (V1), inter-compartment clearance (Q) and volume of distribution at steady state (Vss).

A summary of PK parameter estimates based on reviewer's independent analysis is provided in **Table 1**. Typical model parameters are provided for a 70 kg adult. The median CL is estimated at 1.09 L/h and the individual CL increases with eGFR based on a power model used to analyze the data. The median Vss is estimated at 2.22 L. Estimated median t1/2β is 1.35 hour and the median systemic exposure (AUC) is 666 µmol*h/L. The inter-individual variability on CL and V is relatively high (40 to 45% CV) compared to adults.

Figure 1. Individual Dotarem concentrations over time (left: normal scale; right: log-scale)

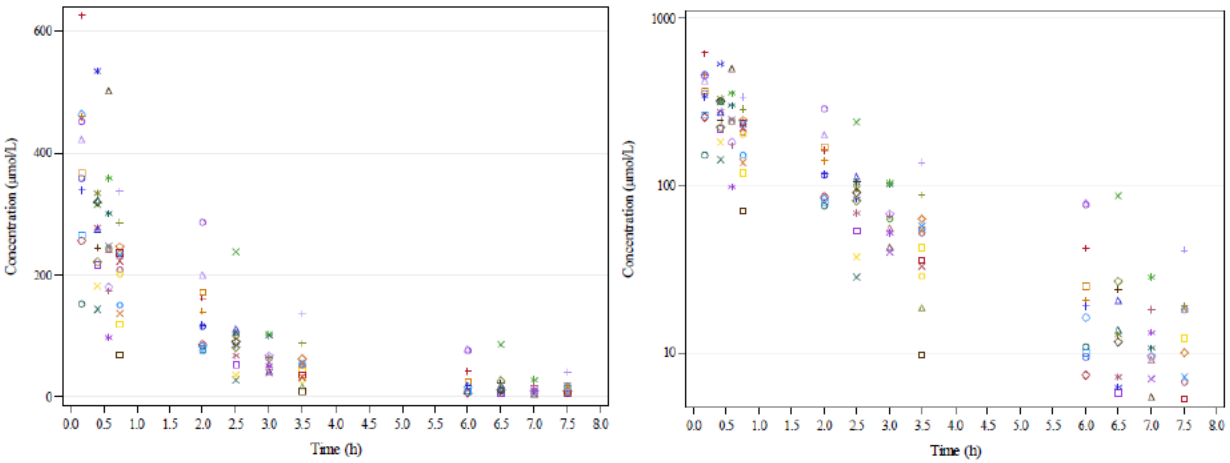


Table 1. Pharmacokinetic parameters in pediatric subjects < 2 years old (reviewer's analysis)

Parameter	*Estimate*	*RSE[%]*	*95% CI*
Fixed Effect			
CL [L/hr/(BW/70)$^{0.75}$]	6.2	6.3	5.4 – 7.0
V [L/(BW/70)]	17.4	8.7	14.4 – 20.4
Q (L/hr)	0.548	40	0.12 – 0.98
Vss-V [L/(BW/70)]	2.87	26.8	1.4 – 4.4
Effect of GFR on CL (Scaling factor)	0.83	11.4	0.6 – 1.0
Random Effects (Inter-individual variability)			
IIV_CL (CV%)	40.1 [1.8%][a]	13	34.9 – 45.3
IIV_V1 (CV%)	45.4 [6.5%][a]	14	39.0 – 51.8
Residual Variability			
Proportional residual error (CV%)	14 [36%][a]	26	10.4 – 17.7

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

2.3. Is proposed dosing regimen (0.1 mmol/kg) of Dotarem appropriate to be used in pediatric patients aged birth (term neonates) to 23 months?

Yes. The proposed dosing regimen (0.1 mmol/kg) for pediatric patients aged birth (term neonates) to 23 months is supported by the overall PK, safety and efficacy data in pediatric study DGD-44-063.

The predicted AUC following 0.1 mmol/kg Dotarem in pediatric patients aged birth (term neonates) to 23 months appear to be similar compared to those in adults with approved dosing regimen, with a trend of lower AUC values with order age after birth (**Figure 2**). The safety concern is therefore minimal considering the high stability of Dotarem and safety findings in the pivotal study.

Figure 2. Distribution of Dotarem AUC in pediatric subjects aged <2 years and in adult healthy volunteers following administration of 0.1 mmol/kg dose (reviewer's analysis)

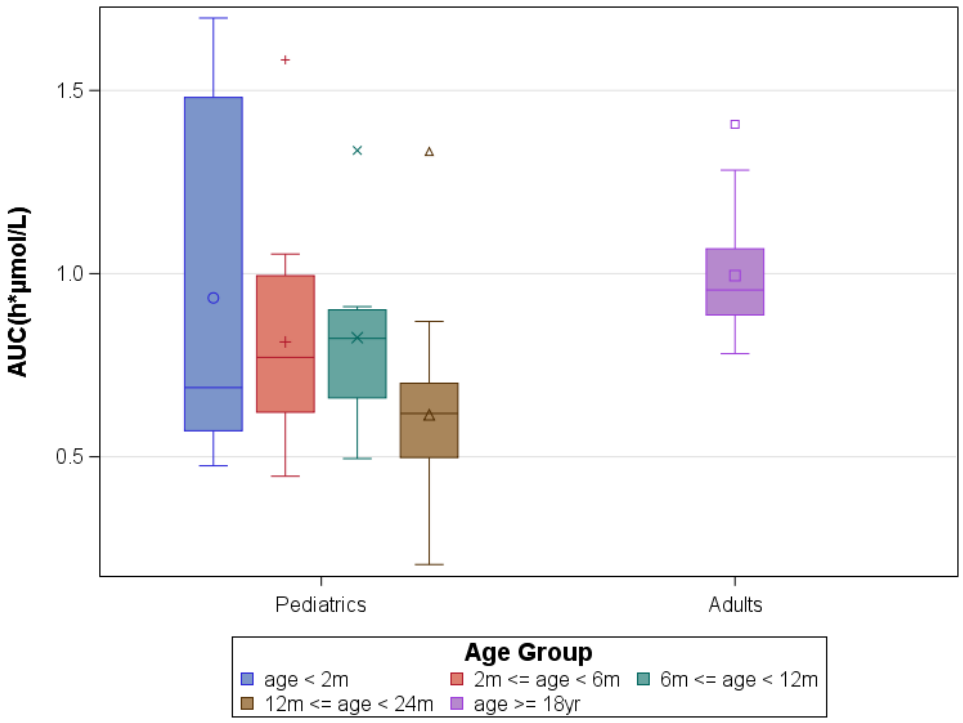
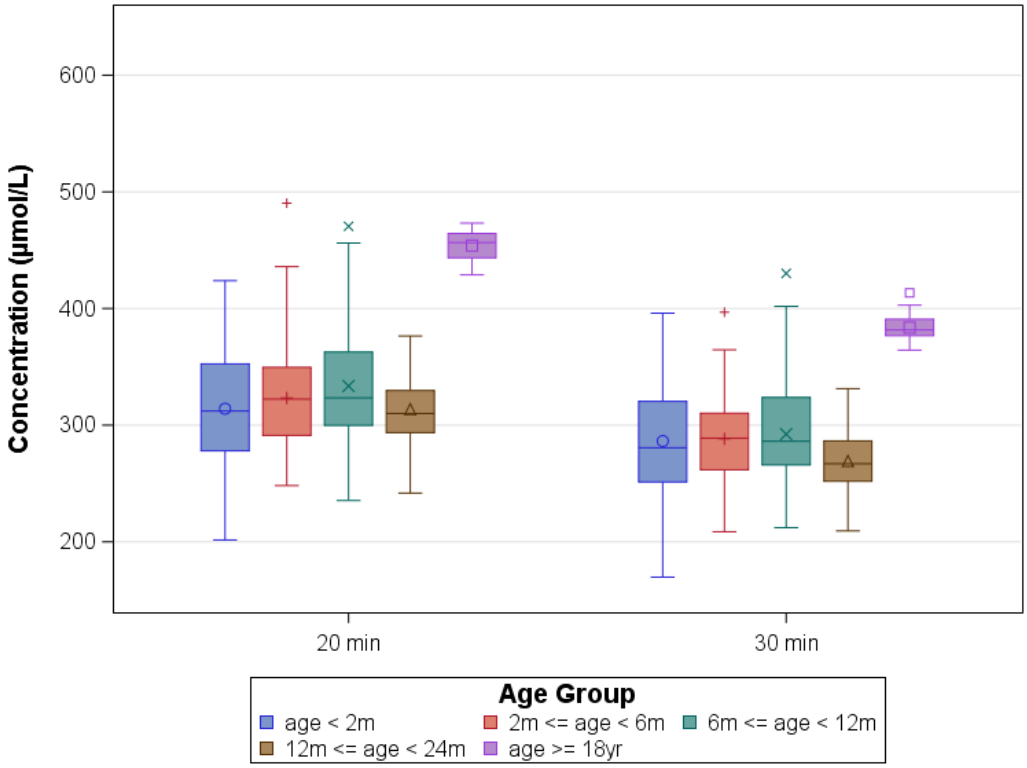


