SAFETY AND PHARMACOKINETICS OF CLINDAMYCIN IN OVERWEIGHT AND OBESE CHILDREN

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Abbreviation Listing

ABBREVIATION	DEFINITION
AAG	Alpha-1 acid glycoprotein
ALB	Albumin
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
BSV	Between-participant variability
CL	Clearance
CV	Coefficient of variation
CWRES	Conditional weighted residuals
DBIL	Direct bilirubin
eECV	Estimated extracellular fluid volume
ELISA	Enzyme-linked immunosorbent assay
FFM	Fat free mass
GA	Gestational age
HILL	Hill coefficient for sigmoidal maturation model
IPRED	Individual prediction
IV	Intravenous
IWRES	Individual weighted residuals
LBW	Lean body weight
LC-MS/MS	Liquid chromatography-tandem spectrometry
MIC	Minimum inhibitory concentration
MRSA	Methicillin-resistant *Staphylococcus aureus*
NFM	Normal fat mass
NONMEM	Nonlinear mixed effects modeling
OFV	Objective function value
PK	Pharmacokinetics
PMA	Postmenstrual age
PNA	Postnatal age
PO	Oral
PopPK	Population pharmacokinetics
POP01	Pharmacokinetics of Understudied Drugs Administered to Children per Standard of Care
PRED	Population prediction
PTN	Pediatric Trials Network
RSE	Relative standard error
SCR	Serum creatinine
SD	Standard deviation
TBW	Total body weight
TBIL	Total bilirubin
TM_{50}	Maturation half-life
WT	Body weight
V	Volume of distribution

Report Summary

1. Introduction

Clindamycin is a lincosamide antibiotic that binds to the 50S ribosomal subunit and results in inhibition of bacterial protein synthesis. Due to its broad spectrum of antimicrobial coverage and favorable safety profile, clindamycin is frequently prescribed in the pediatric population. Limited clindamycin data suggest that there are important differences in drug disposition for the pediatric population relative to adults. However, the effect of obesity on clindamycin disposition in children remains largely unstudied. The goal of the analyses described herein was to assess the effect of obesity on clindamycin disposition in children.

2. Objectives

2.1. Use a previously developed pediatric population pharmacokinetic (PopPK) model and additional data collected from premature infants to adolescents to assess the effect of obesity on clindamycin pharmacokinetics (PK).

2.2. Apply the final PopPK model to assess optimal clindamycin dosing in obese children.

3. Methods

PK samples used to develop the PopPK model described in this report were collected from three trials: 1) Pharmacokinetics of Understudied Drugs Administered to Children per Standard of Care (NICHD-2011-**POP01**; clinicaltrials.gov #NCT01431326; IND# 113,645); 2) Safety and Pharmacokinetics of Multiple-Dose Intravenous and Oral Clindamycin Pediatric Participants with BMI ≥85th Percentile (NICHD-2012-**CLN01**; clinicaltrials.gov #NCT01744730; IND# 115,396); and 3) Pharmacokinetics of Antistaphylococcal Antibiotics in Infants (NICHD-2012-**STA01**; clinicaltrials.gov #NCT01728363; IND# 115,396). The PopPK model was developed using the software NONMEM (version 7.2). PK samples from all studies were analyzed using the same HPLC/MS/MS bioanalytical assay validated according to FDA guidance. A forward inclusion-backward elimination approach was used to identify covariates that explain inter-individual variability in clindamycin disposition across age groups. Total body weight (WT), free fat mass (FFM), normal fat mass (NFM), and lean body weight (LBW) were each evaluated as measures to account for differences in body size. Monte Carlo

simulations were performed using the final model parameters to assess optimal clindamycin dosing.

4. Results

A total of 220 participants contributed 420 PK samples to the analysis; 95 children were overweight or obese (187 PK samples). The final population PK model of the whole study population included body weight (WT), postmenstrual age (PMA), albumin (ALB), and α-1 acid glycoprotein (AAG) as statistically significant covariates for CL and V: CL (L/h) = $13.8*(WT/70)^{0.75}*(PMA^{2.83}/(39.5^{2.83}+PMA^{2.83}))$; V (L)= $63.6*(WT/70)*(ALB/3.3)^{-0.83}*(AAG/2.4)^{-0.25}$. Use of FFM, NFM, or LBW, in place of WT, did not improve fitting of the data. For the >6-12 years and >12 years age categories, statistically significant differences between obese and non-obese children were observed in the absolute (i.e., non-weight normalized) V estimates (P<0.001). Terminal elimination half-life was also significantly different, but only for the >6-12 years age group (P=0.01). No other statistically significant differences were observed between obese and non-obese children. Simulations performed using optimal age-based dosing confirmed that total body weight can be used for drug dosing.

5. Conclusions

After accounting for size-based differences using total body weight and physiologic differences using age, as well as differences in plasma protein concentrations, only V and terminal elimination half-life were significantly different between obese and non-obese children. Clindamycin should be dosed using total body weight in obese and non-obese children.

1. Introduction

Clindamycin is a lincosamide antibiotic that binds to the 50S ribosomal subunit, disrupting peptide bond formation and resulting in inhibition of bacterial protein synthesis. Clindamycin has activity against anaerobic and aerobic gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA). Guidelines recommend clindamycin as a treatment option in children with pneumonia, skin and soft tissue infections, and osteomyelitis, when MRSA is the likely pathogen (1). In the pediatric population, due to a rise in the incidence of MRSA infections (2), use of clindamycin has increased significantly, and it is now the most widely prescribed antibiotic in hospitalized pediatric patients for this indication (3).

Following intravenous administration, clindamycin distributes extensively into tissues (with the exception of cerebrospinal fluid) and has a volume of distribution (V) at steady-state of 0.79 L/kg in healthy adults (4). *In vitro* clindamycin is predominantly metabolized by CYP3A4 to clindamycin sulfoxide and N-demethyl clindamycin (5). When measured *in vivo*, metabolite concentrations although quantifiable in bile and urine (6, 7), are relatively negligible in plasma (7, 8). In adults, clindamycin's clearance (CL) and half-life are ~0.3–0.4 L/h/kg and 2.1 hours, respectively (9, 10). Limited clindamycin data suggest that there are important differences in drug disposition for the pediatric population relative to adults. In neonates (n=12; gestational age [GA] 26–39 weeks; postnatal age [PNA] 1–24 days) receiving clindamycin via intravenous administration, a V of 0.57 L/kg (0.15–1.1) L/kg was reported (11). Weight-normalized estimates of CL appear to be age-dependent: 0.06 L/h/kg in neonates (<28 days age) (11); ~0.26 L/h/kg in older infants (>28 days) (12); and ~0.38 L/h/kg (oral clearance) in children (8–11 years) (6). In addition to age-based differences, drug disposition may also be notably different with obesity (e.g., altered volume of distribution); however, no pharmacokinetic (PK) studies have been performed to assess these differences to date.

The aim of the analyses described herein was to assess the effect of overweight and obesity on clindamycin disposition using a population PK (PopPK) modeling approach. Data used to develop a published clindamycin PopPK model (13) were supplemented with PK samples collected from premature infants to adolescents in two additional trials. Using the combined dataset, additional covariate relationships were explored, and the final model was applied to perform simulations to guide clindamycin dosing in obese children.

2. Objective

a. Use a previously developed pediatric PopPK model and additional data collected from premature infants to adolescents to assess the effect of obesity on clindamycin PK.
b. Apply the final PopPK model to assess optimal clindamycin dosing in obese children.

3. Methods

3.1 Patient population

PK samples used to develop the PopPK model described in this report were collected from three trials: 1) Pharmacokinetics of Understudied Drugs Administered to Children per Standard of Care (POP01); 2) Safety and Pharmacokinetics of Multiple-Dose Intravenous and Oral Clindamycin Pediatric Participants with BMI ≥85th Percentile (CLN01); and 3) Pharmacokinetics of Antistaphylococcal Antibiotics in Infants (STA01).

