OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

NDA	21-357/S006
Drug name	MultiHance®
Dosage Strength	0.1 mmol/kg (0.2 mL/kg)
Applicant:	Bracco Diagnostics Inc.
Pharmacometrics Reviewer	Jeanne Fourie, PhD
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Indication	Magnetic resonance imaging of the CNS in pediatric patients aged 2 years and older
Type of Submission	Safety Supplement
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1 EXECUTIVE SUMMARY

The applicant submitted pediatric pharmacokinetic (PK) data as part of an efficacy supplement to obtain pediatric labeling for NDA 21-357, MultiHance (Gadobenate dimeglumine injection) for magnetic resonance imaging of the CNS in pediatric patients aged 2 years and older.

The sponsor submitted two PK studies (Study Report MH-119 and 43-779-10). PK data were collected in studies MH-119 and 43-779-10 healthy subjects and patients undergoing MRI imaging of the central nervous system aged 2.0 years to 15.6 years. MultiHance (Gadobenate) PK parameters were available from a total of 40 pediatric healthy subjects and patients following a single MultiHance intravenous bolus dose of 0.1 mmol/kg. The sponsor recommended administration of the 0.1 mmol/kg adult dose as a rapid intravenous injection in pediatric patients aged 2 years and older.

The population PK analysis identified that MultiHance clearance and volume of distribution are dependent on body weight. After correcting for the body weight associated difference in MultiHance PK, there was a 21% decrease in the clearance and central volume of distribution of MultiHance in children 2 to 5 years of age, compared to children older than 5 years of age.

The MultiHance AUC and C_{max} values were similar in children 2 to 5 years of age, compared to children older than 5 years of age following 0.1 mmol/kg. In addition, MultiHance safety profiles were similar in patients 2 to 5 years of age compared to patients older than 5 years of age (see medical review for the current submission). These data indicate that a dose adjustment in pediatric patients aged 2 to 5 years is not recommended, and that the adult dose of 0.1 mmol/kg is suitable for administration to pediatric patients aged 2 years and older.

2 SUMMARY OF FINDINGS

2.1 Key Review Questions

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

2.1.1 Is the 0.1 mmol/kg (0.2 mL/kg) adult dose adequate for all pediatric patients aged 2 years and older?

The 0.1 mmol/kg adult dose is adequate for all pediatric patients aged 2 years and older. After correcting for the body weight associated difference in MultiHance PK, there is a 21% decrease in the MultiHance (gadobenate) clearance and volume of distribution in patients 2 to 5 years of age, compared to patients older than 5 years of age. The weight-based dosing regimen of MultiHance corrects for these age-associated changes in PK, (See Section 2.1.2) as shown by the similar gadobenate AUC and C_{max} for patients 2 to 5 years of age compared to patients older than 5 years of age. Furthermore, MultiHance safety profiles were similar in patients 2 to 5 years of age compared to patients older than 5 years of age (see medical review for the current submission). Overall, these data indicate that a dose modification is not warranted in patients 2 to 5 years of age, and the 0.1 mmol/kg adult dose is adequate for pediatric patients 2 years and older.

2.1.2 Is the sponsor's proposed pediatric PK labeling language appropriate?

No, the sponsor's proposed labeling language indicates that there is no clinically meaningful age related differences in the PK of MultiHance. The reviewer population PK analysis showed a 21% decrease in the clearance and central volume of distribution of MultiHance in children 2 to 5 years of age, compared to children older than 5 years of age. Despite this difference in PK, a dose adjustment in children 2 to 5 years of age is not recommended, and is based on the following rationale. There is a well known allometric relationship between body-weight and PK parameters, where for example clearance scales to the 0.75 power of body weight. The observed decreased clearance and central volume of distribution of MultiHance in children 2 to 5 years of age is therefore corrected by the mmol/kg based dosing regimen of MultiHance, where the relationship between clearance and body-weight is assumed to scale directly with body weight (exponent = 1 rather than 0.75). Therefore, the adult 0.1 mmol/kg dose of MultiHance is appropriate in all pediatric patients 2 years and older. For the recommended changes in the sponsor's proposed PK labeling language see Section 2.3.

2.2 Recommendations

The Office of Clinical Pharmacology has reviewed the Efficacy Supplement for gadobenate and found it to be acceptable.

2.3 Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

(b) (4)

3 PERTINENT REGULATORY BACKGROUND

The sponsor's population pharmacokinetic analysis was conducted using P-PHARM software. The sponsor was not able to supply the Office of Clinical Pharmacology with the P-PHARM analysis code when requested during the filing meeting for this submission.

4 RESULTS OF SPONSOR'S ANALYSIS

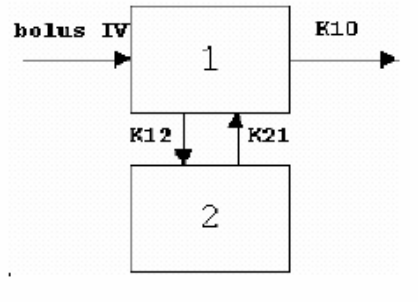
The sponsor used a two-compartment disposition model with first-order elimination for modeling and obtaining PK parameter estimates for IV gadobenate administration using P-Pharm software. Multiple regression analysis by the sponsor revealed that age and gender were not significant covariates for gadobenate clearance and volume. The model derived population estimates of blood clearance, central volume of distribution, k_{12} and k_{21} are summarized in **Table 1** and Figure 1 below:

Table 1 Sponsor's pharmacokinetic model and derived population estimates. (Table Reproduced from study report 43,779-10.

TABLE D
POPULATION ESTIMATES (SD) OF THE PHARMACOKINETIC PARAMETERS OF GADOLINIUM FOLLOWING INTRAVENOUS ADMINISTRATION OF MULTIHANCE TO PEDIATRIC SUBJECTS

Parameters	Estimate (SD)	CV (%)
CLb (L/h/kg)[1]	0.199 (0.016)	7.86
V1 (L/kg)[1]	0.170 (0.031)	18.2
k12 (h^{-1})[1]	2.36 (0.57)	24.3
k21 (h^{-1})[1]	1.98 (0.11)	5.39
Cmax (µg/mL)[2]	64.2 (13.7)	21.3
$t½_{,1}$ (h)[2]	0.137 (0.008)	6.12
$t½_{,2}$ (h)[2]	1.51 (0.27)	17.6
fe (%)[2]	90.8 (5.13)	5.65

[1] Parameters derived from the model
[2] Secondary parameters
Table data derived from Appendix VI, *Supporting Pharmacokinetic Data*
See *List of Abbreviations* on page xiii.



V1=Apparent volume of distribution in the central (blood) compartment. K10, K12, K21 = Intercompartmental rate constants from Compartment 1 to Compartment 2

Figure 1 Sponsor's two-compartment model for pharmacokinetic analysis (Figure reproduced from study report MH-119).