Figure 3. Distribution of predicted Dotarem concentrations in pediatric subjects aged <2 years and in adult healthy volunteers at 20 and 30 min following administration of 0.1 mmol/kg dose (reviewer's analysis)



As the MRIs are often conducted at 10 to 30 min after administration of the contrast agent, the early plasma concentrations at 20 and 30 min (C20 and C30) are considered most relevant to imaging efficiency. Based on population PK analysis and simulation, the C20 and C30 following a single dose administration of 0.1 mmol/kg in both pediatric subjects aged <2 years and adults were predicted using the estimates from the final models. The results are plotted in **Figure 3** comparing these exposure metrics across age groups (0-<2 months, 2-<6 months, 6-<12 months, 12-<24 months, 18 years and above). Overall the predicted C20 and C30 in pediatrics appear to be 25 - 35% lower than that in adults, potentially due to the higher volumes of extracellular fluid and total body water (per body weight) in neonates and infants. However, the efficacy in pediatric patients under 2 years of age is not expected to be affected because the predicted plasma levels in this population are within the range of exposure associated with pediatric patients under 2 years of age with Gadavist®, an approved GBCA product (**Table 1**).

Table 2. Predicted C20 in pediatric patients 0 to < 2 years (Median [range])

	Dotarem (N=45)	Gadavist (N=43)*
C20 (µmol/L)	321 [213, 383]	367 [280, 427]

*Source: Package insert for Gadavist®, 2016, available from:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/201277s011lbl.pdf

2.4. Is Dotarem dialyzable in patients with end-stage renal failure who required hemodialysis treatment?

Yes. Dotarem was shown to be dialyzable after an IV injection of 0.1 mmol/kg in 10 patients with end-stage renal failure who required hemodialysis treatment.

Decrease in Dotarem concentration following 3 hemodialysis sessions were calculated according the following formula: [(Gd before dialysis-Gd after dialysis)/Gd before dialysis] *100, and presented in **Table 2**. Dotarem serum concentration decreased over time by 88%, 93% and 97% at 0.5 hr, 1.5 hr, and 4 hrs after start of dialysis, respectively. A second and third hemodialysis session allowed further removal of Dotarem from the body, with a 99.7% of Gd serum concentration decrease after the third dialysis.

Table 3. Percentage Dotarem concentration decrease over time

Time Point	*N*	*N'*	*Arithmetic Mean*[a]	*Geometric Mean*[b]	*95% CI*	*%CV*
First hemodialysis						
0.5 h	10	10	88.2	88.1	86.4; 90.0	2.9
1.5 h	10	10	93.4	93.4	92.2; 94.6	1.8
4 h	10	10	97.1	97.1	95.3; 98.9	2.6
Second hemodialysis						
4 h	10	7	66.4	94.8	33.5; 99.3	69.2
Third hemodialysis						
4 h	10	2	18.0	89.9	-9.2; 45.2	211.2

N = number of subjects with data, N' = number of subjects with data above the limit of detection (0.954 µmol/L) , %CV = coefficient of variation
[a] Arithmetic mean was calculated based on N.
[b] Geometric mean was calculated on values above the limit of detection (0.954 µmol/L), i.e., based on N'.
(Source: Applicant's Study Report for DGD-44054, Table 8)

Eight (80.0%) subjects had one or more treatment-emergent AEs (TEAEs) following Dotarem injection. Treatment-emergent AEs reported in more than 2 subjects were hypotension (5 [50.0%] subjects),

headache (3 [30.0%] subjects), and muscle spasms (3 [30.0%] subjects). Four (40.0%) subjects had one or more SAEs following Dotarem injection, however none were considered related to the study drug by the investigator. None of the TEAEs led to discontinuation of the study.

2.5. What bioanalytical methods were used to assess the plasma concentrations?

DOTAREM® concentrations in plasma were analyzed using a validated LC-MS-MS method by (b) (4) (b) (4) The bioanalytical methods used in the pediatric study was the same as that used in adult studies, and has been reviewed in the original NDA application (Clinical Pharmacology review by Dr. John dated 20 February 2013).

3. Appendices

4.1. Pharmacometrics Review

4.1.1. Applicant's Population PK Analysis

The applicant initially submitted population PK (PopPK) analysis based on data from pediatric study DGD-44-063 only. No comparison was made to adults and children >2 years of age. Upon FDA's request, the applicant clarified that the data obtained in in 0-2 years of age pediatric patients were not combined with data from studies in older pediatric patients and adults for the following reasons:

- There is no PK study available from pediatric patients aged 2 to 17 y.o., so no data to combine with.
- Regarding the adult PK study (DGD-3-48), this study was done according to a "traditional PK design" (i.e. multiple PK points per subject allowing to have a precise determination of the PK profile and parameters for each subject at each dose tested), and it was not judged useful to develop a population PK model on this population in order to combine it with the newly obtained PopPK data in the 0 to 2 years of age population.

The applicant subsequently developed a PopPK model on the adult data. The final models for pediatrics < 2 years of age and adults were then used to simulate and compare Dotarem exposure in both population at the dose of 0.1 mmol/kg.

The PopPK models were built on the population of subjects who received Dotarem, regardless of the quantity and for whom at least one blood sample for PK was available, and who had no major protocol deviations. The adult dataset comprised a total of 415 serum samples from 32 subjects. The pediatric dataset comprised 135 samples from 45 subjects. Subject characteristics for both datasets are summarized in Table 3 and Table 4.

Table 4. Subjects Baseline Demographic Characteristics in Adult Study DGD-3-48

			Treatment group		
Covariate	Category	Statistics	All	Group A (0.1 mmol/kg)	Group B (0.1+0.2 mmol/kg)
Gender	Female	n (%)	16 (50.0)	8 (50.0)	8 (50.0)
	Male	n (%)	16 (50.0)	8 (50.0)	8 (50.0)
Age (years)		N/Nmiss	32/0	16/0	16/0
		Mean (SD)	29.8 (6.7)	30.7 (6.1)	28.8 (7.3)
		Min/Median/Max	20.0/27.00/44.0	26.0/28.50/44.0	20.0/27.00/44.0
Height (cm)		N/Nmiss	32/0	16/0	16/0
		Mean (SD)	172.5 (9.3)	172.3 (10.4)	172.7 (8.3)
		Min/Median/Max	152/172.5/189	152/170.0/187	160/174.0/189
Weight (kg)		N/Nmiss	32/0	16/0	16/0
		Mean (SD)	67.5 (9.6)	67.6 (9.6)	67.4 (9.9)
		Min/Median/Max	52/65.8/88	52/68.5/82	54/65.5/88
Creatinine clearance (mL/min)		N/Nmiss	32/0	16/0	16/0
		Mean (SD)	112.4 (20.6)	114.4 (23.1)	110.5 (18.2)
		Min/Median/Max	84/112.4/169	84/114.7/169	85/110.0/153

(Source: Applicant's PopPK Report for DGD-3-48, Table 3)

Table 5. Subjects Baseline Demographic Characteristics in Pediatric Study DGD-44-063

Covariate	Category	Statistics	Results
Gender	Female	n (%)	23 (51.1)
	Male	n (%)	22 (48.9)
Age (week)		N/Nmiss	45/0
		Mean (SD)	42.0 (31.8)
		Min/Median/Max	0.5/38.00/103.0
Height (cm)		N/Nmiss	45/0
		Mean (SD)	68.8 (11.5)
		Min/Median/Max	47/71.0/87
Weight (kg)		N/Nmiss	45/0
		Mean (SD)	8.1 (3.1)
		Min/Median/Max	3/8.0/15
eGFR (mL/min/1.73m²)		N/Nmiss	45/0
		Mean (SD)	133.8 (46.5)
		Min/Median/Max	52/138.0/281

(Source: Applicant's PopPK Report for DGD-44-063, Table 11.1.2-1)

It should be specified that children model was built on gadoteric acid concentrations (obtained by LC-MSMS) while adult's model was built on total gadolinium concentrations (obtained by ICP-OES). Due to the absence of metabolism of Dotarem®, the difference between total gadolinium and Dotarem® blood concentrations were expected to be minimal, however, it should be noted that the two models were built with non-strictly comparable absolute values of circulating compound.