POP01 (NICHD-**POP01**-2012, clinicaltrials.gov #NCT01431326; IND # 113,645) is a multi-center (N=27), prospective, PK, and safety study of understudied drugs administered to children (<21 years of age) per standard of care. Children who received one of 21 drugs of interest (including clindamycin) per standard of care as administered by their treating caregiver were eligible for enrollment. Exclusion criteria included failure to obtain consent/assent or a known pregnancy as determined by interview or testing, if available. PK samples were collected with standard-of-care lab collections. Because this was a standard-of-care study, dosing and PK sample collection times varied between participants. Standard-of-care laboratory assessments (e.g., basic metabolic panel) were recorded if collected within 24 hours of a study dose of the drug. GA and PNA were collected in infants <120 days PNA. Participants were enrolled in the study for up to 90 days.

NICHD-2012-**CLN01** (clinicaltrials.gov #NCT01744730; IND# 115,396) is a prospective, multi-center (N=6), open-label, multiple-dose PK study of intravenous and oral clindamycin. Pediatric participants were enrolled in the trial if they met the following inclusion criteria: 2 years – <18 years of age at the time of first dose of study drug; suspected or confirmed infection or receiving intravenous clindamycin per standard of care; negative pregnancy test; body mass index (BMI) ≥85th percentile for age and sex,

based on Centers for Disease Control and Prevention recommendations; and signed informed consent. For participants not receiving clindamycin per standard of care, exclusion criteria included: history of hypersensitivity or allergic reaction to clindamycin or lincomycin; history of *C. difficile* colitis with previous administration of clindamycin; aspartate transaminase (AST) >120 units/L; alanine transaminase (ALT) >210 units/L; total bilirubin >3 mg/dL; and those receiving a neuromuscular blocker as part of their therapy. In addition, patients who were post-cardiac bypass (within 24 hours) or receiving inotropes/vasopressors were excluded.

NICHD-2012-**STA01** (clinicaltrials.gov #NCT01728363; IND # 115,396) is a multi-center (N=8), prospective, multiple-dose PK and safety study of clindamycin, rifampin, and ticarcillin-clavulanate in premature infants. Infants with suspected systemic infection or receiving one of the study drugs per local standard of care were eligible for enrollment. For the clindamycin group, infants were <30 weeks GA and <121 days PNA. Infants meeting any of the following criteria were excluded: allergic reactions to a study drug; urine output <0.5 mL/hr/kg over the prior 24 hours; serum creatinine >1.7 mg/dL; and any condition that, in the judgment of the investigator, precludes participation because of safety concerns.

Each study protocol was reviewed and approved by the institutional review board of each participating institution or a federated institutional review board.

3.2 Drug dosing and sample collection

For the POP01 study, dosing information was collected for up to eight doses prior to the sampling dose (last dose prior to first biological sample collection). As POP01 used an opportunistic study design, the timing of blood sample collection was dependent on standard-of-care laboratory assessments. However, parents/guardians were also given the option to allow sample collection for research purposes only (Table 1).

Table 1. Research-only sample collection scheme for clindamycin following intravenous administration

	Dosing Interval (hours)		
Sample Name	**6**	**8**	**12**
Sample #1[a]	0	0	0
Sample # 2	1–4	2–5	2–8
Sample # 3[b]	Pre	Pre	Pre
Sample # 4	12–18	16–24	24–36

[a]Time=0: end of infusion; sample collected after flush ends.
[b]Pre: within 1 hour prior to next administration of study drug.

In the CLN01 trial, intravenous and/or oral administration of clindamycin was prescribed at a dose of 30–40 mg/kg/day (based on total body weight [TBW]) every 6 or 8 hours. Optimal PK sampling times are noted in Table 2.

Table 2. PK sampling times in the CLN01 trial

Time (hours)	**IV Dose**		**PO Dose**	
	Q6H	Q8H	Q6H	Q8H
Pre-dose 0 (within 15 minutes prior to the dose)	X**	X**	X**	X**
0.5 (± 5 minutes)	X**	X**	N/A	N/A
1–1.5	X	X	X**	X**
3–4	X**	X**	X**	--
5–6	--	X	--	X**
Pre-dose (will depend if on Q6H or Q8H dose schedule)	X**	X**	X**	X**
Total number of samples	5	6	4	4

IV: intravenous; PO: oral.
*Time starts at end of flush after the 30-minute infusion.
**Priority samples.

In the STA01 trial, all infants received clindamycin 10 mg/kg every 6, 8, or 12 hours unless prescribed clindamycin per standard of care, in which case dosing was at the discretion of the treating caregiver. The dosing interval and sampling schedule were stratified by GA and PNA (Tables 3 and 4). Up to eight PK samples were collected based on the predetermined sampling window.

Table 3. Clindamycin dosing in STA01 trial

Cohort	**GA**	**PNA**	**Dose**
1	<30 weeks	<14 days	10 mg/kg Q 12 hours x 6 doses
2	<30 weeks	≥14 days–45 days	10 mg/kg Q 8 hours x 6 doses
3	<30 weeks	>45 days–120 days	10 mg/kg Q 6 hours x 6 doses

Table 4. Optimal plasma sampling collection windows for study drug by dosing interval in STA01 trial

	Dosing Interval (hours)		
Sample #	**6**	**8**	**12**
1	0–15 min*	0–15 min*	0–15 min*
2	30–60 min	30–60 min	30–60 min
3	1–2 hr	1–2 hr	1–2 hr
4	2–3 hr	2–3 hr	2–4 hr
5	3–4 hr	3–4 hr	5–8 hr
6	4–5 hr	4–6 hr	8–10 hr
7	15 min prior to next dose	15 min prior to next dose	15 min prior to next dose
8 (elimination)	12–18 hr	16–24 hr	24–36 hr

*All sample times other than Sample 7 are relative to the end of flush.

3.3 Analytical methods

For all studies, blood was collected (200 µL) in an EDTA-K2 Microtainer and was processed immediately prior to freezing at the study sites. PK samples were sent to the Pediatric Trials Network (PTN) central laboratory (OpAns, LLC, Durham, NC, USA) for storage and analysis. Clindamycin concentrations collected from the three trials were quantified using a validated liquid chromatography-tandem spectrometry (LC-MS/MS) assay (Document #OPR-NIH-0024.01). The chromatography system and mass spectrometer used for sample analysis were the Agilent 1200 series high-performance liquid chromatography (HPLC) and an Agilent 6400 series triple quadrupole system, respectively. The Pursuit XRS Ultra C18 column (50 x 2 mm i.d., 2.8 µm, Agilent) and a gradient mobile phase (water containing 0.5% [v/v] formic acid; methanol containing 0.1% [v/v] formic acid) were used. The validation range for the assay was 50–50,000 ng/mL. Quality control samples included the following nominal concentrations: 50, 150, 4000, and 40,000 ng/mL. The lower limit of quantification was 50 ng/mL. Accuracy and precision assessed using five determinations at theoretical levels 150, 4000, and 40,000 ng/mL were within the Food and Drug Administration bioanalytical assay validation criteria (e.g., ±15%).

An enzyme-linked immunosorbent assay (ELISA [Assaypro LLC, St Charles, MO]) was used for the measurement of alpha-1 acid glycoprotein (AAG) in plasma. The method was qualified over the range 0 to 4 µg/mL for human AAG in MIX Diluent (a buffered protein base supplied with the kit) representing 0 to 4 mg/mL corrected for dilution. Freshly prepared calibration standards were processed in duplicate for each run, and quality controls provided with the kit were analyzed in duplicate. Both calibration standards and

quality control samples met assay validation criteria. Each study sample was diluted 1:1000 into MIX Diluent and then processed in duplicate.

3.4 PK dataset

The PK analysis datasets for each respective study were generated and formatted by The Emmes Corporation (Rockville, MD, USA). Locked datasets for the POP01 (July 15, 2015), STA01 (January 20, 2015), and CLN01 (January 19, 2015) datasets were merged to create a dataset containing combined PK data for the analyses described herein. Clinical, dosing, and drug concentration information were included in the dataset. Missing clinical data were imputed using the last value carried forward if at least one measurement was available per participant. If no measurement was available for a participant, then the sample median value was imputed for the covariate screen performed as part of the population PK analysis.