4.1 Reviewer's Comments on the Sponsor's Population Pharmacokinetic Analysis

The reviewer identified the following limitations in the sponsor's population pharmacokinetic analysis:

- The efficacy supplement was submitted to provide dosing recommendations for pediatric patients 2 years and older. The sponsor's population PK analysis was not done adequately. The PK model predictions were based on pharmacokinetic data from healthy subjects 3.1 to 15.6 years of age from study 43,779-10. This data set only contained one subject in the age group less than 5 years of age, and the model was not adequate to describe the PK in patients 2 to 5 years of age. The sponsor should have combined PK data from study 43,779-10 and study MH-119, which enrolled 15 patients 2 to 5 years of age, to develop the final PK model.
- The sponsor could not provide the analysis code used for the pharmacokinetic analysis, and therefore, OCP was unable to produce an exact replicate of the sponsor's analysis to verify the PK parameter estimates. As the sponsor's analysis could not be verified, PK parameters reported in the label were obtained from the FDA analysis.
- The sponsor's population PK model predictions, using pharmacokinetic data from patients 3.1 to 15.6 years of age enrolled in study 43,779-10 are not consistent with those from the FDA analysis. Based on the applicant's results, it is claimed in the label that age and gender have no clinically meaningful effects on the pharmacokinetics of gadobenate. In contrast, the FDA analysis showed that after correcting for the body weight associated difference in MultiHance PK, there is a 21% decrease in the MultiHance clearance and volume of distribution in patients 2 to 5 years of age, compared to patients older than 5 years of age. In addition, the gadobenate Cmax for patients 2 to 5 years of age was similar to that in patients older than 5 years of age. The results form the reviewer's population PK analysis were added to the label.

5 REVIEWER'S ANALYSIS

The above mentioned limitations of the sponsor's analysis were addressed in the reviewer's analysis below.

5.1 Objectives

Analysis objectives are:

1. To develop a population pharmacokinetic model to describe the MultiHance (gadobenate) blood concentration time data from study 43,779-10 and study MH-119 which were conducted in pediatric healthy subjects and pediatric patients undergoing MRI imaging of the central nervous system, respectively.
    - To identify and characterize patient factors which influence the pharmacokinetics and pharmacokinetic variability of gadobenate.

5.2 Studies

5.2.1 Study 43,779-10

This was an open label, single center phase 1 study of the pharmacokinetics of gadobenate. The study population to be enrolled consisted of male and female healthy normal subjects between the ages of 2 to 16 years of age. Twenty-five subjects were enrolled in this trial (See Table 2).

A single intravenous dose of 0.1 mmol/kg (105.8 mg/kg) of 0.5M MultiHance was administered to subjects over a period of 5 minutes. Blood samples for PK analysis were drawn at the following nominal times: Pre-dose and 5 min, 10 min, 15 min post-dosing from each subject as well as at another single time point either at 1, 2 or 6 hours post-dosing.

5.2.2 Study MH-119

This was an open-label pharmacokinetic and safety study of MultiHance in patients from 2 to 5 years of age undergoing a clinically indicated MRI imaging of the central nervous system. Fifteen patients were enrolled in this trial (See Table 2).

A single intravenous bolus dose of 0.1 mmol/kg (105.8 mg/kg) of 0.5M MultiHance was administered to subjects at a rate not exceeding 2 mL/sec followed by a saline flush that ensured adequate delivery of the investigational product to the patient. Blood samples for PK analysis were drawn at the following nominal times: One hour pre-dose and at 5 min, 10 min, 30 min, 1 hour, 2 hours and 6 hours post-dosing from each subject.

Blood samples were analyzed for gadobenate in all patients. The lower limit of quantification (LOQ) was set at 1.022 µg gadobenate/mL of blood.

Table 2 Summary Statistics of Demographics and Other Baseline Characteristics for study 43,779-10 and study MH-119.

43,779-10:

Demographic (units)	**Mean (SD)**	**Range**
Children Age (y)	7.7 (2.2)	3.2-11.2
Adolescent Age (y)	13.4 (1.0)	12-15.6
Children Height (cm)	127.7 (12.0)	101-147
Adolescent Height (cm)	157.4 (12.4)	137-175
Children Weight (kg)	98.04 (19.53)	63.10-150
Adolescent Weight (kg)	55.6 (10.3)	45-79
Sex (n(%))	Children: Males: 11 (69); Females: 5 (31) Adolescent: Males: 3 (33); Females: 6 (67)	
Race (n(%))	Children: Hispanic: 16 (100); Black 0 Adolescent: Hispanic: 5 (56); Black: 4(44)	

MH-119:

Demographic (units)	**Mean (SD)**	**Range**
Age (y)	3.53 (1.107)	2.0-5.1
Height (cm)	99.7 (10.54)	82-120
Weight (kg)	16.6 (3.07)	11-22
Sex	Males (N= 7); Females (N= 8)	
Race	Caucasian (N= 15); Non Caucasian (N= 0)	

5.3 Methods

5.3.1 Data Sets

Data sets used are summarized in Table 3.

Table 3 Analysis Data Sets

Study Number	**Name**	**Link to EDR**
43,779-10	blood.xpt	\\FDSWA150\NONECTD\N21357\S_006\2009-04-17
MH-119	ncablood.xpt	\\FDSWA150\NONECTD\N21357\S_006\2009-04-17
Combined dataset: 43,779-10 and MH-119	bloodcomb.csv	\\cdsnas\pharmacometrics\MultiHance_NDA21357_S006_JF\PPK Analyses

5.3.2 Software

The population pharmacokinetic analysis was conducted using NONMEM software (Version VI). Models were compiled using the Census. R 2.6.2 and S-plus were utilized for compiling data and generating diagnostic plots. WinNonlin (Version 5.2.1) was used for non-compartmental pharmacokinetic analysis.

5.3.3 Models

A two-compartment model was used to adequately describe the gadobenate concentration-time profile following intravenous (IV) administration over five minutes.

5.4 Results

In order to evaluate the ability to predict the exposure and concentration-time profiles following 0.1 mmol/kg dose in the 43,779-10 and MH-119 studies, a population PK model was developed using the clearance and volume of distribution models described in Section 5.4.1 to Section 5.4.4 using the data described in Section 5.3.

5.4.1 Reviewer's Base PK Model

The PK parameter estimates for the reviewer's base gadobenate linear PK two-compartment model are shown in Table 4.

Table 4 Reviewer's Base PK Model Parameter Estimates.

Parameter	Unit	Population parameters		Inter-individual variability	
		Estimate	%RSE	Estimate (CV%)	%RSE
CL	[L/hr]	37.8	11.9	50.1	23.3
Q	[L/hr]	66	33.9	69.5	84.5
V_1	[L]	38.5	11.6	68.8	21
V_2	[L]	17.2	11	-	-
Proportional residual error	[CV%]	15.2	15.8	-	-

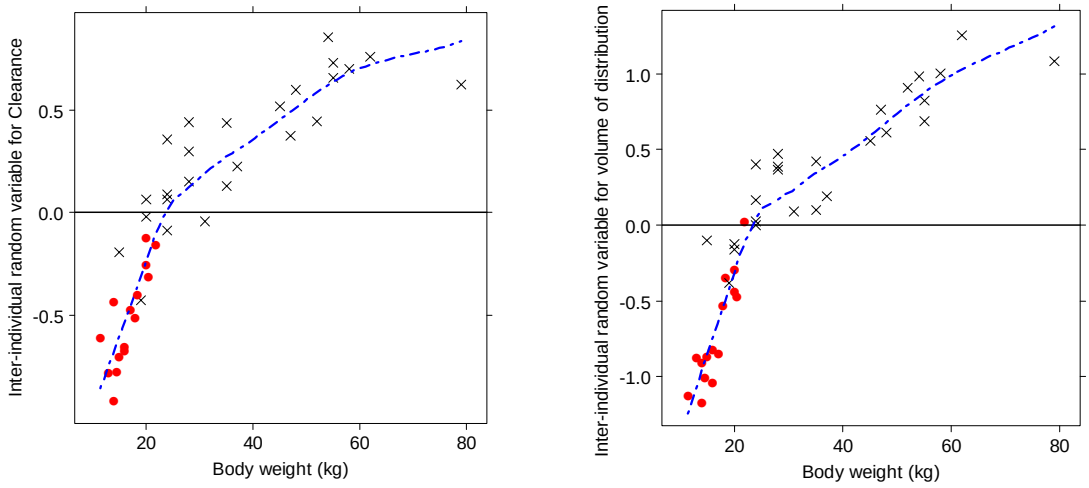


Figure 2 Residual plots for the base PK model for study 43,779-10 (black crosses) and study MH-119 (red circles). Residuals vs. age (top) and body weight (bottom) with a superimposed smoothing local regression line (broken blue line).