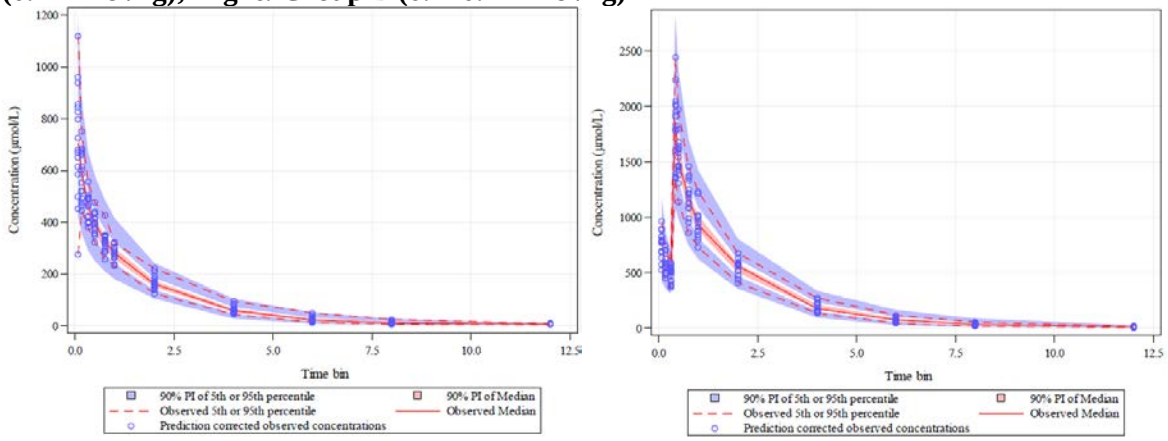
For adults model, a three-compartment model with elimination from the central compartment provided the best fit. The model was parameterized in terms of clearance (CL), central volume of distribution (V1), first and second peripheral compartments (respectively V2 and V3), and intercompartment clearances (Q2 and Q3). Exponential models were used to describe the inter-individual variability on CL, V1 and V2. Moreover, the covariance term between CL and V1 was estimated and improved significantly the model. A mixed (proportional and additive) model was considered as the best model for error. The only covariate that was found to impact significantly CL was creatinine clearance calculated according to Cockroft and Gault. The parameter estimates for the final model is summarized in **Table 5**. The final model was validated through goodness of fit plots, and prediction corrected visual predictive check (**Figure 4**).

Table 6. Parameter estimates of the applicant's final adult model

Parameter	Estimate (%RSE)	95% CI	Variability
$CL(L/h)=[\theta_1(Weight/70)^{0.75}+\theta_7(CLCr-112)]*EXP(\eta_1)$			
θ_1: CL typical value	7.07 (2.35%)	6.74; 7.40	
θ_7:Creatinine clearance effect	0.0210 (30.2%)	0.00855; 0.0334	
η_1 (IIV CL)	0.0174 (24.3%)	0.00913; 0.0257	CV = 13.2%
$V_1 (L)=\theta_2(Weight/70)*EXP(\eta_2)$			
θ_2: V_1 typical value	7.52 (5.69%)	6.68; 8.36	
η_2 (IIV V1)	0.0505 (26.3%)	0.0244; 0.0766	CV=22.5%
Cov (CL,V_1)	0.0205 (28.7%)	0.00898; 0.0320	R=0.692
$Q_2 (L/h)=\theta_3(Weight/70)^{0.75}*EXP(\eta_3)$			
θ_3: Q_2 typical value	18.1 (8.90%)	14.9; 21.3	
η_3 (IIV Q_2)	0 FIX		
$V_2 (L)=\theta_4(Weight/70)*EXP(\eta_4)$			
θ_4: V_2 typical value	4.92 (6.83%)	4.26; 5.58	
η_4 (IIV V_2)	0.0568 (29.9%)	0.0235; 0.0901	CV=23.8%
$Q_3 (L/h)=\theta_5(Weight/70)^{0.75}*EXP(\eta_5)$			
θ_5: Q_3 typical value	0.454 (20.4%)	0.272; 0.636	
η_5 (IIV Q_3)	0 FIX		
$V_3 (L)=\theta_6(Weight/70)*EXP(\eta_6)$			
θ_6: V_3 typical value	1.49 (6.91%)	1.29; 1.69	
η_6 (IIV V_3)	0 FIX		
Residual error			
ε_1: proportional component	0.00621 (18.7%)	0.00394; 0.00848	CV = 7.88%
ε_2: additive component	1.72 (48.2%)	0.0952; 3.34	SD=1.31
OFV: 2707.654 - Run number R204			

(Source: Applicant's PopPK Report for DGD-3-48, Table 6)

Figure 4. Prediction Corrected Visual Predictive Check of the Final Adult Model- Left: Group A (0.1 mmol/kg); Right: Group B (0.1+0.2 mmol/kg)



(Source: Applicant's PopPK Report for DGD-3-48, Table 15.4.7-15.4.8)

Pediatrics' PK data was best fitted with a two-compartment model with elimination from the central compartment. The model was parameterized in terms clearance (CL), central volume of distribution (V1), intercompartment clearance (Q) and volume of distribution at steady state (Vss). Exponential models were used to describe the inter-individual variability on CL and Vss and a proportional model was considered as the best model for error. After the univariate screening, the following covariates were considered as significant affecting CL:

Power model for age on CL: $CL_{TV} = CL_{pop} \times (\frac{Age}{38})^{Scaling\ factor}$

Power model for eGFR on CL: $CL_{TV} = CL_{pop} \times (\frac{eGFR}{238})^{Scaling\ factor}$

However, as age and eGFR were not independent variables, only eGFR (calculated using Schwartz equation), which provided the best model improvement, was included in the final model. The parameter estimates for the final model is summarized in **Table 4**. The final model was validated through goodness of fit plots (**Figure 5**), and prediction corrected visual predictive check (**Figure 6**).

Table 7. Parameter estimates of the applicant's final pediatric model

Parameter	Estimate (%RSE)	95% CI	Variability
CL (L/h)=θ_1(Weight/70)$^{0.75}$*(eGFR/138) ^{65}*EXP(η_1)			
θ_1: CL typical value	2.51 (11.7%)	1.93; 3.09	
θ_5: eGFR exponent	0.268 (42.9%)	0.0426; 0.493	
η_1 (IIV CL)	0.0593 (21.9%)	0.0338; 0.0848	CV = 24.4%
V (L)=θ_2(Weight/70)*EXP(η_2)			
θ_2: V typical value	0.161 (37.6%)	0.0422; 0.280	
η_2 (IIV V)	0 FIX		
Q (L/h)=θ_3*EXP(η_3)			
θ_3: Q typical value	0.335 (28.1%)	0.150; 0.520	
η_3 (IIV Ka)	0 FIX		
V_{ss} (L)=θ_4*EXP(η_4)			
θ_4: V_{ss} typical value	0.408 (20.1%)	0.247; 0.569	
η_4 (IIV V_{ss})	0.0267 (39.3%)	0.00612 0.0473	CV=16.3%
Residual error			
ε_1: proportional component	0.0266 (22.7%)	0.0148; 0.0384	CV = 16.3%
OFV: 963.175 - Run number R106			

(Source: Applicant's PopPK Report for DGD-44-063, Table 11.2.3-1)

Figure 5. Goodness of fit plots of the applicant's final Pediatric Model (Reviewer's plot)