3.5 Statistical analysis

Using the value at the time of first recorded dose, the median and range were calculated for demographic and dosing variables. The range of variables denotes the minimum and maximum values in the data set. We tested the equality of distribution of each PK parameter of interest among the obese and non-obese population using the non-parametric Wilcoxon rank-sum test and stratified the analysis by participant age: 2-6 years, >6-12 years, and >12 years. With the exception of the PK modeling, all statistical analyses were performed using the software R (version 3.0.2, R Foundation for Statistical Computing, Vienna, Austria) or Stata (version 13.1, College Station, TX, USA).

3.6 Population PK analysis

Clindamycin plasma PK data collected following intravenous administration were analyzed with a nonlinear mixed effects modeling approach using the software NONMEM (version 7.2, Icon Solutions, Ellicott City, MD, USA). The first-order conditional estimation method with interaction (FOCE-I) was used for all model runs. Run management was performed using Pirana (version 2.8.1) (14). Visual predictive checks and bootstrap methods were performed with Perl-speaks-NONMEM (version 3.6.2) (15). Data manipulation and visualization was performed using the software R (version 3.0.2, R Foundation for Statistical Computing, Vienna, Austria) and RStudio (version 0.97.551, RStudio, Boston, MA, USA); with the packages lattice, Xpose, and ggplot2 used for the latter (16–18).

A previously developed clindamycin PopPK model was used in the analyses described herein (13). A similar model development/evaluation approach was used. Briefly, between subject variability (BSV) was assessed for PK model parameters using an exponential relationship (Equation 1).

$$P_{ij} = \theta_{Pop,j} * \exp(\eta_{ij}) \quad (1)$$

Where *Pij* denotes the estimate of parameter *j* in the *i*th individual; $\theta_{Pop,j}$ is the population value for parameter *j*; and ηij denotes the deviation from the average population value for parameter j in the *i*th individual with mean zero and variance ω^2. The correlation between random effect parameters was calculated according to Equation 2. A proportional error model was used to estimate the intra-individual variability (Equation 3).

$$\rho = \frac{\omega_{CL,V}}{\sqrt{\omega_{CL}{}^2 * \omega_V{}^2}} \quad (2)$$

$$C_{obs,ij} = C_{pred,ij} * (1 + \varepsilon_{prop,ij}) \quad (3)$$

Where $\omega_{CL,V}$ denotes the off-diagonal element between clearance and volume of distribution parameters; η_{CL} $C_{obs,ij}$ is the *j*th observed clindamycin concentration in the *i*th individual; $C_{pred,ij}$ is the *j*th predicted concentration in the *i*th individual; and $\varepsilon_{prop,ij}$ is a random variable with mean zero and variance $\sigma_{prop,ij}^2$. Because data was combined from three trials, separate proportional residual errors were used for each study.

The published final PopPK model included a relationship between total body weight (WT) and postmenstrual age with CL and V as depicted in equations 4–6 (13).

$$CL = CL_{std} * \left(\frac{WT_i}{70\ kg}\right)^{0.75} \quad (4)$$

$$V = V_{std} * \left(\frac{WT_i}{70\ kg}\right)^{1} \quad (5)$$

$$F_{PMA} = \frac{PMA^{HILL}}{TM_{50}{}^{HILL} + PMA^{HILL}} \quad (6)$$

Where CL_{std} and V_{std} represent population estimates of CL and V in a 70 kg adult; WT_i denotes body weight for the *i*th participant; F_{PMA} denotes the fraction of the adult clearance value; TM_{50} represents the value of postmenstrual age (PMA; weeks) when 50% adult clearance is reached; and *HILL* is a slope parameter for the sigmoidal maturation model.

To assess whether use of other indirect measures of body size, namely, normal fat mass (NFM), free fat mass (FFM), and lean body weight (LBW), resulted in superior model performance, we tested these first in place of WT, and in the absence of accounting for PMA. The following equations were used:

i. *Fat free mass (FFM).* FFM was estimated using the following equations (19):

$$FFM = WHS_{max} * H^2 * \left[\frac{TBW}{(WHS_{50} * H^2 + TBW)}\right] \quad (7)$$

WHS$_{max}$ and *WHS*$_{50}$ are sex-specific values: *WHS*$_{max}$=42.92 kg/m^2 and *WHS*$_{50}$=30.93 kg/m^2 for men; *WHS*$_{max}$=37.99 kg/m^2 and *WHS*$_{50}$=35.98 kg/m^2 for women. If height (H) was missing, TBW was used in place of FFM.

ii. *Normal fat mass (NFM).* NFM was estimated using the following equations (20):

$$NFM = FFM + F_{fat} * (TBW - FFM) \quad (8)$$

The parameter, *F*$_{fat}$, is estimated from the observed data and accounts for different contributions of fat for each PK parameter (e.g., CL, V). If height was missing, NFM was assumed to be 90% TBW.

iii. *Lean body weight (LBW)*. An approach whereby estimated extracellular fluid volume (eECV) is calculated from TBW and height (H) was applied (21):

$$eECV = 0.0215 * WT^{0.6469} * H^{0.7236} \quad (9)$$

$$LBW = 3.8 * eECV \quad (10)$$

If height was missing, TBW was used.

Following assessment of the ideal measure of body size, additional covariates were tested for model inclusion, beginning with PMA which was in the originally published model. Determination of which covariates to test for model inclusion was assessed by visual inspection of scatter and box plots (continuous and categorical variables, respectively) of the individual deviations from the population-typical value PK parameters (ETAs) against covariates. The following covariates were explored: postmenstrual age (PMA), alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine (SCR), bilirubin (total [TBIL] and direct [DBIL]), serum albumin, AAG, body mass index (BMI), obese status (BMI ≥ 95th percentile), ethnicity, and sex. A forward inclusion ($p<0.05$ and Δ objective function value [OFV] >3.8) and backward elimination ($p<0.001$ and ΔOFV >10.8) approach was used to evaluate statistical significance of obesity.

3.7 Population PK model evaluation and validation

During assessment of obesity covariates and indirect measures of body size, standard model diagnostic methods were used and included successful minimization, diagnostic plots, plausibility and precision of parameter estimates, as well as objective function and shrinkage values. Diagnostic plots generated included: individual predictions (IPRED) and population predictions (PRED) vs. observations; conditional weighted residuals (CWRES) vs. PRED and time; and individual weighted residuals (IWRES) vs. IPRED.

Parameter precision for the final PopPK was evaluated using non-parametric bootstrapping (1000 replicates) to generate the 95% confidence intervals for parameter estimates. Visual predictive checks were performed whereby the base and final models were used to generate 1000 Monte Carlo simulation replicates per time point of clindamycin exposure, and simulated results were compared with those observed in the study. The dosing and covariate values used to generate the simulations in the visual predictive check were the same as those used in the study population.

3.8 Exposure-response relationship

The final model parameter estimates were used to perform dosing simulations and assess proportion of participants with an unbound clindamycin concentration above the minimum inhibitory concentration (MIC) for at least half the dosing interval (22). Pediatric dosing regimens recommended in the package insert were simulated and optimized to match adult (70 kg WT) clindamycin exposure following intravenous administration of 600 mg every 8 hours (dose for complicated intra-abdominal infections). The following parameters were calculated for each virtual participant: total drug steady-state AUC from 0 to 8 hours ($AUC_{0\text{-}8,ss}$); maximal drug concentration at steady-state ($C_{MAX,SS}$); minimum concentration at steady-state ($C_{MIN,SS}$); and the concentration at half the dosing interval ($C_{50,SS}$) for doses administered every 8 hours using a 30 minute intravenous infusion. Model equations are shown in Equations 11-14.

$$AUC_{0-8,SS} = \frac{Dose}{CL} \quad (11)$$

$$C_{MAX,SS} = \frac{Dose}{(CL*DUR)} * \frac{(1-EXP(-Ke*DUR))}{(1-EXP(-Ke*\tau))} \quad (12)$$

$$C_{MIN,SS} = C_{MAX,SS} * EXP(-Ke * (\tau - DUR)) \quad (13)$$

$$C_{50,SS} = C_{MAX,SS} * EXP(-Ke * 3.5) \quad (14)$$

Where *Ke* denotes the first-order elimination rate constant calculated as CL/V; *DUR* denotes the infusion duration (0.5 hours for all dosing simulations); and *τ* is the dosing interval (8 hours for all dosing simulations).