5.4.2 Covariate Models

Body weight was found to be a significant covariate for gadobenate blood clearance and central volume of distribution (V_1) (See Figure 2).

5.4.2.1 Clearance

The weight only model (Model 1 in Table 5) for clearance explored an allometric function between CL and WT. The residual plots for Model 1 showed a clear negative

trend at low body weight, suggesting that body weight is not the only factor influencing clearance for patients with low body weight (see Figure 3).

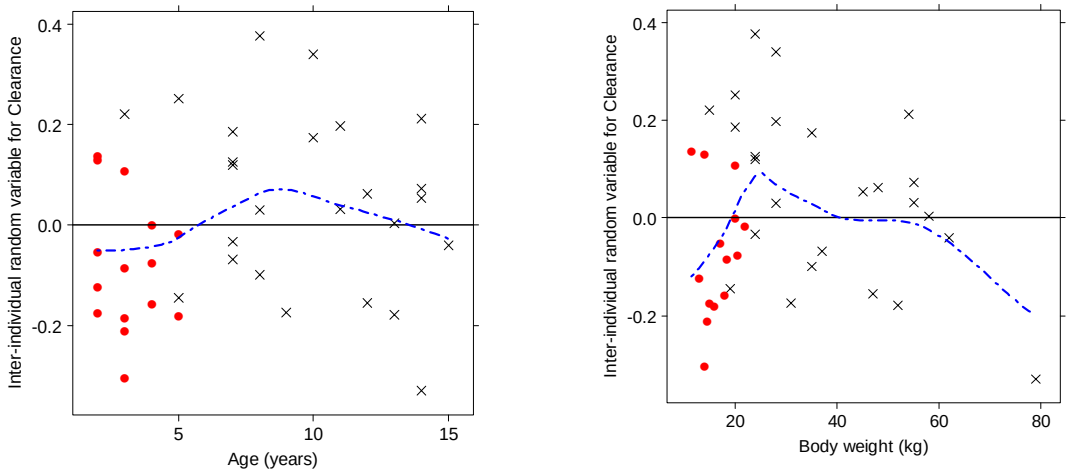


Figure 3 Residual plots for the Weight Only clearance model (Model 1 in Table 5) for study 43,779-10 (black crosses) and study MH-119 (red circles). Residuals vs. age (left panel) and body weight (right panel) with a superimposed smoothing local regression line (broken blue line).

It is known from developmental pharmacology that renal functional maturation occurs until age 2 to 3 years, after which renal function is at par with adults after body-size adjustment (See Appendix for references). Therefore, age-dependent immature renal function was explored as a covariate that can influence gadobenate clearance in children 2 to 5 years of age. Specifically, a renal function maturation factor, Age/(Age+A_{50}), was added to the clearance model (Model 1 in Table 5) to account for this effect (Model 2 in Table 5). The A_{50} estimate using the gadobenate data, i.e. the age required for achieving 50% of full renal maturation, is 0.94 years (~12 months).

According to the predictions, for a one year old child, the renal CL is 52% of mature renal function, whereas in a child aged 3 years old the renal CL is 76% of mature renal function. The model predicted that mature renal function does not occur until age 20 years, and therefore this model was inconsistent with the established developmental biology of the human kidney which indicates that renal function matures at age 2 to 3 years (See Figure 4). Therefore, the decreased renal CL in patients 2 to 5 years of age could not be explained through this age-dependent renal maturation factor, and it was not explored further.

Figure 4 shows the model predicted age-dependent maturation factor that influences V_1, such that V_1 is decreased in patients less than 5 years old. This age-dependent maturation factor that influences V_1 was also not biologically plausible, and has not been previously reported in the scientific literature (See Figure 4). For further discussion of this age-dependent maturation factor influence on V_1, refer to the Section 5.4.3 which discusses the volume of distribution Model 2.

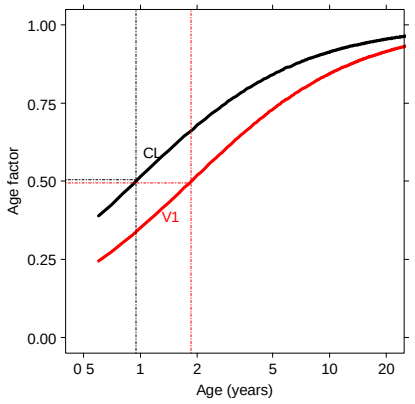


Figure 4 Estimated renal function maturation and V_1 maturation curve vs. age.

As shown in Figure 5, subsequent to including weight and age in the CL model (Model 2 in Table 5), the negative trend in the residuals at low body weight was decreased from that observed in Model 1. However, the model still did not adequately describe the clearance for patients aged 2 to 5 years with low body weight, as the residuals were still not distributed evenly across the horizontal line drawn at the value '0.0".

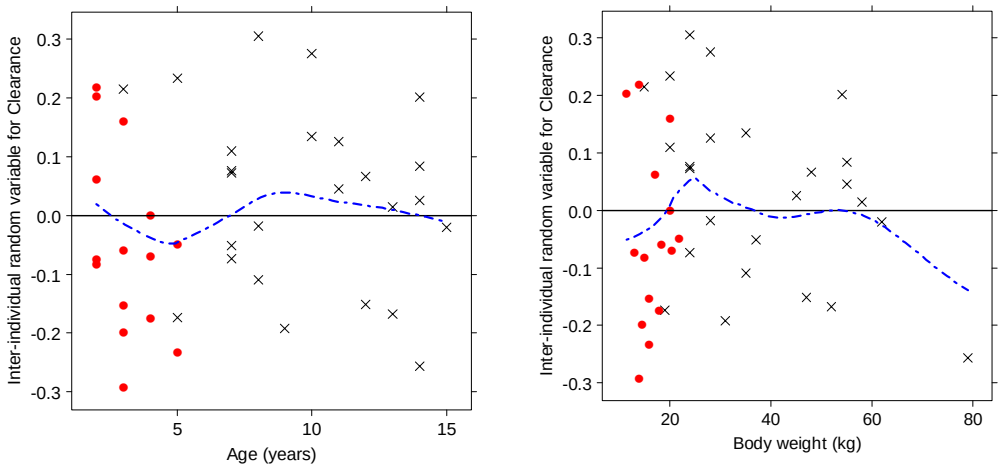


Figure 5 Residual plots for the weight and age clearance model (Model 2 in Table 5) for study 43,779-10 (black crosses) and study MH-119 (red circles). Residuals vs. age (left) and body weight (right panel) with a superimposed smoothing local regression line (broken blue line).

To better describe the pharmacokinetics in patients 2 to 5 years, age was included as a categorical covariate (age 2 to 5 years vs. age greater than 5 years) instead of a continuous covariate in the CL model (Model 3 in Table 5).