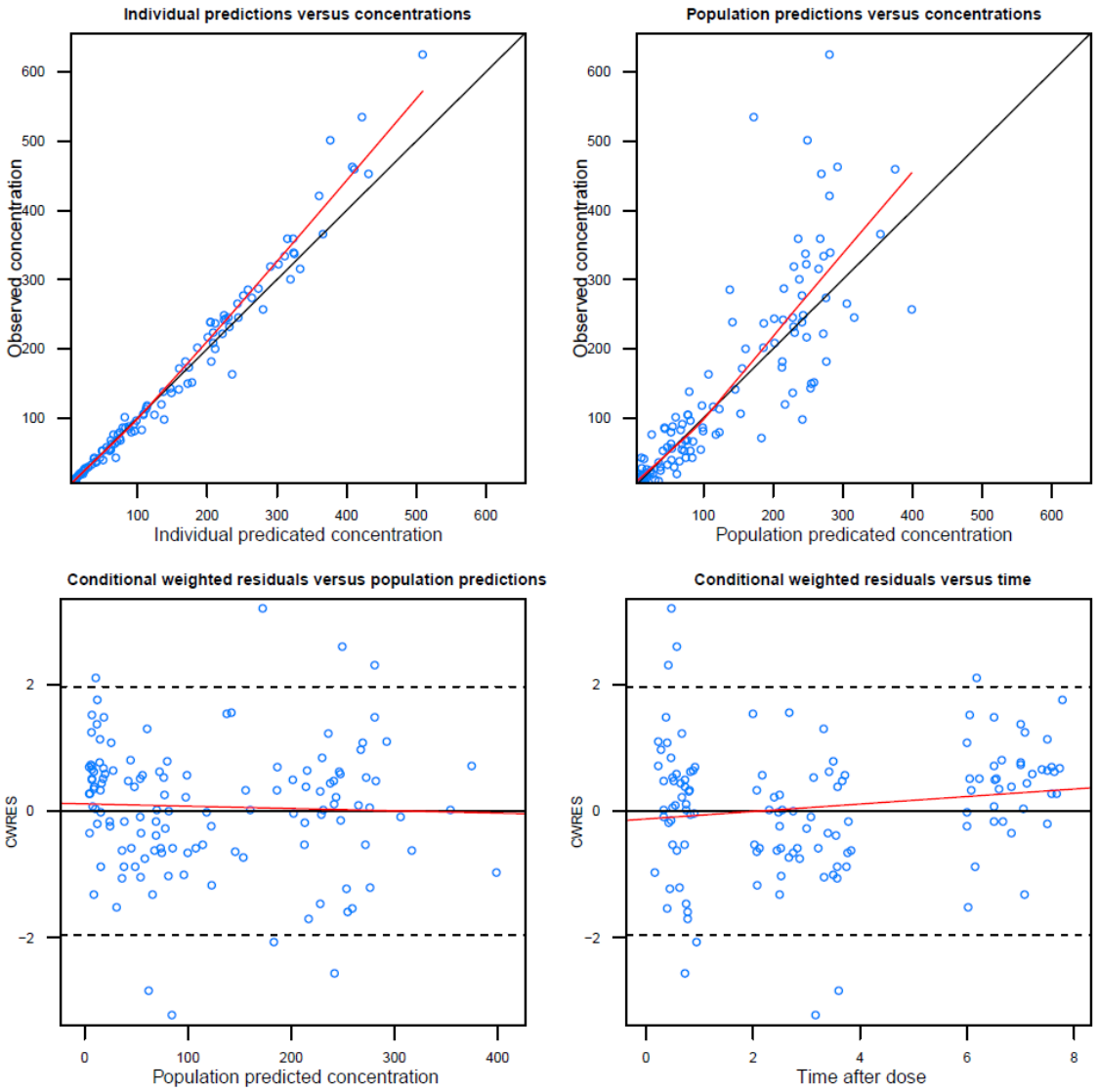
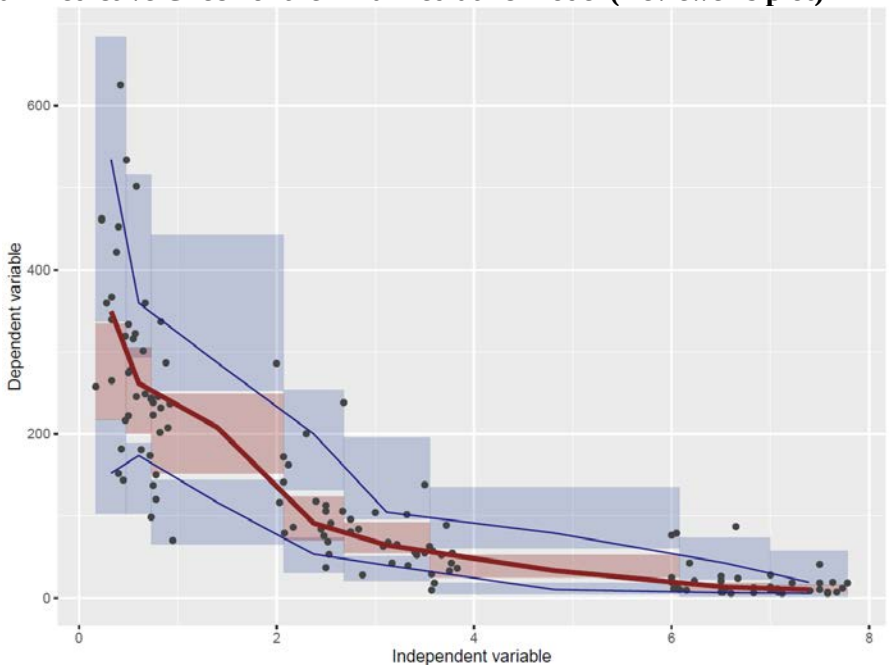


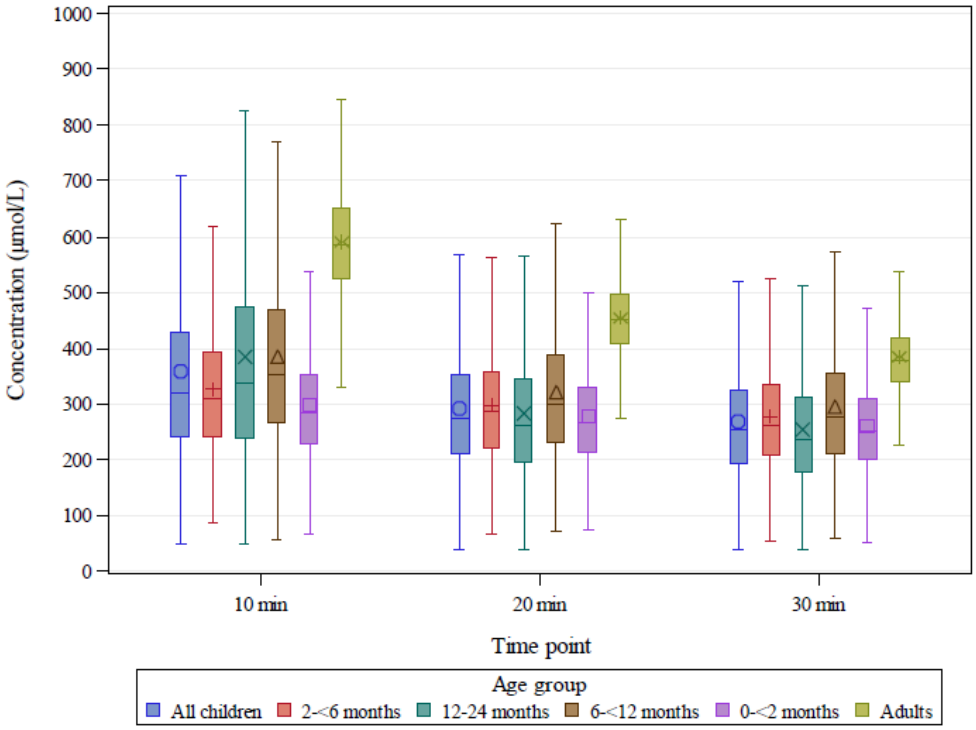
Figure 6. Visual Predictive Check of the Final Pediatric Model (Reviewer's plot)



Typical CL and Vdtotal for 70 kg adults were estimated as 7 L/h and 14 L respectively, which were different from those obtained in pediatrics aged <2 years. The typical value of CL scaled to a 70 kg body weight was estimated at 4.2 L/h and Vss at 3.29 L in pediatrics.