The covariate values for virtual patients were the same as those in the study population used for model development. Using PK parameter estimates from the final population model, 200 concentrations vs. time profiles were simulated for each virtual patient and then related to adult simulated exposure. A maximum absolute dose of 900 mg every 8 hours was used in all dosing simulations. Unbound, steady-state clindamycin concentrations at half the dosing interval ($fC_{50,SS}$) were calculated assuming a fraction unbound of 17% (23). The proportion of virtual participants with an $fC_{50,SS}$ greater than a minimum inhibitory concentration of 0.12 mcg/mL (MIC_{90} for *Staphylococcus aureus*) following optimal dosing was calculated (24).

4. Results

4.1 Patient demographics

A total of 268 samples collected from 178 participants in the POP01 study were included in the analysis. One sample had a likely sampling time error and was dropped from the analysis. Two additional samples were below the quantification limit and not included in the analysis. The median (range) number of samples per participant and dose was 1 (1–11) sample and 10.0 mg/kg/dose (3.8–15.1), respectively. Demographic variables are summarized in Tables 5 and 6. Sixty-three (35%) of participants were obese. Forty-two (24%) participants were ≤120 days PNA; of these 47% (20/42) were ≤32 weeks GA and were studied at median (range) 9.1 days PNA (3.7–62.1) and 28.8 weeks PMA (23.6–37.6). Six participants in POP01 had total body weight measurements but were missing height values, and thus additional indirect body size measures (i.e., BMI, FFM, NFM, and LBW) could not be calculated.

Table 5. Demographics table for POP01 dataset: continuous variables

Covariate[a]	N[b]	Mean	SD	CV	Median	Range
GA (weeks)	42	32.7	6.0	18.4	33.3	22.9-42
PNA (years)	178	7.2	6.9	95.8	5.2	0.01-20.5
Weight (kg)	178	36.7	35.6	97.0	23.0	0.5-139.8

BMI (kg/m^2)[c]	104	25.6	7.2	28.2	24.8	13.7-46.7
SCR (mg/dL)	93	0.6	0.5	81.8	0.4	0.1-3.4
AST (U/L)	36	61.1	72.2	118.0	35.5	8-389
ALT (U/L)	36	59.1	63.1	106.6	31.5	5-266
TBIL (mg/dL)	40	2.3	2.7	116.8	1.1	0-11
Albumin (g/dL)	48	3.2	0.7	22.5	3.3	1.9-4.5
AAG (mg/mL)	174	2.7	1.1	40.9	2.5	0.5-6.3

GA: gestational age; PNA: postnatal age; BMI: body mass index; SCR: serum creatinine; AST: aspartate aminotransferase; ALT: alanine transaminase; TBIL: total bilirubin; SD: standard deviation; CV: coefficient of variation (%); AAG: alpha-1 acid glycoprotein.
[a]Descriptive statistics are calculated based on values at the time of first recorded dose.
[b]N signifies the number of participants with a measurement available for each respective variable.
[c]Age >2 years.

Table 6. Demographics table for POP01 dataset: categorical variables

Covariate	N (%)
Sex	
Male	104 (58%)
Race	
White	132 (74%)
Black or African American	28 (16%)
Other	18 (10%)
Ethnicity	
Hispanic or Latino	52 (29%)
Obese status[a]	
Yes	63 (35%)

[a]BMI ≥95th percentile.

A total of 21 participants were enrolled in the CLN01 trial. These participants contributed a total of 91 samples; 2 of which were scavenged samples and were not included in the analysis. The median samples per participant and dose were 4 samples (1–6) and 10.0 mg/kg/dose (1.0–14.3), respectively. Demographic characteristics are shown in Tables 7–9 for CLN01 participants and in Tables 10 and 11 for all obese participants. Height and weight measurements were available for all participants. Concentration versus time data for the CLN01 trial is shown in Figure 1.

Table 7. Demographic characteristics for CLN01 participants: continuous variables

Covariate[a]	N[b]	Mean	SD	CV	Median	Range
PNA (years)	21	13.0	2.9	22.5	13.0	6.5-17.4
Weight (kg)	21	78.2	41.3	52.9	69.5	27.9-224.0
Height (cm)	21	160.3	19.0	11.9	162.0	122.5-188.0
BMI (kg/m^2)	21	29.1	11.4	39.2	27.1	18.6-74

SCR (mg/dL)	21	0.6	0.3	46.7	0.6	0.2-1.5
AST (U/L)	21	33.2	29.9	89.9	25.0	8.0-151.0
ALT (U/L)	21	32.5	25.5	78.5	25.0	10.0-114.0
TBIL (mg/dL)	21	0.7	0.9	120.9	0.5	0.2-3.8
Albumin (g/dL)	21	3.7	0.7	20.0	3.7	2.1-4.6
AAG (mg/mL)	21	2.0	0.8	40.0	2.0	0.5-3.8

PNA: postnatal age; BMI: body mass index; SCR: serum creatinine; AST: aspartate aminotransferase; ALT: alanine transaminase; TBIL: total bilirubin; AAG: Alpha-1 acid glycoprotein; SD: standard deviation; CV: coefficient of variation (%);
[a]Descriptive statistics are calculated based on values at the time of first recorded dose. Age is calculated based on the value at enrollment.
[b]N signifies the number of participants with a measurement available for each respective variable.

Table 8. Demographic characteristics for CLN01 dataset: categorical variables

Covariate	N (%)
Sex	
Male	17 (81%)
Race[a]	
White	17 (81%)
Black or African American	2 (10%)
Other	2 (10%)
Ethnicity	
Hispanic or Latino	2 (10%)
Obese status[b]	
Yes	13 (62%)

[a]Race unavailable for one participant.
[b]BMI ≥95th percentile.

Table 9. Demographic characteristics for CLN01 dataset: continuous variables stratified by age and BMI percentile

Covariate	2 – <12 Years		>12 Years	
	BMI 85th –<95th Percentile (N=4)	BMI >95th Percentile (N=3)	BMI 85th –<95th Percentile (N=4)	BMI >95th Percentile (N=10)
Age (years)	9.5 (6.5-11.9)	10.7 (9.1-11.9)	14.6 (12.6-16.8)	14.6 (12.5-17.4)
Weight (kg)	42.7 (27.9-58.9)	52.3 (49.5-68.7)	78.8 (50.9-90.2)	90.7 (50.2-224)
Height (cm)	143.5 (122.5-162.3)	148.5 (145.7-154.8)	175.9 (146.1-185)	170.5 (134.4-188)
BMI (kg/m^2)	20 (18.6-22.4)	23.7 (23.3-28.7)	25.2 (23.7-27.1)	32.3 (26.8-74)
SCR (mg/dL)	0.4 (0.2-0.6)	0.4 (0.3-0.5)	0.7 (0.5-0.9)	0.6 (0.4-1.5)
AST (U/L)	33.5 (25-70)	28 (22-151)	24.5 (14-33)	22.5 (8-40)
ALT (U/L)	28 (14-70)	33 (31-114)	14 (11-27)	24.5 (10-67)
TBIL (mg/dL)	0.6 (0.4-0.7)	0.5 (0.3-3.8)	0.6 (0.3-0.7)	0.4 (0.2-2.8)
Albumin (g/dL)	3.7 (2.1-4.4)	3.7 (2.6-4.5)	4.2 (3.7-4.4)	3.4 (2.3-4.6)
AAG (mg/mL)	1.7 (1.2-3.8)	1.9 (0.5-2.4)	1.9 (1.2-2.4)	2.1 (1.1-3.3)

PNA: postnatal age; BMI: body mass index; SCR: serum creatinine; AST: aspartate aminotransferase; ALT: alanine transaminase; TBIL: total bilirubin; AAG: alpha-1 acid glycoprotein; SD: standard deviation; CV: coefficient of variation (%).