In Figure 6, the final weight and age clearance model predicted population mean clearance (solid red and green lines) and patients' empirical Bayes individual clearance

estimates (black circles) for patients aged 2 to 5 years and patients aged older than 5 years across body weights are plotted. A summary of the tested clearance models and volume models are summarized in Table 5 and Table 6, respectively. The final model (Model 3 in Table 5 and Model 3 in Table 6) was chosen based on physiological knowledge and visual inspection of residual plots (Figure 7).

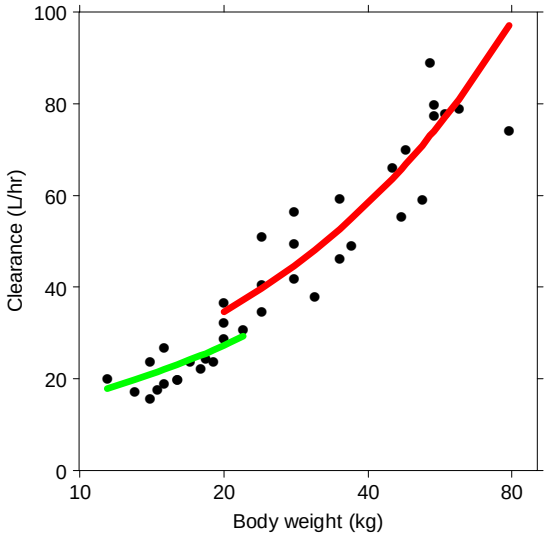


Figure 6 Plot of empirical Bayes individual clearance estimates (black circles) and model predicted (solid red line (age >5) and solid green line (age 2-5)) clearance for the final weight and age clearance model (Model 3 in Table 5)

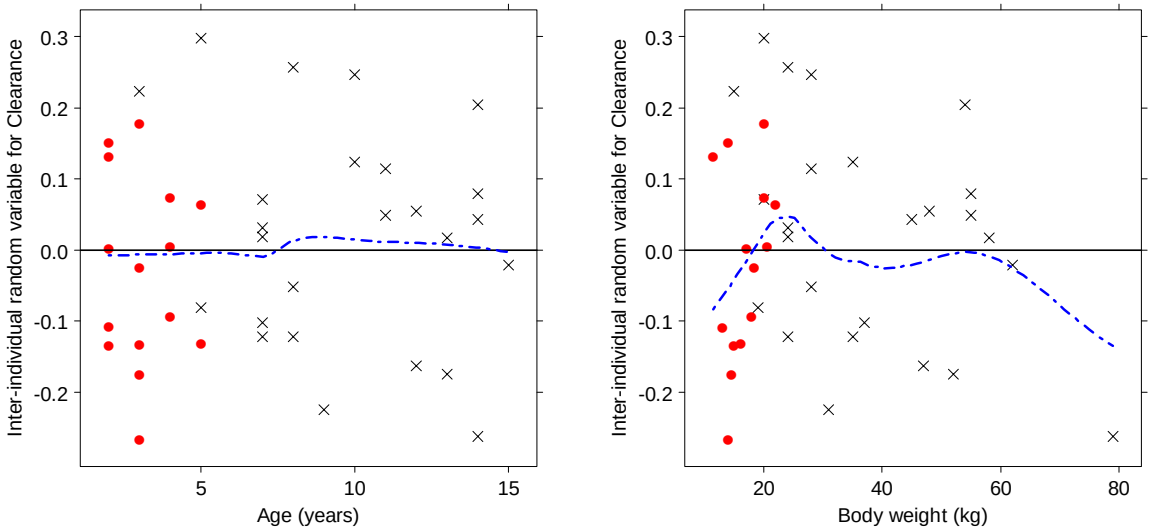


Figure 7 Residual plots for the final weight and age clearance model (Model 3 in Table 5) for study 43,779-10 (black crosses) and study MH-119 (red circles). Residuals vs. age (left) and body weight (right panel) with a superimposed smoothing local regression line (broken blue line).Model 3 in Table 5.

Table 5 Tested clearance models.

Model	Description	Parameter	Estimate (SE)	Between subject variability (CV%)	Residual error (CV%)
1	$CL = \alpha \cdot WT^{\beta} .exp(\eta)$	α β	35.3 (1.48) L/h 0.75	19.8%	15.7
2	$CL = \alpha \cdot WT^{\beta} \cdot age/(age+a50) \cdot exp(\eta)$	α β a_{50}	42.1 (3.78) L/h 0.75 0.94 (0.40) years	17.5%	15.3
3 FINAL	**Age > 5 years:** $CL = \alpha \cdot WT^{\beta} exp(\eta)$ **Age 2 to ≤ 5 years:** $CL = \chi . \alpha . WT^{\beta} exp(\eta)$	α β χ	39.7 (2.16) L/h 0.75 0.79 (0.05)	16.6%	15.1

5.4.3 Volume of Distribution

The weight only model (Model 1 in Table 6) for volume explored a linear and an allometric function between the V_1 and WT, and the linear function was adequate to describe the relationship between V_1 and WT. The residual plots for the weight only V_1 model showed a clear negative trend at low body weight, suggesting that body weight is not the only factor influencing V_1 for patients with low body weight (See Figure 8).

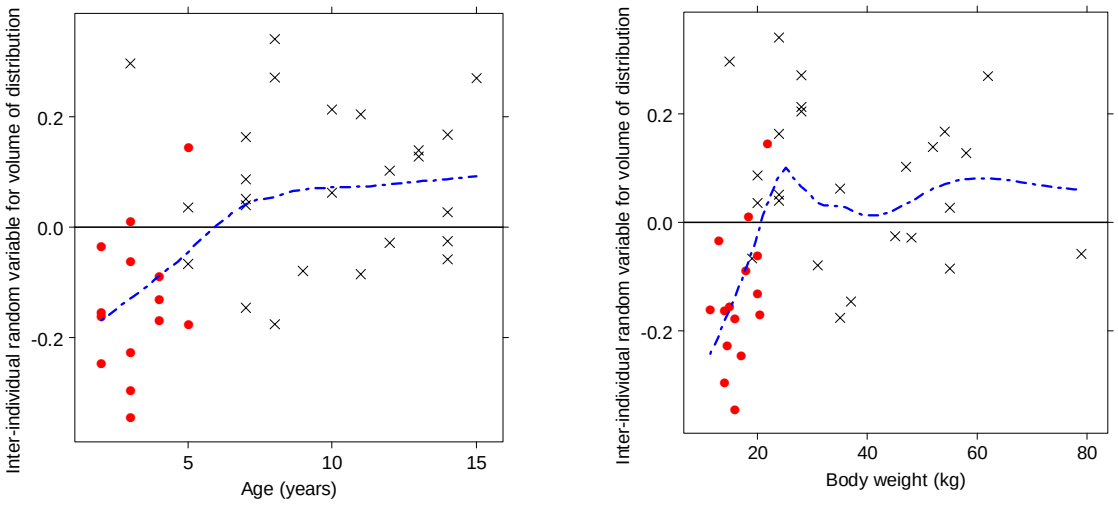


Figure 8 Residual plots for the weight only volume model (Model 1 in Table 6) for study 43,779-10 (black crosses) and study MH-119 (red circles). Residuals vs. age (left panel) and body weight (right panel) with a superimposed smoothing local regression line (broken blue line).