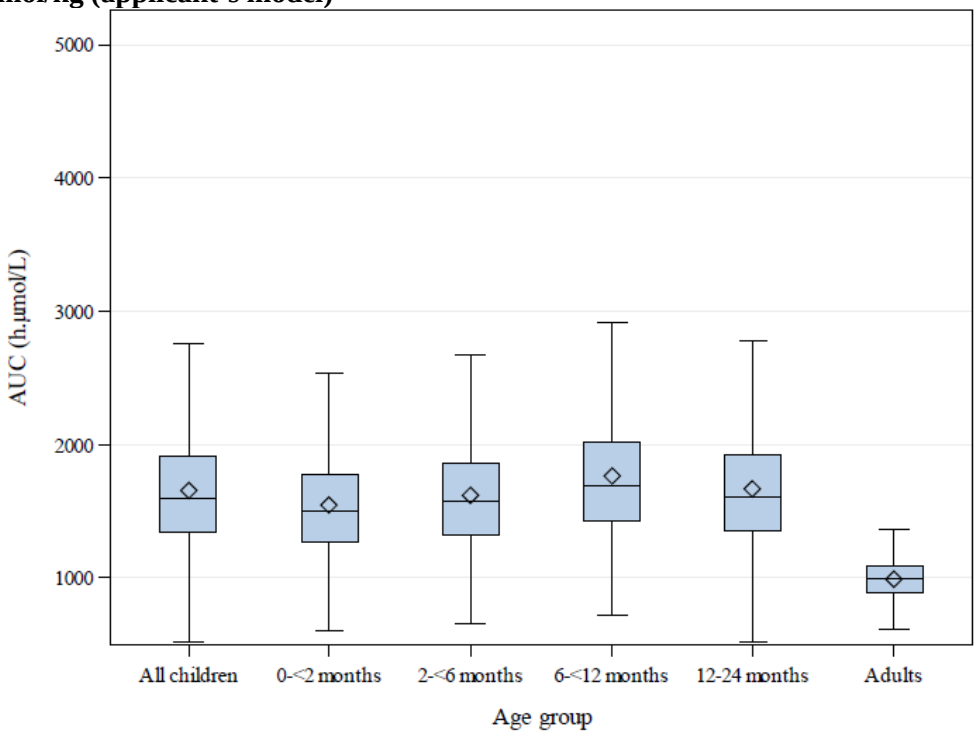
Based on the final models and respective datasets, Dotarem exposure between adults and children aged <2 years were further compared through simulations. These simulations showed that concentrations in children at 10, 20, and 30 min following the injection of a dose of 0.1 mmol/kg were lower than those in adults (**Figure 7**), with geometric mean ratios between adults and children varying from 1.8 to 1.5 and proportions of children's concentrations outside adults' 95% prediction interval (PI) between 64% and 76%. Moreover, AUC in children were shown higher than those of adults (**Figure 8**), as a consequence of the lower clearance and proportion of children's AUC outside adults' 95% PI was 79%.

Figure 7. Simulated concentrations in pediatric subjects aged <2 years and in adults healthy volunteers at 10, 20 and 30 min at the dose 0.1 mmol/kg (applicant's model)



(Source: Applicant's PopPK Report for DGD-3-48, Figure 15.5.1)

Figure 8. Simulated AUC in pediatric subjects aged <2 years and in adults healthy volunteers at the dose 0.1 mmol/kg (applicant's model)



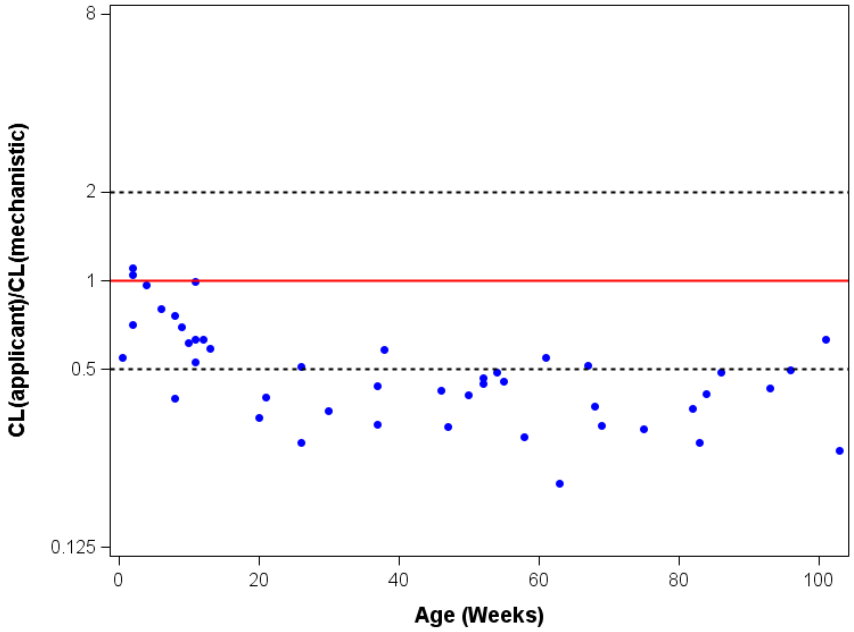
(Source: Applicant's PopPK Report for DGD-3-48, Figure 15.5.3)

Reviewer's Comments:

The applicant's population PK analyses appear to be able to describe the PK of Dotarem in both adults and pediatric patients reasonably well. However, the reviewer does not agree with applicant's final pediatric model based on the following concerns:

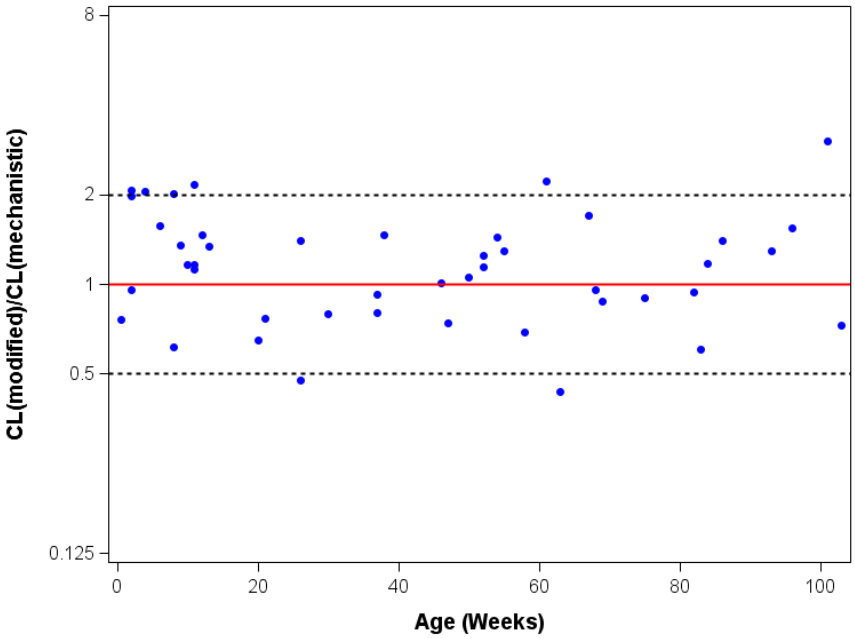
- *Neonates and infants are known to have proportionately higher total body water than adults. Since the distribution of Dotarem is limited in extracellular water, the body weight adjusted volume of distribution in pediatrics is expected to be higher than that in adults as well. However, based on applicant's pediatric model, Vss was estimated to be 0.047 L/kg, much lower than the estimate of total volume of distribution in adults, 0.20 L/kg (roughly equivalent to the physiological volume of extracellular water in an average adult of 70 kg). This is physiologically unrealistic and thus should be interpreted with caution.*
- *Gadolinium-based contrast agents are cleared by kidney through glomerular filtration, with negligible non-renal elimination. Therefore, the clearance of different GBCAs should be similar in the same population and should reflect the glomerular filtration rate. However, the estimated CL based on applicant's model appears to be much lower than the predicted CL in the same age group (< 2 years old) based on a public mechanistic model describing effect of body size and maturation of renal function on GFR by Anderson BJ et al. 2009 (https://www.ncbi.nlm.nih.gov/pubmed/19252334).(**Figure 9**)*

Figure 9. Ratio of estimated CL based on applicant's model to reference CL (predicted CL based on the mechanistic model by Anderson BJ et al. 2009) for each subject over age



*Accordingly, the reviewer has conducted independent analysis based on applicant's final model in pediatrics. The reviewer's modified model is consistent with the public mechanistic model (**Figure 10**).*

Figure 10. Ratio of estimated CL based on reviewer's modified model to reference CL (predicted CL based on the mechanistic model by Anderson BJ et al. 2009) for each subject over age



4.1.2. Reviewer's Simulation

4.1.3.1. Objectives

The purpose of the reviewer's simulation is to evaluate the utility of a mechanistic model (using body size and maturation) in describing/predicting clearance of Dotarem in pediatric patients < 2 years of age.