*Median (range) reported.

Table 10. Demographic characteristics for obese participants in the POP01 and CLN01 datasets: continuous variables

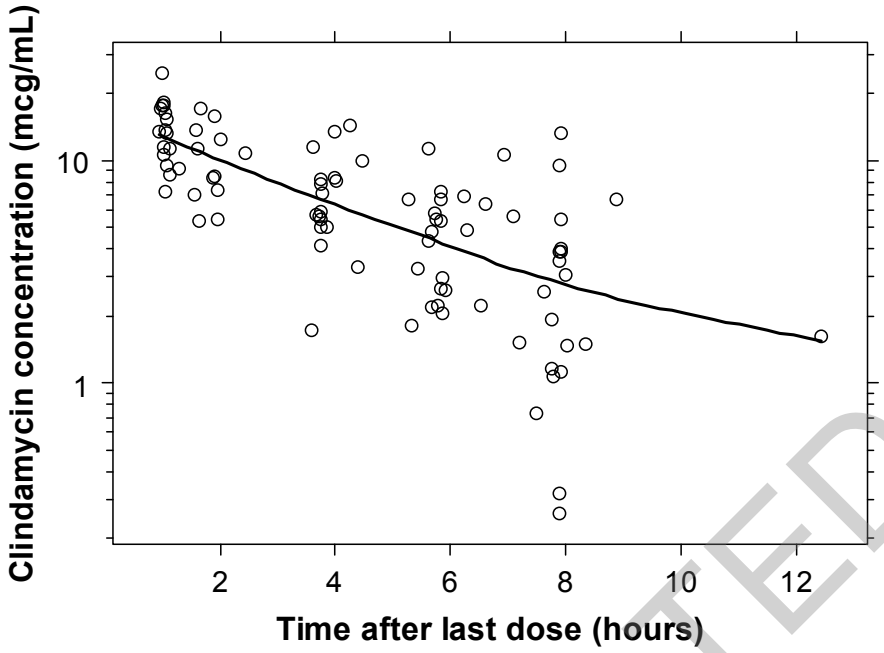
Covariate[a]	N[b]	POP01 (N=63)	N[b]	CLN01 (N=13)	N[b]	Total (N=76)
Age (years)	63	12.4 (2.1-20.1)	13	13.5 (9.1-17.4)	76	13.0 (2.1-20.1)
Weight (kg)	63	61.2 (12.8-139.8)	13	76.4 (49.5-224)	76	67.0 (12.8-224)
Height (cm)	63	147 (81-188)	13	155 (134.4-188)	76	153.4 (81-188)
BMI (kg/m^2)	63	29.0 (18.9-46.7)	13	28.9 (23.3-74)	76	28.9 (18.9-74)
SCR (mg/dL)	29	0.6 (0.2-1.6)	13	0.6 (0.3-1.5)	42	0.6 (0.2-1.6)
AST (U/L)	12	36 (15-165)	13	23 (8-151)	25	29 (8-165)
ALT (U/L)	12	33.5 (9-165)	13	28 (10-114)	25	31 (9-165)
TBIL (mg/dL)	12	0.6 (0.1-11)	13	0.4 (0.2-3.8)	24	0.5 (0.1-11)
Albumin (g/dL)	19	2.9 (1.9-4.2)	13	3.4 (2.3-4.6)	32	3.4 (1.9-4.6)
AAG (mg/mL)	63	2.5 (0.8-5.7)	13	2.0 (0.5-3.3)	76	2.4 (0.5-5.7)

PNA: postnatal age; BMI: body mass index; SCR: serum creatinine; AST: aspartate aminotransferase; ALT: alanine transaminase; TBIL: total bilirubin; SD: standard deviation; CV: coefficient of variation (%); AAG: alpha-1 acid glycoprotein.
*Median (range).
[a]Descriptive statistics are calculated based on values at the time of first recorded dose.
[b]N signifies the number of participants with a measurement available for each respective variable.

Table 11. Demographic characteristics for obese participants in the POP01 and CLN01 datasets: categorical variables

	POP01 (N=63)	CLN01 (N=13)	Total (N=76)
Covariate	**N (%)**	**N (%)**	**N (%)**
Sex			
Male	33 (52)	12 (92)	45 (59)
Race			
White	44 (70)	11 (85)	55 (72)
Black or African American	10 (16)	1 (8)	11 (14)
Other	9 (14)	1 (8)	10 (13)
Ethnicity			
Hispanic or Latino	20 (32)	1 (8)	21 (28)

Figure 1. Clindamycin PK data collected in the CLN01 trial



Data from the STA01 trial was included in the population PK model development. A total of 21 participants contributed 75 samples; 8 of which are scavenged samples and were not included in the analysis. One sample had a likely sampling time error and was dropped from the analysis. Two samples were below the quantification limit and not include in the analysis. The median (range) number of samples per participant and dose in the STA01 data set was 3 samples (2–7) and 9.8 mg/kg/dose (4.3–13.0), respectively. Demographic variables are summarized in Tables 12-13. Height/length measurements were not available for any of the participants. Concentration versus time data for all three clinical trials is shown in Figure 2.

Table 12. Demographics table for STA01 participants: continuous variables

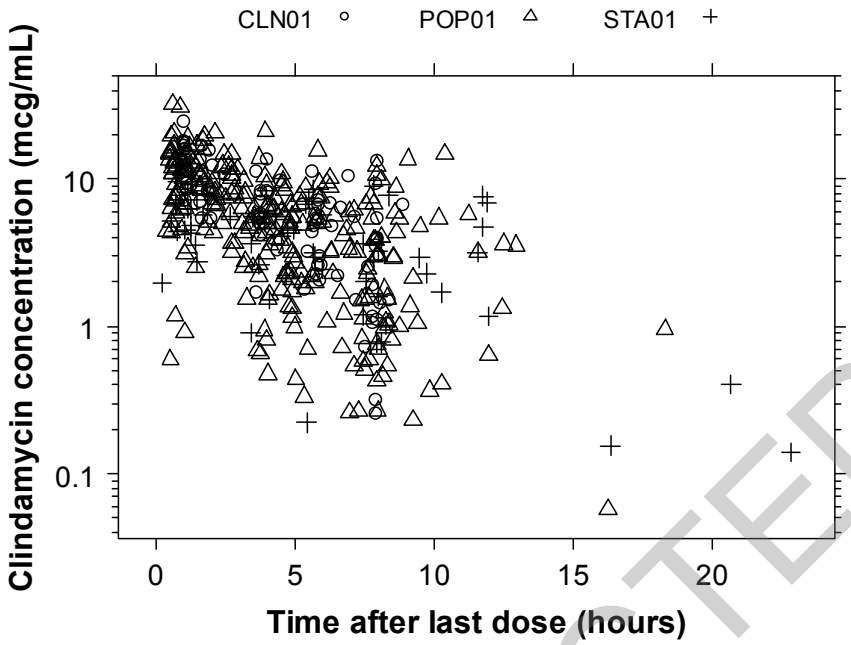
Covariate[a]	N[b]	Mean	SD	CV	Median	Range
GA (weeks)	21	26.0	1.8	6.8	26	23-29
PNA (days)	21	28.0	19.9	70.9	23	5-65
PMA (weeks)	21	29.8	3.9	13.2	28.6	23.7-37.1
Weight (kg)	21	1.2	0.7	53.3	1.0	0.5-3.0
SCR (mg/dL)	21	0.6	0.4	61.2	0.7	0.2-1.5
AST (U/L)	17	39.1	32.5	83.2	25	15-116
ALT (U/L)	17	18.2	15.8	86.7	11	6-55
TBIL (mg/dL)	18	4.4	2.6	58.3	4.7	0.5-8.2
Albumin (g/dL)	14	2.3	0.4	17.5	2.3	1.3-2.8
AAG (mg/mL)	21	0.9	0.5	52.8	0.8	0.4-1.8

GA: Gestational age; PNA: postnatal age; PMA: post-menstrual age; BMI: body mass index; SCR: serum creatinine; AST: aspartate aminotransferase; ALT: alanine transaminase; TBIL: total bilirubin; SD: standard deviation; CV: coefficient of variation (%); AAG: alpha-1 acid glycoprotein.
[a]Descriptive statistics are calculated based on values at the time of first recorded dose.
[b]N signifies the number of participants with a measurement available for each respective variable.