The V_1 was decreased in pediatric patients less than 5 years of age (Figure 8). Therefore, a maturation factor, Age/(Age+A_{50}), was added to the volume model (Model 1 in Table 6) to account for this effect (Model 2 in Table 6). The A_{50} estimate using the gadobenate data, i.e. the age required for achieving 50% of the V_1 (central compartment (V_1)) of a child over the age of 5 is 1.85 years (~22 months) (See Figure 4).

The model predicted age-dependent maturation factor that influences V_1, such that V_1 is decreased in patients less than 5 years old was not biologically plausible and has not been previously reported in the scientific literature. Therefore, Model 2 in Table 6 was not further explored (See Figure 9).

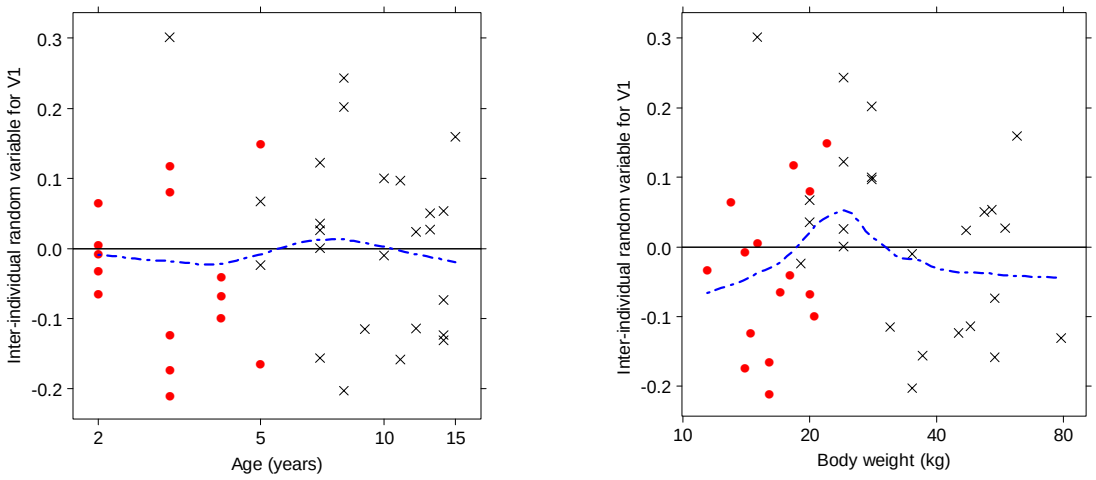


Figure 9 Residual plots for the weight and age volume model (Model 2 in Table 6) for study 43,779-10 (black crosses) and study MH-119 (red circles). Residuals vs. age (left panel) and body weight (right panel) with a superimposed smoothing local regression line (broken blue line).

Figure 10 shows the final model predicted population mean central volume of distribution (solid line) and patients' empirical Bayes individual central volume of distribution estimates (black circles) for patients 2 to 5 years of age and for patients more than 5 years of age. The final model (Model 3 in Table 6) was chosen based on physiological knowledge and visual inspection of residual plots (Figure 11).

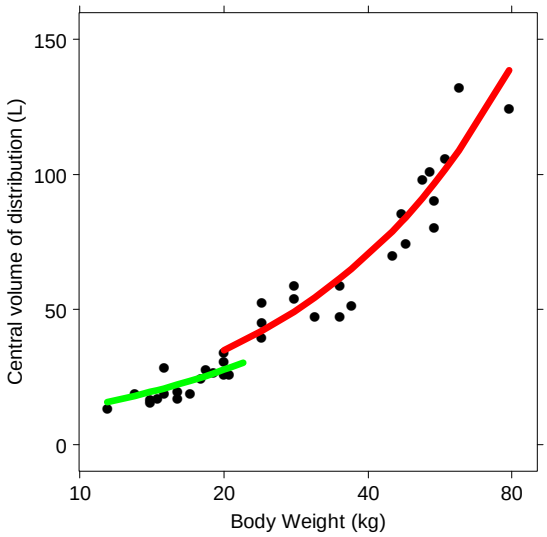


Figure 10 Plot of empirical Bayes individual central volume of distribution estimates (black circles) and model predicted (solid red line (age >5) and solid green line (age 2-5) central volume of distribution for the final weight and age volume model (Model 3 in Table 6)

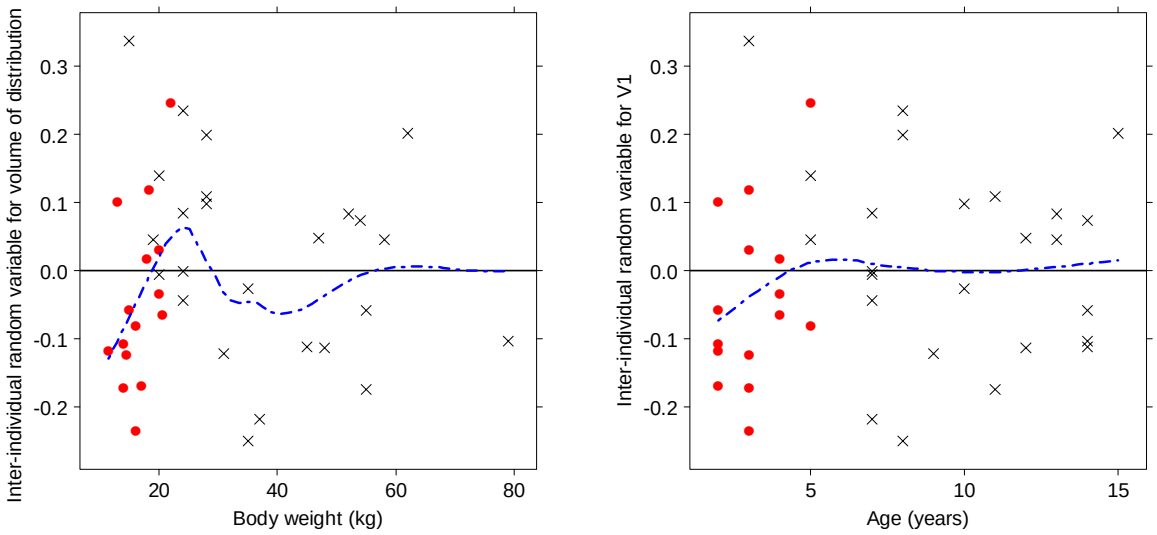


Figure 11 Residual plots for the weight only volume model (Model 3 in Table 6) for study 43,779-10 (black crosses) and study MH-119 (red circles). Residuals vs. age (left panel) and body weight (right panel) with a superimposed smoothing local regression line (broken blue line).

Table 6 Tested volume models.