4.1.3.2. Methods

Data sets used are summarized below.

File	Name	Location in \\cdsnas\pharmacometrics\
NONMEM dataset for simulation	sim_DOTA_V1.csv	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Dotarem_NDA204781_LM\

On the basis of adults model, a maturation function of renal clearance was introduced on CL:

$$CL_{TV} = CL_{pop} \times (\frac{BW}{70})^{0.75} \times (\frac{PMA^{Hill}}{TM_{50}{}^{Hill} + PMA^{Hill}})$$

Where PMA is the postmenstrual age; TM_{50} describes the maturation half-time; and the Hill coefficient relates to the slope of this maturation profile. The values for Hill and TM_{50} were fixed to typical values of 3.4 and 47.7, respectively (*Anderson BJ et al. 2009*).

100 simulations were conducted using the original dataset in pediatric study DGD-44-063 as input, based on observed demographics and sampling times.

4.1.3.3. Results

The simulated PK profiles are overlaid with observed values (**Figure 11**), showing good prediction in general in pediatric patients < 2 years of age. This is also consistent across age groups (0-<2 months, 2-<6 months, 6-<12 months, 12-<24 months) (**Figure 12**).

In summary, the results demonstrated good agreement between the prediction and observation, indicating that the combination of mechanistic model and adult PK was able to predict the effect of age (maturation) and body weight on PK of Dotarem in pediatric population reasonably well.

The individual predicted CL values were then used as a reference to compare with estimated CLs based on applicant's model and reviewer's modified model (**Figure 9** and **Figure 10**).

Figure 11. Predicted profiles in pediatric patients < 2 years of age based on Anderson's model overlaid with observation

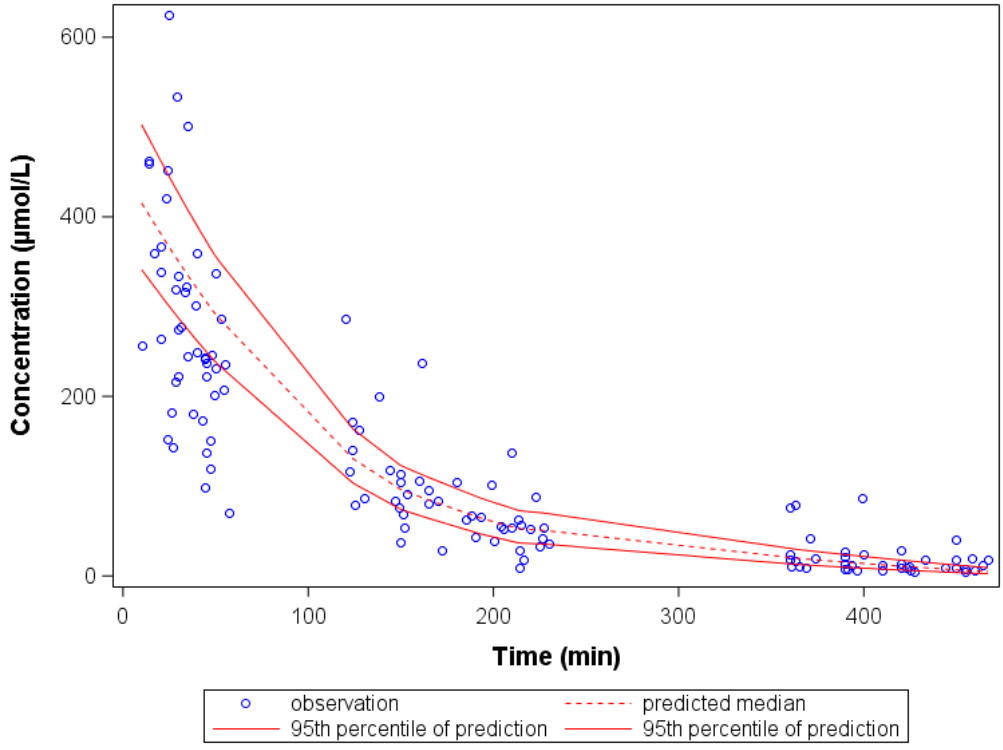
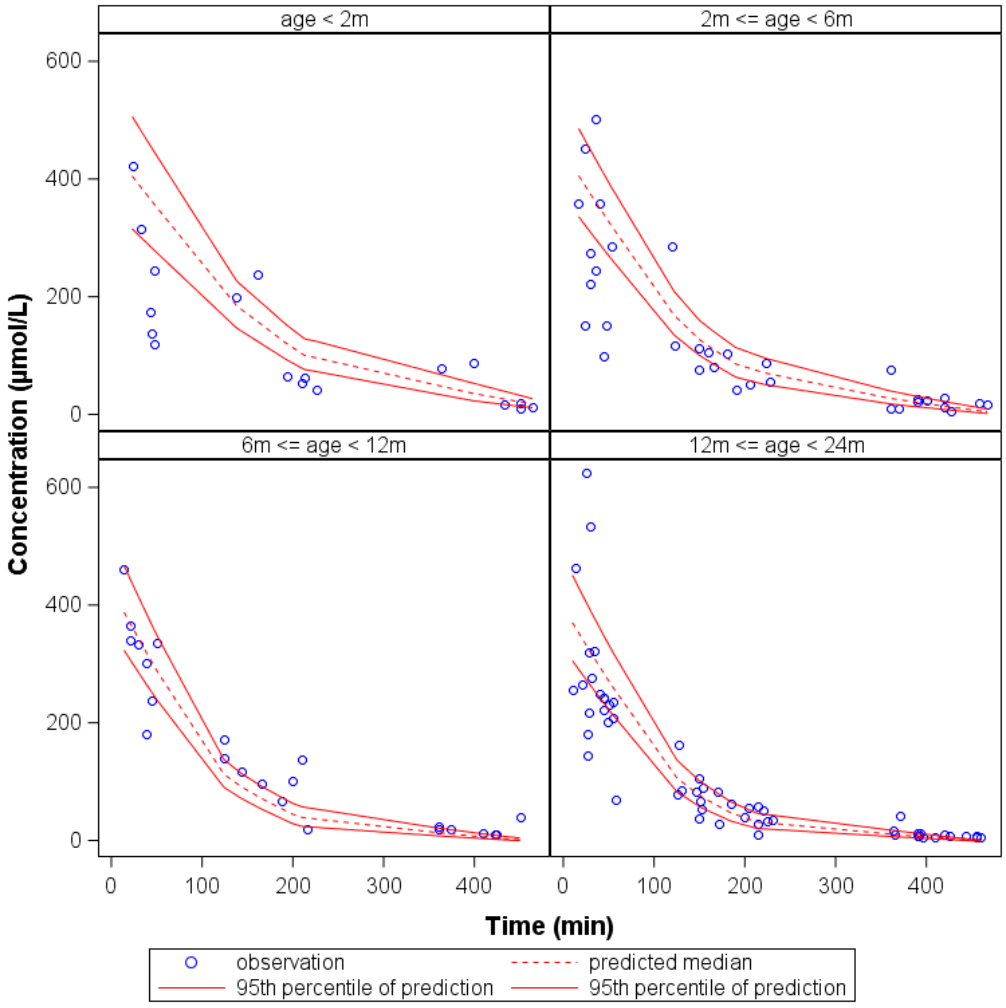


Figure 12. Predicted profiles in pediatric patients < 2 years of age based on Anderson's model overlaid with observation, stratified by age groups



4.1.3. Reviewer's Population PK Analysis

4.1.3.4. Objectives

The purpose of the reviewer's analysis was to re-evaluate the applicant's population PK model to address the issue for the unrealistic estimates of CL and Vss.