Table 13. Demographics table for STA01 dataset: categorical variables

Covariate	**N (%)**
Sex	
Male	12 (57%)
Race	
White	17 (81%)
Black or African American	3 (14%)
Ethnicity	
Hispanic or Latino	4 (19%)

Figure 2. Clindamycin concentration vs. time data for merged dataset.



4.2 Population PK model development and evaluation

As previously described, a one compartment PK model described the clindamycin concentration vs. time data well (13). For the base model, use of WT was compared with FFM, NFM, and LBW. WT resulted in the lowest OFV: 7157.9, WT; 7173.0, FFM; 7173.0, NFM; and 7164.8, LBW. Thus, all additional covariate models were evaluated after accounting for body size using WT (Table 14). Consistent with previous findings, after accounting for body size, use of a sigmoidal maturation function with PMA resulted in the largest reduction in the OFV (-115.6 points). Thereafter, albumin (ALB) and AAG on V and serum creatinine on CL reached statistical significance; however, the latter was not included in the final model because its retention during the backward elimination step was largely a result of one influential individual (with a value of 3.4 mg/dL). Therefore, the final model included body weight, a sigmoidal maturation relationship between PMA and CL, and exponential relationships between ALB and AAG on V: CL (L/h) = $13.8*(WT/70)^{0.75}*(PMA^{2.83}/(39.5^{2.83}+PMA^{2.83}))$; V (L)= $63.6*(WT/70)*(ALB/3.3)^{-0.83}*(AAG/2.4)^{-0.25}$ (Table 15). Maturation reached 50% adult CL values at ~40 weeks PMA. Diagnostic plots for the final model are shown in Figures 3 and 4. Visual predictive checks

for all studies combined and then stratified by study are shown in Figures 5 and 6, respectively. Shrinkage estimates were <30% for all random effect parameters.

Table 14. Summary of Population PK model development

Description	Population Model	OFV	ΔOFV[a]
Univariable analysis			
Base model	$CL = 10.2*(WT/70)^{0.75}$; $V = 77.1*(WT/70)$	7157.9	-
Post-menstrual age on CL	**$CL = 14.6*(WT/70)^{0.75}*(PMA^{3.39}/(41.1^{3.39}+PMA^{3.39}))$**	**7042.3**	**-115.6**
α-1 acid glycoprotein on V	$V = 66.7*(WT/70)*(AAG/2.4)^{-0.47}$	7126.2	-31.7
Albumin on V	$V = 73.6*(WT/70)*(ALB/3.3)^{-1.04}$	7138.1	-19.8
Total bilirubin on CL	$CL = 10.5*(WT/70)^{0.75}*(TBIL/0.8)^{-0.23}$	7144.8	-13.1
Serum creatinine on CL	$CL = 10.2*(WT/70)^{0.75}*(SCR/0.5)^{-0.36}$	7145.2	-12.7
Albumin on CL	$CL = 10.7*(WT/70)^{0.75}*(ALB/3.3)^{0.93}$	7149.2	-8.7
Obese Status[b] on V	$V = 84.3*(WT/70)*0.73^{OBESE}$	7149.9	-8.0
α-1 acid glycoprotein on CL	$CL = 10.2*(WT/70)^{0.75}*(AAG/2.4)^{-0.04}$	7157.7	-0.2
Multivariable analysis –first step			
Post-menstrual age on CL **Albumin on V**	**$CL = 14.3*(WT/70)^{0.75}*(PMA^{3.26}/(39.7^{3.26}+PMA^{3.26}))$** **$V = 67.1*(WT/70)*(ALB/3.3)^{-0.79}$**	**7023.8**	**-18.5**
Postmenstrual age and serum creatinine on CL	$CL = 15.1*(WT/70)^{0.75}*(PMA^{2.15}/(48.9^{2.15}+PMA^{2.15}))*(SCR/0.5)^{-0.32}$	7029	-13.3
Postmenstrual age on CL α-1 acid glycoprotein on V	$CL = 14*(WT/70)^{0.75}*(PMA^{3.05}/(40^{3.05}+PMA^{3.05}))$ $V = 65.7*(WT/70)*(AAG/2.4)^{-0.23}$	7035.6	-6.7
Postmenstrual age and albumin on CL	$CL = 14.7*(WT/70)^{0.75}*(PMA^{3.22}/(40.9^{3.22}+PMA^{3.22}))*(ALB/3.3)^{0.44}$	7038.1	-4.2
Postmenstrual age and total bilirubin on CL	$CL = 14.6*(WT/70)^{0.75}*(PMA^{3.32}/(40.4^{3.32}+PMA^{3.32}))*(TBIL/0.8)^{-0.09}$	7038.8	-3.5
Postmenstrual age on CL Obese status on V	$CL = 14.4*(WT/70)^{0.75}*(PMA^{3.46}/(40.3^{3.46}+PMA^{3.46}))$ $V = 70.4*(WT/70)*0.93^{OBESE}$	7041.7	-0.6
Multivariable analysis - second step			
Postmenstrual age on CL **Albumin and α-1 acid glycoprotein on V**	**$CL = 13.8*(WT/70)^{0.75}*(PMA^{2.83}/(39.5^{2.83}+PMA^{2.83}))$** **$V = 63.6*(WT/70)*(ALB/3.3)^{-0.83}*(AAG/2.4)^{-0.25}$**	**7014.6**	**9.2**

Postmenstrual age and serum creatinine on CL Albumin on V	$CL = 14.8*(WT/70)^{0.75}*(PMA^{2.12}/(46.4^{2.12}+PMA^{2.12}))*(SCR/0.5)^{-0.28}$ $V = 67.8*(WT/70)*(ALB/3.3)^{-0.75}$	7014.6	9.2
Postmenstrual age and albumin on CL Albumin on V	$CL = 14.3*(WT/70)^{0.75}*(PMA^{3.31}/(40.2^{3.31}+PMA^{3.31}))*(ALB/3.3)^{-0.16}$ $V = 67*(WT/70)*(ALB/3.3)^{-0.86}$	7023.4	0.4
Multivariable analysis – full model			
Postmenstrual age and serum creatinine on CL Albumin and α-1 acid glycoprotein on V	**$CL = 14.8*(WT/70)^{0.75}*(PMA^{1.43}/(51.6^{1.43}+PMA^{1.43}))*(SCR/0.5)^{-0.34}$ $V = 63.6*(WT/70)*(ALB/3.3)^{-0.77}*(AAG/2.4)^{-0.29}$**	**7003.0**	**-11.6**
Backward elimination			
Drop postmenstrual age	$CL = 10*(WT/70)^{0.75}*(SCR/0.5)^{-0.37}$ $V = 64.5*(WT/70)*(ALB/3.3)^{-0.84}*(AAG/2.4)^{-0.46}$	7093.3	+90.3
Drop albumin	$CL = 15*(WT/70)^{0.75}*(PMA^{1.53}/(53.5^{1.53}+PMA^{1.53}))*(SCR/0.5)^{-0.37}$ $V = 65.2*(WT/70)*(AAG/2.4)^{-0.26}$	7020.4	+17.4
Drop α-1 acid glycoprotein	$CL = 14.8*(WT/70)^{0.75}*(PMA^{2.12}/(46.4^{2.12}+PMA^{2.12}))*(SCR/0.5)^{-0.28}$ $V = 67.8*(WT/70)*(ALB/3.3)^{-0.73}$	7014.6	+11.6
Drop serum creatinine[c]	$CL = 13.8*(WT/70)^{0.75}*(PMA^{2.83}/(39^{2.83}+PMA^{2.83}))$ $V = 63.6*(WT/70)*(ALB/3.3)^{-0.83}*(AAG/2.4)^{-0.25}$	7014.6	+11.6
Multivariable analysis – final model			
Postmenstrual age on CL Albumin and α-1 acid glycoprotein on V	**$CL = 13.8*(WT/70)^{0.75}*(PMA^{2.83}/(39.5^{2.83}+PMA^{2.83}))$ $V = 63.6*(WT/70)*(ALB/3.3)^{-0.83}*(AAG/2.4)^{-0.25}$**	**7014.6**	**-**

OFV: objective function value; CL: clearance (L/h); V: volume of distribution (L); PMA: postmenstrual age (weeks); SCR: serum creatinine (mg/dL); ALB: albumin (g/dL); AAG: alpha (α)-1 acid glycoprotein.