Model	Description	Parameter	Estimate (SE)	Between subject variability (CV%)	Residual Error (CV%)
1	$Vd = \alpha \cdot WT^{\beta}.\exp(\eta)$	α β	38.9 (2.39) L 1	19.4%	15.7
2	$Vd = \alpha \cdot WT^{\beta} \cdot age/(age+a50) \cdot \exp(\eta)$	α β a_{50}	48.6 (3.9) L 1 1.85 (0.79) years	15.9%	15.3
FINAL 3	**Age > 5 years:** $Vd = \alpha \cdot WT^{\beta}.\exp(\eta)$ **Age 2 to ≤ 5 years:** $Vd = \chi.\alpha \cdot WT^{\beta}.\exp(\eta)$	α β χ	42.1 (2.28) L 1 0.79 (0.06)	17%	15.1

Vd: Volume of distribution

5.4.4 Final PK Model

Body weight was found to be a significant covariate for gadobenate blood clearance and central volume of distribution. After correcting for the body weight associated difference in the MultiHance PK, there was a 21% decrease in the clearance and central volume of distribution of MultiHance in children 2 to 5 years of age, compared to children older than 5 years of age. Inclusion of the covariates weight and age (categorical covariate) in the model to describe the pharmacokinetics of gadobenate decreased the intersubject variation for clearance from 50.1 to 16.6% and changed the intersubject variation for volume of distribution from 68.8 to 17% (Model 3 in Table 5 and Table 6). Gender and race were not significant covariates for gadobenate blood clearance or central volume of distribution. See Table 4 and Table 7 for inter-individual random variable estimates vs. covariates for the base and final PK models, as well as the Appendix (Figure 13, Figure 14, Figure 17 and Figure 18) for covariate-PK parameter relationships for the base and final models and the goodness-of-fit graphs for the reviewer's final model (Figure 15 and Figure 16).

Table 7 Reviewer's Final PK Model Parameter Estimates.

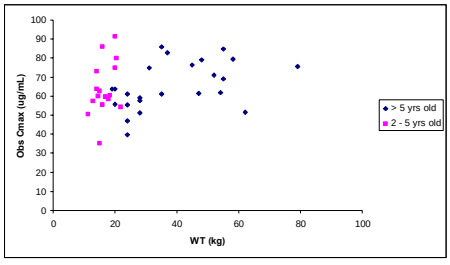
		Population parameters		**Inter-individual variability**	
Parameter	**Unit**	**Estimate**	**%RSE**	**Estimate (CV%)**	**%RSE**
Fixed-Effects Parameters					
CL	[L/hr]	39.7	5.44	16.6	28.5
Q	[L/hr]	47.9	34.7	87.2	49.3
V_1	[L]	42.1	5.42	17	40.7
V_2	[L]	15	10.5	-	-
Covariate-relationships					
CL-WT exponent	[-]	0.75	-	-	-
V_1-WT exponent	[-]	1	-	-	-
CL fraction for 2-5 year olds compared to >5 year olds	[-]	0.79	6.97	-	-
V_1 fraction for 2-5 year olds compared to > 5 year olds	[-]	0.79	7.77	-	-
Intra-Individual Variability					
Proportional Residual error	[CV%]	15.1	10.5	-	-

Table 8 summarizes the whole blood pharmacokinetic parameters of gadobenate for patients 2 to 5 years of age and for patients greater than 5 years of age. The pharmacokinetic parameters were determined by non-compartmental analysis using the individual observed concentrations obtained from studies MH-119 and 43,779-10. The Cmax and AUC were similar in patients aged 2-5 years vs. patients older than 5 years (Figure 12).

The population parameter estimates from the sponsor's population pharmacokinetic analysis were similar to those the sponsor reported in the label. However, these estimates for some parameters (CL and Volume) were not similar to those estimated in the reviewer's population pharmacokinetic analysis. This may be because the sponsor only used data from study 43,779-10, whereas all available data from study 43,779-10 and study MH-119 where used in the reviewer's analysis. In addition, the sponsor could not provide the analysis code used for the pharmacokinetic analysis for review by OCP. OCP was therefore not able to produce an exact replicate of the sponsor's analysis, and the PK parameters reported in the label are thus from the FDA analysis.

Table 8 Gadobenate Pharmacokinetic Parameters (Geometric Mean (CV%))

Parameters	**Age 2-5 Years (N=16)**	**Age older than 5 years (N=24)**
Cmax (µg/mL)	62.29 (23.24)	64.17 (20.04)
T1/2 λz (hr)	1.19 (13.09)	0.93 (38.49)
AUC0-∞ (µg.hr/mL)	77.86 (17.99)	82.63 (50.23)
AUC0-last (µg.hr/mL)	74.19 (22.04)	62.09 (71.66)
Tmax (hr)	0.084 (19.01)	0.083 (15.48)
CL (L/hr)	22.16 (27.31)	32.33 (66.05)
V (L)	31.44 (24.39)	26.34 (109.72)



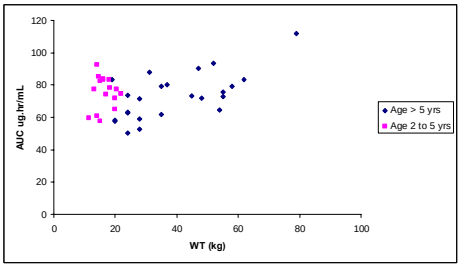


Figure 12 Scatter plots of the observed Cmax values vs. body weight and final model predicted AUC values vs. body weight for patients 2-5 years old and greater than 5 years old.

6 CONCLUSIONS

The overall pharmacokinetic conclusions from the Pharmacometrics review are:

- A two-compartment pharmacokinetic model with first-order elimination adequately described the time-course of the observed gadobenate concentrations following IV administration over 5 minutes.
- The estimated distribution population half-life ($t1/2,\alpha$) is 10 min and the terminal population half-life ($t1/2,\beta$) is approximately 1 hour.
- Body weight and age (as a categorical variable) were significant covariates for gadobenate blood clearance and central volume of distribution. This result supports the current body weight based dosing strategy of gadobenate.
- Gadobenate blood clearance and central volume of distribution were found not to be influenced by gender or race (Hispanic, Black and Caucasian).
- The population parameter estimates for central volume of distribution and blood clearance from the sponsor's population pharmacokinetic analysis were not similar to those obtained by the reviewer, possibly due to a sub optimum analysis performed by the sponsor. The pharmacokinetic parameters (C_{max}, AUC and $t_{1/2,\beta}$) obtained from the reviewer's non-compartmental analysis using the observed data from study MH-119 and study 43,779-10 were reported in the label.
- The efficacy of imaging agents such as MultiHance is known to be dependent on the Cmax value. The gadobenate C_{max} and AUC values were similar in patients 2 to 5 years of age, compared to patients older than 5 years. Furthermore the safety profile of gadobenate was similar for patients 2 to 5 years of age, compared to patients older than 5 years (see Table 9 below and Medical Review for the current submission). These findings support the recommendation not to adjust the dose of MultiHance in patients 2 to 5 years of age. In conclusion, doses normalized for body weight are appropriate with a dosage recommendation of 0.1 mmol/kg MultiHance in children aged 2 years and older.

Table 9 Safety profile similar in patients aged 2-5 years vs. > 5 years. Source: Medical Review for current submission).