4.1.3.5. Methods

Data sets used are summarized below.

File	Name	Location in \\cdsnas\pharmacometrics\
NONMEM dataset for	pedpk.csv	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Dotarem_NDA204781_LM\

adults		
NONMEM dataset for pediatrics	dota_adult_v1_reduced.csv	\\Cdsnas\pharmacometrics\Reviews\ Ongoing PM Reviews\Dotarem_NDA204781_LM\

To be consistent with the adult model, BW was included on Vss using an allometric scaling model. Vss was centered on 70 kg and scaled to BW (see below), with scaling factor fixed to 1. In addition, the covariance term between CL and V was also estimated.

$$Vss_{TV} = Vss_{pop} \times (\frac{BW}{70})^{1}$$

4.1.3.6. Software

SAS 9.4, NONMEM 7.3, PsN, and Pirana were used for the reviewer's analyses

4.1.3.7. Results

After the modification, the objective function value decreased by 7 points (from 963 to 956) compared to the applicant's final model, indicating an improved model fitting. The parameter estimates of this modified model are presented in **Table 1**. Goodness-of-fit plots are presented in **Figure 13**. The plots show a random and equal distribution of the observed versus predicted concentrations around the line of identity for the overall population. The VPC plot in **Figure 14** confirmed that the central tendency and the variability of concentrations over time were well captured by the modified model. The individual fitting plots are presented in **Figure 15**.

Figure 13. Goodness of fit plots

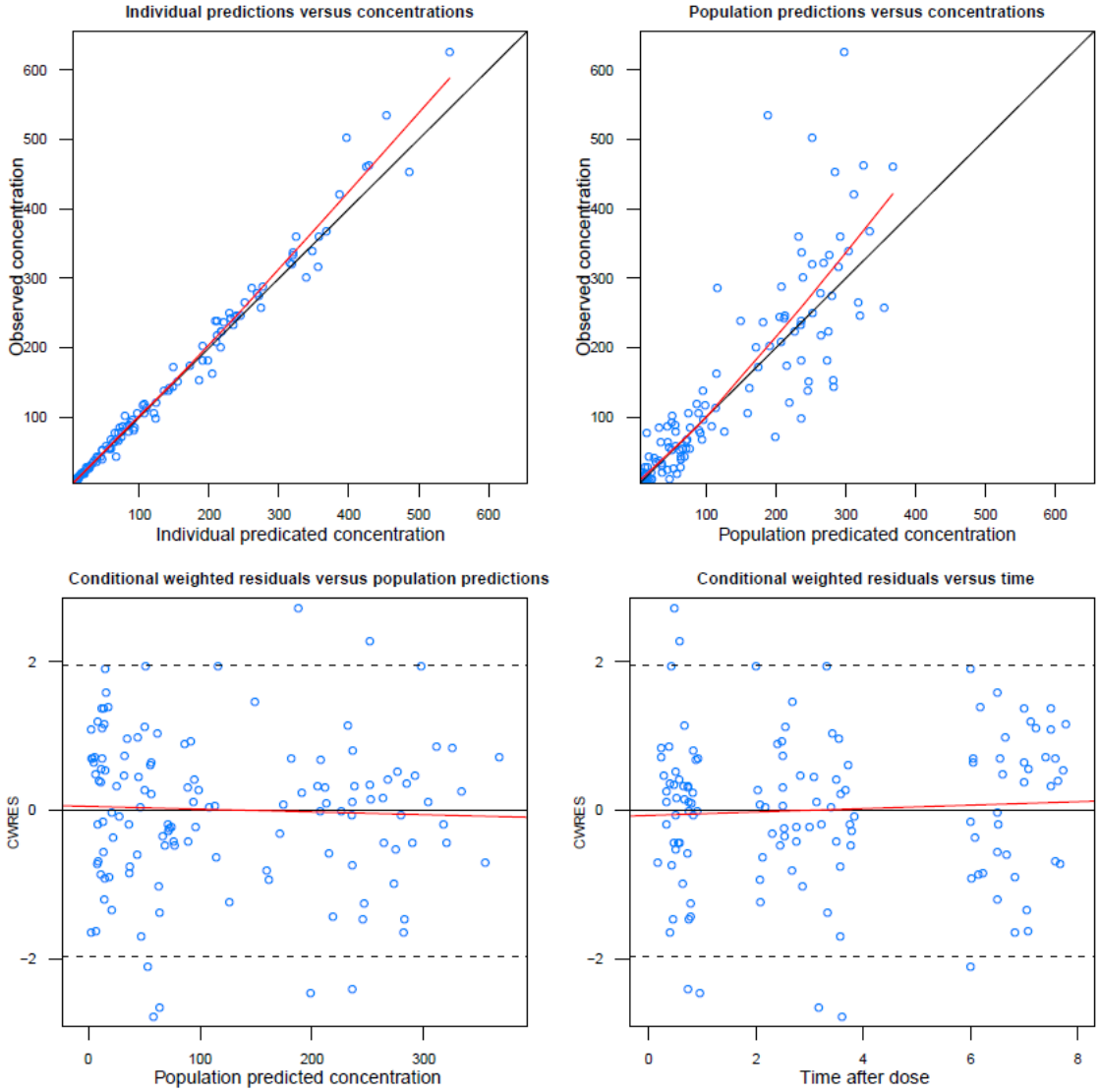
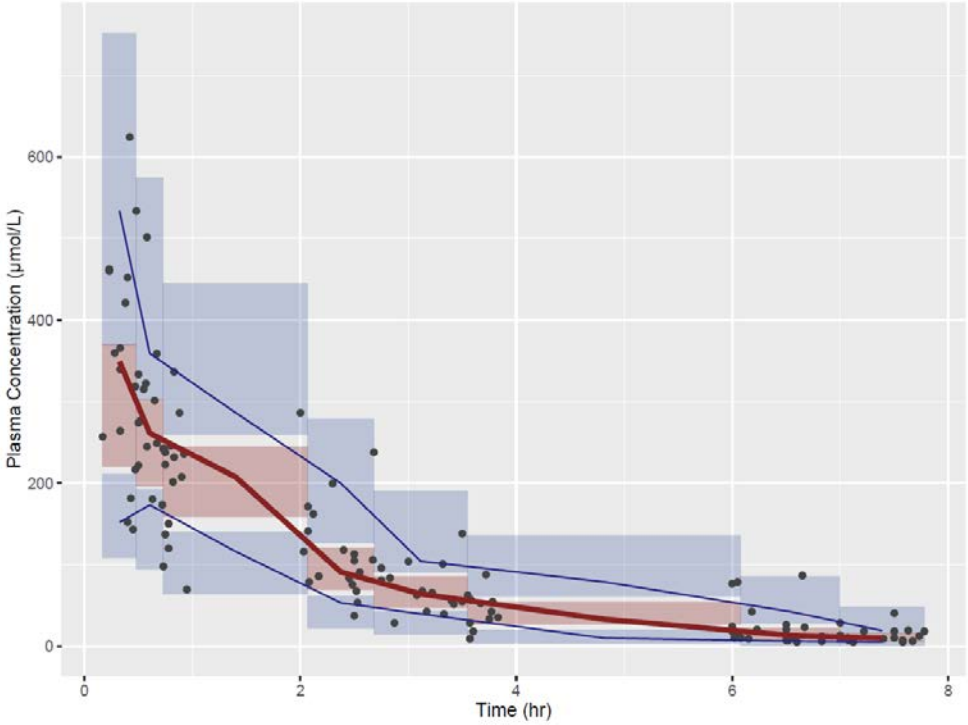


Figure 14. Visual Predictive Check of for the modified model. (Solid cycles: observations; red lines: 50% predicted percentiles; blue lines: 95% prediction intervals; red rectangles: 95% confidence intervals of 50% predicted percentiles; blue rectangles: 95% confidence intervals of 5% predicted percentiles and 95% predicted percentiles)