[a]Change in OFV for the univariable analysis is relative to the base model and for the multivariable analysis is relative to the intermediate PMA on CL model.

[b]OBESE: If obese (BMI ≥95th percentile) equal to 1; if not assessed (<2 years age) or non-obese, then equal to 0.

[c]Backward elimination of serum creatinine reached statistical significance, but was not included in the model because this significance was largely a result of one influential individual with a serum creatinine of 3.4 mg/dL. When this participant was dropped, elimination of serum creatinine no longer reached statistical significance.

Table 15. Population PK parameter estimates for the final model

	Final Model		Bootstrap (n=1,000)		
Parameter	**Estimate**	**RSE (%)**	**2.5th percentile**	**Median**	**97.5th percentile**
CL_{70KG} (L/H)	13.8	6.2	12.3	13.8	15.7
V_{70KG} (L)	63.6	5.0	59.0	64.1	71.4
TM_{50} (weeks)	39.5	12.1	32.5	39.4	53.4
HILL	2.8	33.7	1.5	3.0	5.1
Albumin on V exponent	-0.8	27.9	-1.3	-0.9	-0.4
α-1 acid glycoprotein on V exponent	-0.3	44.0	-0.4	-0.3	0
BSV (CL, %)	58.5	11.5	52.1	58.4	64.8
BSV (V, %)	11.6	145.5	5.9	15.7	27.9
p CL-V	0.8	64.5	0	0.7	0.8
Prop., POP01 (%)	33.6	16.5	26.7	32.7	38.0
Prop., STA01 (%)	32.1	28.8	19.3	31.1	40.1
Prop., CLN01 (%)	20.3	30.4	13.0	18.7	25.0

RSE: relative standard error; CL_{70KG}: population clearance estimate scaled to a 70-kg adult; V_{70KG}: population volume of distribution estimate scaled to a 70-kg adult; TM_{50}: maturation half-life calculated as a function of PMA (weeks); HILL: Hill coefficient in sigmoidal maturation function; BSV (CL): between subject variability in drug clearance; and BSV (V): between subject variability in V.

Empirical Bayesian estimates (EBE) obtained from the final model were stratified by obese status and age (Table 16). For the >6-12 years and >12 years age categories, statistically significant differences were observed in the absolute (i.e., non-weight normalized) V estimates (P<0.001). Half-life of elimination was also significantly different, but only for the >6-12 years age group (P=0.01). No other statistically significant differences were observed between obese and non-obese children.

Figure 3. Population and individual predictions versus observations for the combined dataset.

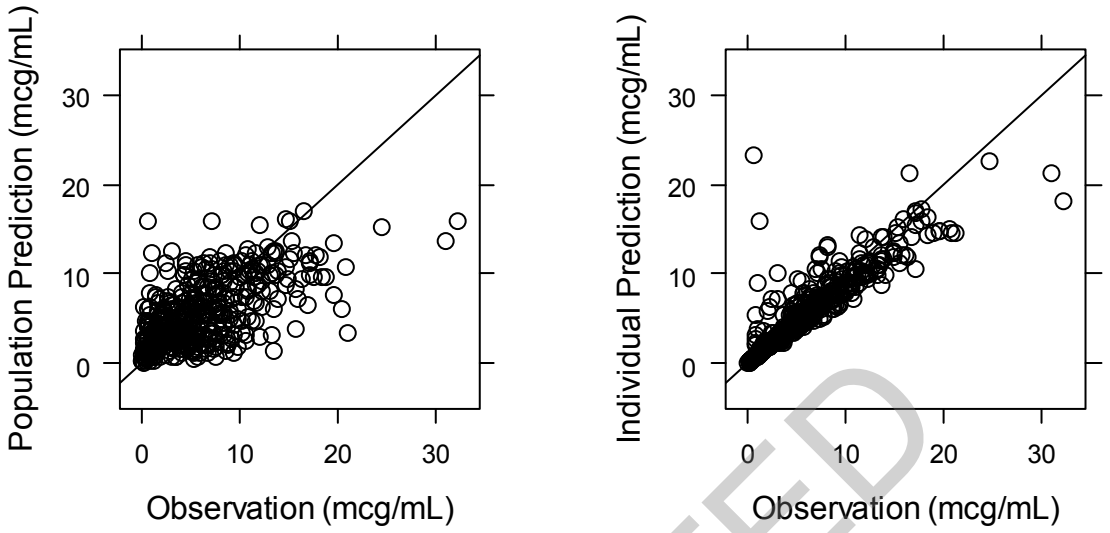


Figure 4. Conditional weighted residuals (CWRES) versus time and population predictions for the combined dataset.

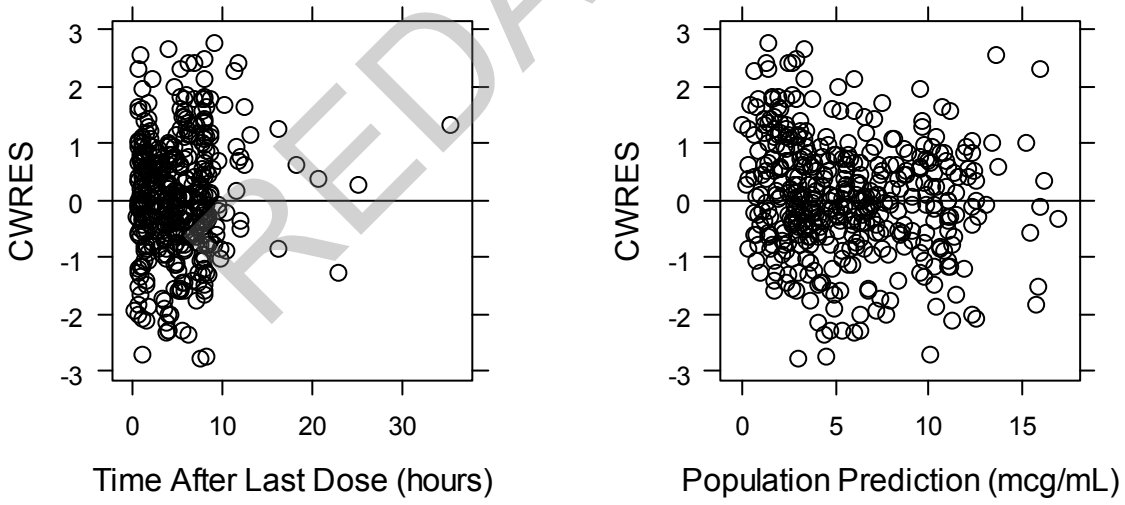


Figure 5. Visual predictive check for final model using combined dataset. The shaded region denotes the 90% prediction interval of the simulated data.