			No. (%) of patients with at least 1 AE	
Subgroup	**Category**	**N**	**All AE**	**Related AE[a]**
All subjects		217	24 (11.1)	14 (6.5)
Gender:	Male	112	14 (12.5)	8 (7.1)
	Female	105	10 (9.5)	6 (5.7)
Age:	< 2yrs	15	2 (13.3)	1 (6.7)
	2 to 5 yrs	55	8 (14.5)	4 (7.3)
	6 to 10 yrs	71	5 (7.0)	4 (5.6)
	11 to 17 yrs	76	9 (11.8)	5 (6.6)

7 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
run4.mod	Base population PK model code	MultiHance_NDA21357_S006_JF\PPK Analyses\Structural Model
run4.lst	Base population PK model output file	MultiHance_NDA21357_S006_JF\PPK Analyses\Structural Model
run10.mod	WT only PK model code (model 1)	MultiHance_NDA21357_S006_JF\PPK Analyses\Structural Model
run10.lst	WT only PK model output file	MultiHance_NDA21357_S006_JF\PPK Analyses\Structural Model
run15.mod	WT and Age PK model code (model 2)	MultiHance_NDA21357_S006_JF\PPK Analyses\Structural Model
run15.lst	WT and Age PK model output file	MultiHance_NDA21357_S006_JF\PPK Analyses\Structural Model
run16.mod	Final population PK model code (model 3)	MultiHance_NDA21357_S006_JF\PPK Analyses\Structural Model
run16.lst	Final population PK model output file	MultiHance_NDA21357_S006_JF\PPK Analyses\Structural Model

8 APPENDICES

8.1 Covariate-PK Parameter Relationships for Base PK Model

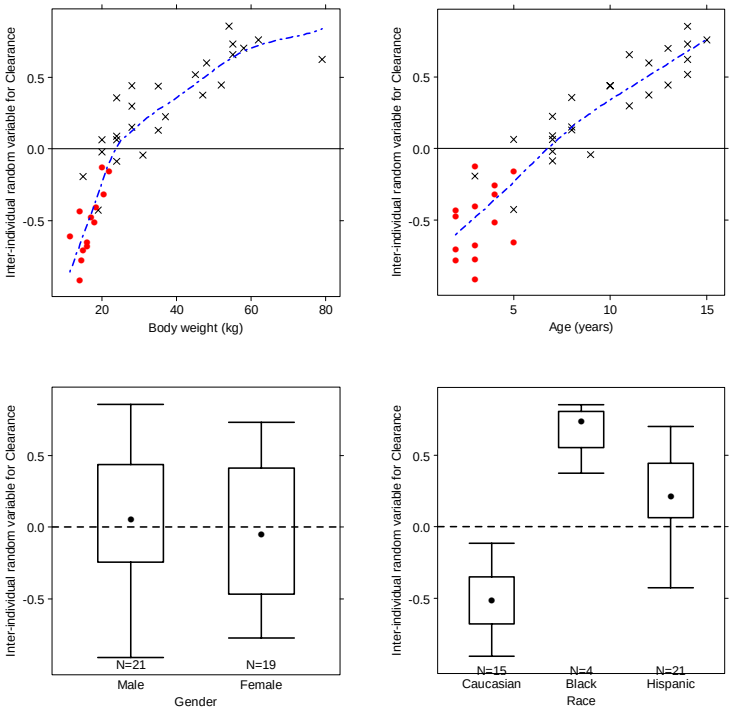


Figure 13 Graphical analyses of clearance-covariate relationships from base PK model.

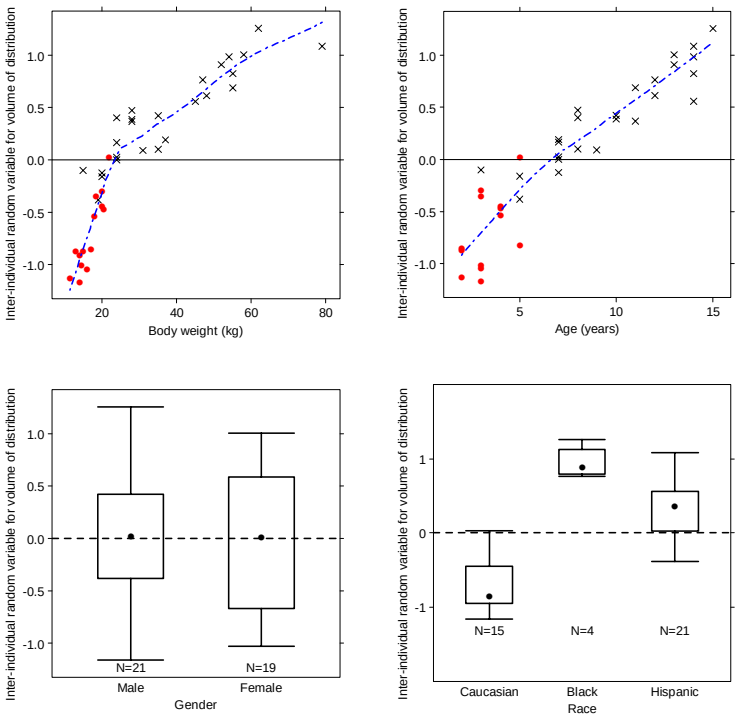


Figure 14 Graphical analyses of volume-covariate relationships from base PK model.

8.2 Goodness-of-Fit Graphs for Reviewer's Final Model

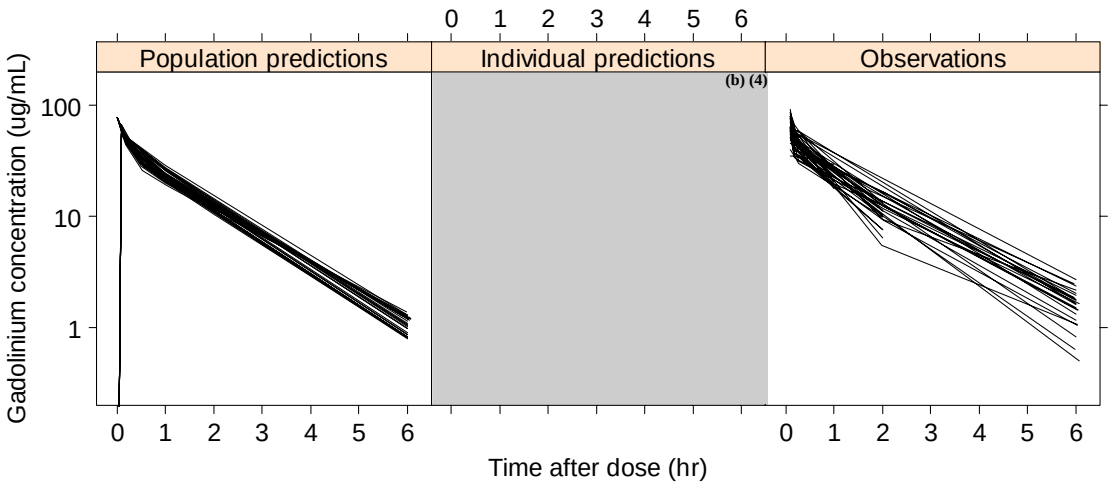


Figure 15 Gadobenate concentration-time profiles for population predicted (left), individual predicted (middle), and observed (right) gadobenate concentrations for study 43,779-10 and study MH-119.

Covariate-PK Parameter Relationships for Final PK Model

Figure 16 illustrates the goodness-of-fit of the population predictions and the individual final model predictions to the observed data used to build the population PK model. The final model predictions are very close to the observed data illustrated by the close proximity of the circles (study MH-119) and crosses (study 43-779-10) to the black line of unity.