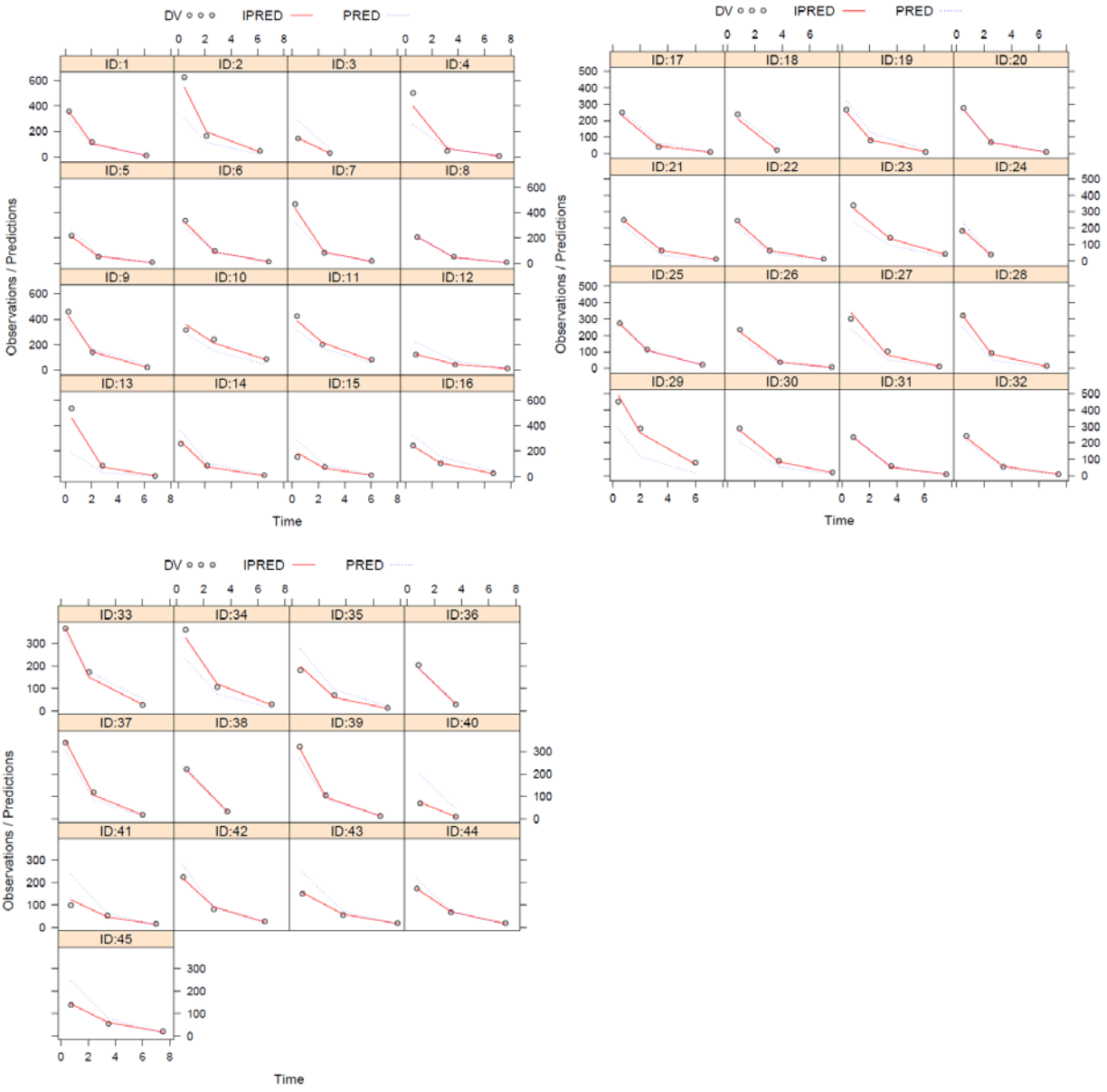


The estimated values of CL and V have increased significantly compared to the applicant's model and the individual CL values are consistent with the predicted CL values based on the published model in the same age group (< 2 years old), and make more physiological sense (**Figure 10**). Both CL and V values are associated with large between-subject variability (40.1% and 45.4%, respectively).

Based on the modified model, simulations were also conducted to predict and compare C20 and C30 following the 1 mmol/kg Dotarem in pediatric patients < 2 years of age and adults (**Figure 3**). These early concentrations are still lower in pediatrics than that in adults, but the concern for efficacy is minimal since the predicted levels in pediatrics appear to be consistent with efficacious exposure associated with Gadavist®, an approved GBCA product in the same patient population (term neonates to 23 months). The predicted AUC now appear to be comparable to those in adults with approved dosing regimen (**Figure 2**).

In summary, this modified model is justified based on physiological relevance and it further supports the proposed dosing in pediatrics < 2 years of age.

Figure 15. Individual fitting plots



4.2. Highlights of clinical pharmacology for Dotarem

Therapeutic dose	0.1 mmol/kg
Maximum tolerated dose	NA
Principal adverse events	The most frequent (≥ 0.2%) adverse reactions associated with Dotarem in clinical studies were nausea, headache, injection site pain, injection site coldness and rash.
Maximumdose tested	Single dose: 0.1 mmol/kg Multiple dose: 0.1 mmol/kg followed by 0.2 mmol/kg twenty minutes after.
Exposures achieved at Maximum dose tested	<u>Single dose (0.1 mmol/kg)</u> Adults: AUC $_{0\text{-inf}}$: 867 to 1061 µmol.h.l^{-1} # C_{max} : 799 to 837 µmol.l^{-1} Pediatrics (0-2 years): AUC: 1591 µmol.h.l^{-1} Calculated C10 min : 320.9 µmol.l^{-1} <u>Multiple dose (0.1 + 0.2 mmol/kg, adults)</u> AUC $_{0\text{-t}}$: 2897 to 3015 µmol.h.l^{-1} # C_{max} 2nd injection : 1778 to 2166 µmol.l^{-1}
Range of linear PK	Linear across dose range studied
Accumulation at steady state	NA
Metabolites	Gadoteric acid is not metabolized
Absorption	NA

Distribution	Vd = 11 to 17 L (adults [#]), 0.05 L/kg (pediatric 0-2 years) % bound : < 4% (in vitro)
Elimination	Route : renal via glomerular filtration T ½ (h) =1.3 to 2.0 (adults [#]), 1.35 (pediatric 0-2 years) Cl^T (mL/min) = 107 to 140 [#]
Intrinsic factors	Age : No relevant difference. See also renal impairment below Sex : no relevant difference Race : not studied but no race effect expected due to the lack of protein binding and metabolism Hepatic impairment : not studied but no effect expected due to the lack of metabolism Renal impairment: elimination is proportionally decreased with the degree of renal impairment. Effect of renal impairment was studied comparing healthy volunteers (group 1), patients with moderate renal impairment (creatinine clearance between 30 and 60 mL/min – group 2), and patients with severe renal impairment (creatinine clearance between 10 and 30 mL/min – group 3). Elimination half-life was 1.6 ± 0.2 hrs, 5.1 ± 1.0 hrs and 13.9 ± 1.2 hrs in groups 1, 2 and 3, respectively. AUC_{0-t} was 870 ± 80 µmol.h.l^{-1}, 3013 ± 645 µmol.h.l^{-1} and 8122 ± 665 µmol.h.l^{-1} in groups 1, 2 and 3, respectively. Total clearance was 108 ± 8 mL/min, 40 ± 9 mL/min and 14 ± 1 mL/min in groups 1, 2 and 3, respectively. Dialyzability : gadoteric acid is dialyzable
Extrinsic factors	Drug interactions and food effects: Dotarem is an extracellular gadolinium-based contrast agent which is rapidly distributed in the extracellular space after administration. It is not metabolized and is eliminated by the kidneys via glomerular filtration. The extrarenal elimination is negligible. There is no potential risk for drug-drug or drug-food interactions. No relevant drug-drug or drug-food interactions have been identified in clinical trials or in post marketing experience, although no specific studies have been carried-out.
Expected high clinical exposure scenario	Such scenario is very unlikely due to the size of containers marketed in the USA and because Dotarem will be administered only by healthcare professionals.

[#] : several studies

(Source: Applicant's Summary of Clinical Pharmacology, Table 1)

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/s/

LIAN MA
08/04/2017

YANING WANG
08/04/2017

NAM ATIQUR RAHMAN
08/04/2017
I concur.