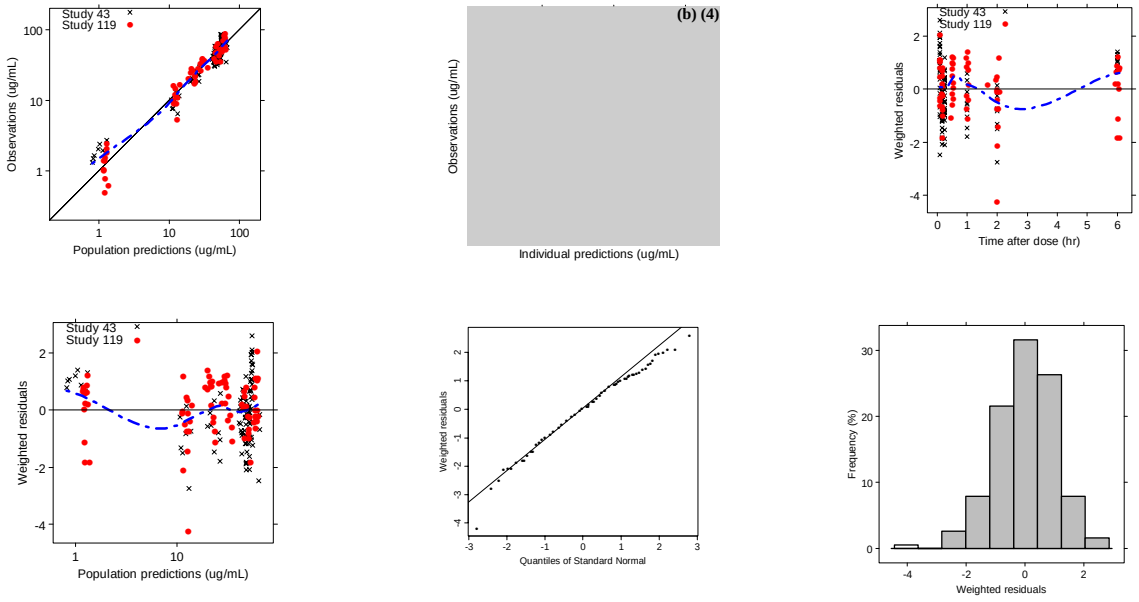


Figure 16 Goodness-of-fit graphs for reviewer's final PK model. Observations vs. population (top left) and individual (top center) predictions, weighed residuals vs. time after dose (top right), population predictions (bottom left), quantiles of standard normal (bottom center), and a histogram of weighted residuals (bottom right). The solid black line is the line of unity/identity and the dashed blue line is a local smoothing regression line. The red circles are subjects from study MH-119 and the black crosses are subjects from study 43-779-10.

8.3 Covariate-PK Parameter Relationships for Final PK Model

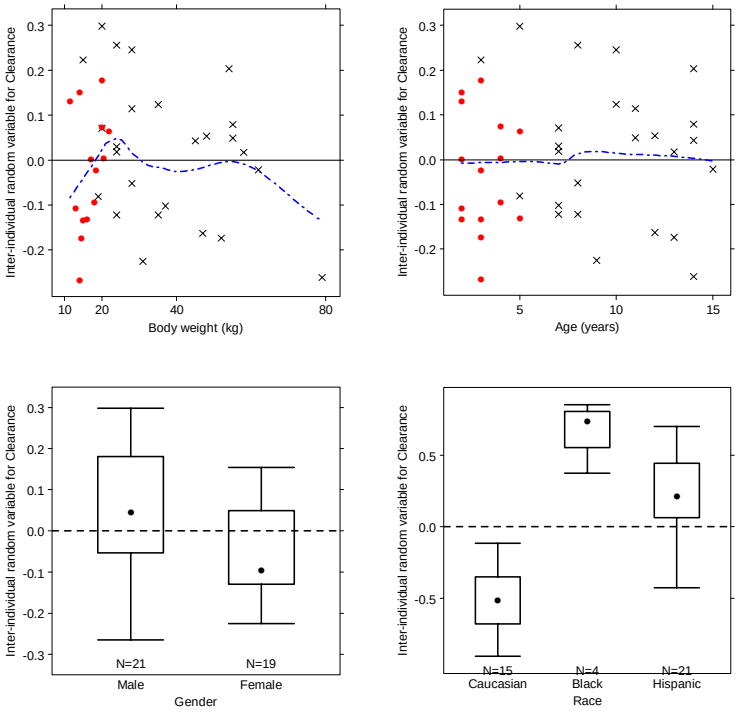


Figure 17 Graphical analyses of covariates vs. clearance inter-individual variability estimates. The red circles are subjects from study MH-119 and the black crosses are subjects from study 43-779-10.

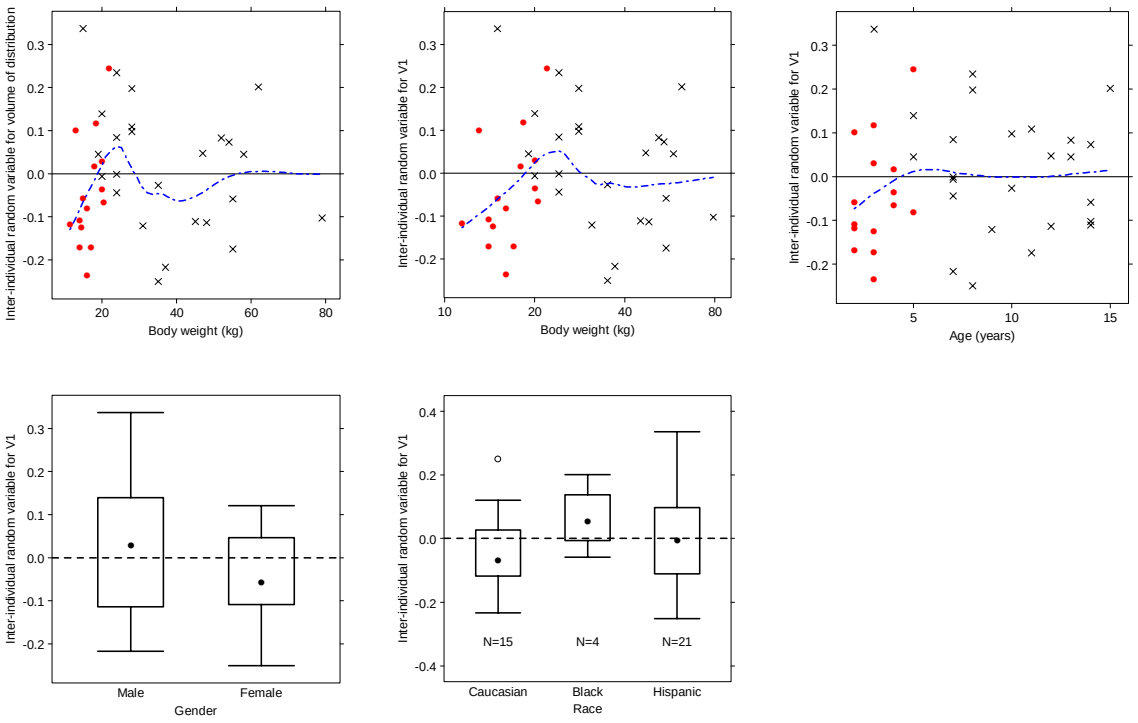


Figure 18 Graphical analyses of covariates vs. volume inter-individual variability estimates. The red circles are subjects from study MH-119 and the black crosses are subjects from study 43-779-10.

9 REFERENCES

Rebecca L. Milsap, Malcolm R. Hill, and Stanley J. Szefler: Pharmacokinetic Considerations in Children. In Book Applied Pharmacokinetics Principles of Therapeutic Drug Monitoring, third edition

Christoffer W. Tornoe, Jeffrey J. Tworzyanski, Menfo A. Imoisili et al. Optimizing piperacillin/tazobactam dosing in pediatrics, International Journal of Antimicrobial Agents 30 (2007) 320-324.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21357	SUPPL-6	BRACCO DIAGNOSTICS INC	MULTIHANCE(GADOBENATE DIMEGLUMINE INJ)

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/s/

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12/07/2009

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