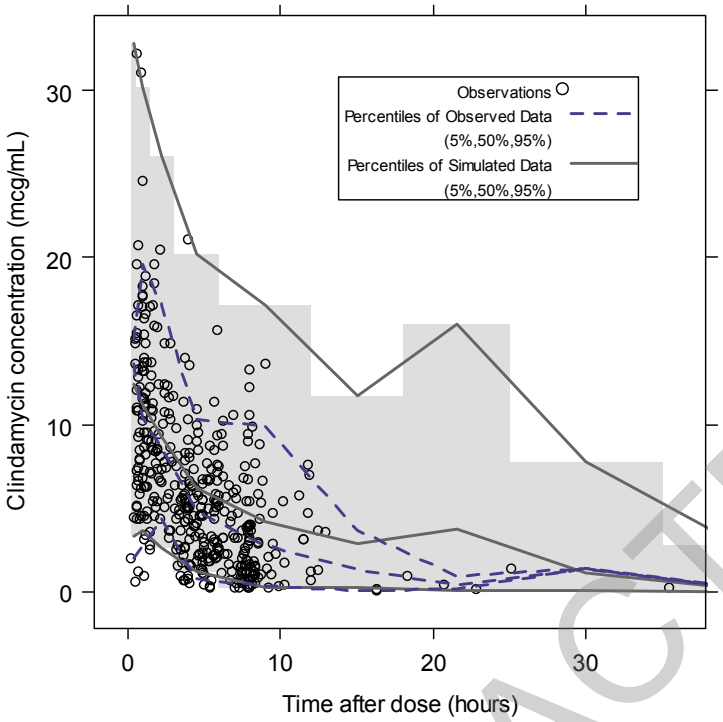


Figure 6**.** Visual predictive check stratified by study for final model using combined dataset.

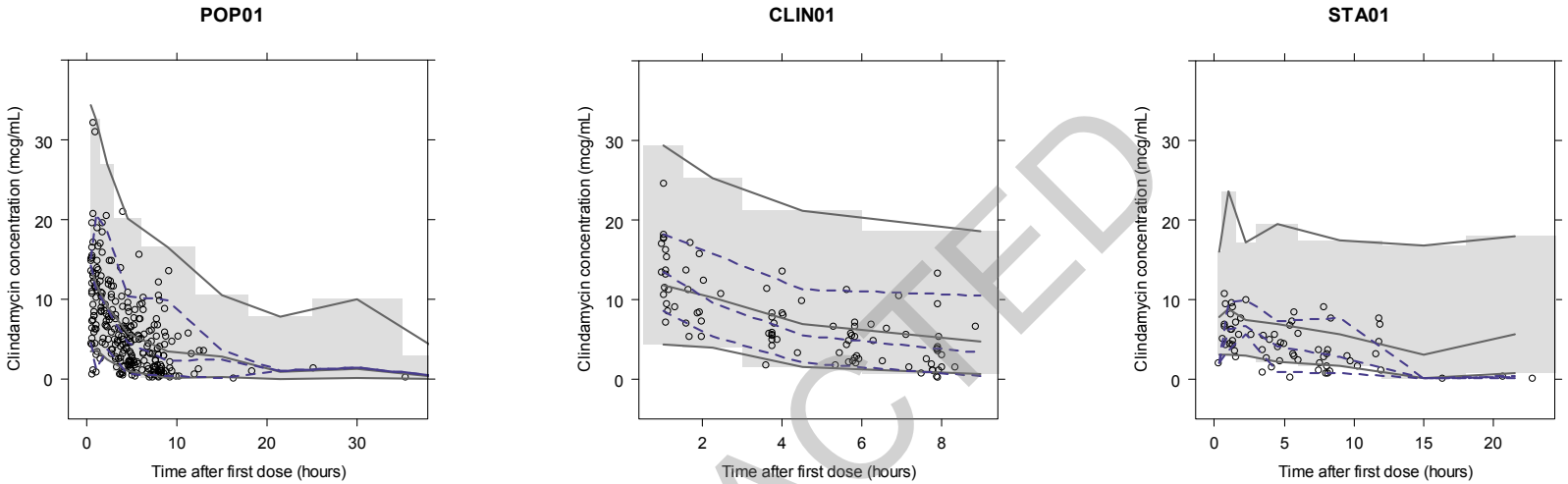


Table 16. Comparison of empirical Bayesian estimates for the final model using TBW to correct for body size

Age Categories	>2–6 Years[a]		>6–12 Years		>12 Years[b]	
Parameters*	**Non-Obese (N=8)**	**Obese (N=12)**	**Non-Obese (N=15)**	**Obese (N=20)**	**Non-Obese (N=26)**	**Obese (N=44)**
CL (L/h)	4.2 (0.9-9.1)	5.7 (1.8-8.3)	12.5 (3.6-34.4)	10.7 (4.7-26.7)	14.3 (5.6-37.4)	19.2 (3.9-33.7)
CL (L/h/kg)	0.2 (0.1-0.8)	0.3 (0.1-0.4)	0.3 (0.1-0.8)	0.2 (0.1-0.6)	0.2 (0.1-0.5)	0.2 (0-0.7)
CL (L/h/70 kg)	10.6 (3.6-35.0)	14.8 (5.5-20.3)	20.7 (7.1-48.5)	14.7 (5.9-39.2)	15.8 (4.7-34.7)	14.0 (3.1-37.9)
V (L)	15.3 (7.6-19.7)	17.6 (8.4-25.2)	29.0 (17.5-57.4)	46.9 (32.9-85.8)**	60.1 (22.5-94.6)	85.8 (28.5-160.0)**
V (L/kg)	0.8 (0.7-1.3)	0.9 (0.7-1.0)	0.9 (0.7-1.1)	1.0 (0.7-1.3)	0.9 (0.7-1.3)	0.9 (0.6-1.6)
Half-life (h)	2.4 (1.1-5.9)	2.2 (1.5-4.4)	2.2 (0.9-5.8)	3.0 (1.2-6.3)**	2.8 (1.2-7.6)	3.6 (0.9-11.3)

*Median (range).
**Statistically significant differences were observed using a rank sum test.
[a]Three participants with missing height (and BMI) were not included in this parameter summary.
[b]Ten participants (6 non-obese, 4 obese) who were >18 years of age were included in the parameter summary.

4.3 Dosing simulations

Previously recommended clindamycin dosing regimens (13) were simulated using the final PopPK model described herein and compared to simulated adult exposure (weight, 70 kg; age, 18 years of age; albumin, 4 g/dL; AAG, 2.4 mg/mL) following 600 mg every 8 hours intravenously. The median (2.5^{th}, 97.5^{th} percentiles) simulated $AUC_{0\text{-}8,SS}$ when stratified by age-based dosing were: 44.2 mcg*h/mL (14.0-146.0), 12 mg/kg every 8 hours if 2-6 years; 44.8 mcg*h/mL (14.4-144.0), 10 mg/kg every 8 hours if >6-12 years; and 48.6 mcg*h/mL (15.4-156.0), 10 mg/kg every 8 hours if >12 years. Median exposure of these dosing regimens were within 25% of the median observed in a 70 kg simulated adult receiving 600 mg intravenously every 8 hours: 44.7 mcg*h/mL (13.6-134.2). Patients that would receive greater than 900 mg following weight based dosing (>75 kg for 12 mg/kg and >90 kg for 10 mg/kg), received a maximum dose of 900 mg. Scatter and box plots of simulated $AUC_{0\text{-}8,SS}$ stratified by age are shown in Figure 7 and 8, respectively. Box plots stratified by age and obese status are shown in Figure 9.

Simulated $C_{MAX,SS}$ were also within 20% of that simulated for a 70 kg adult receiving 600 mg every 8 hours (12.2 mcg/mL [7.9-23.6]): 14.1 mcg/mL (8.9-27.3), 12 mg/kg every 8 hours if 2-6 years; 12.2 mcg/mL (7.3-25.2), 10 mg/kg every 8 hours if >6-12 years; and 12.2 mcg/mL (6.6-26.3), 10 mg/kg every 8 hours if >12 years. Scatter and box plots of simulated $C_{MAX,SS}$ stratified by age are shown in Figure 10 and 11, respectively. Box plots stratified by age and obese status are shown in Figure 12.

After correcting for protein binding and using an optimal dosing regimen, the simulated unbound, steady-state clindamycin concentrations were above a minimum inhibitory concentration of 0.12 mcg/mL for at least half the dosing interval in >95% of participants across age groups (Table 17).

Figure 7. Simulated $AUC_{0\text{-}8,SS}$ vs. weight and stratified by age group. The solid blue line denotes the loess curve.

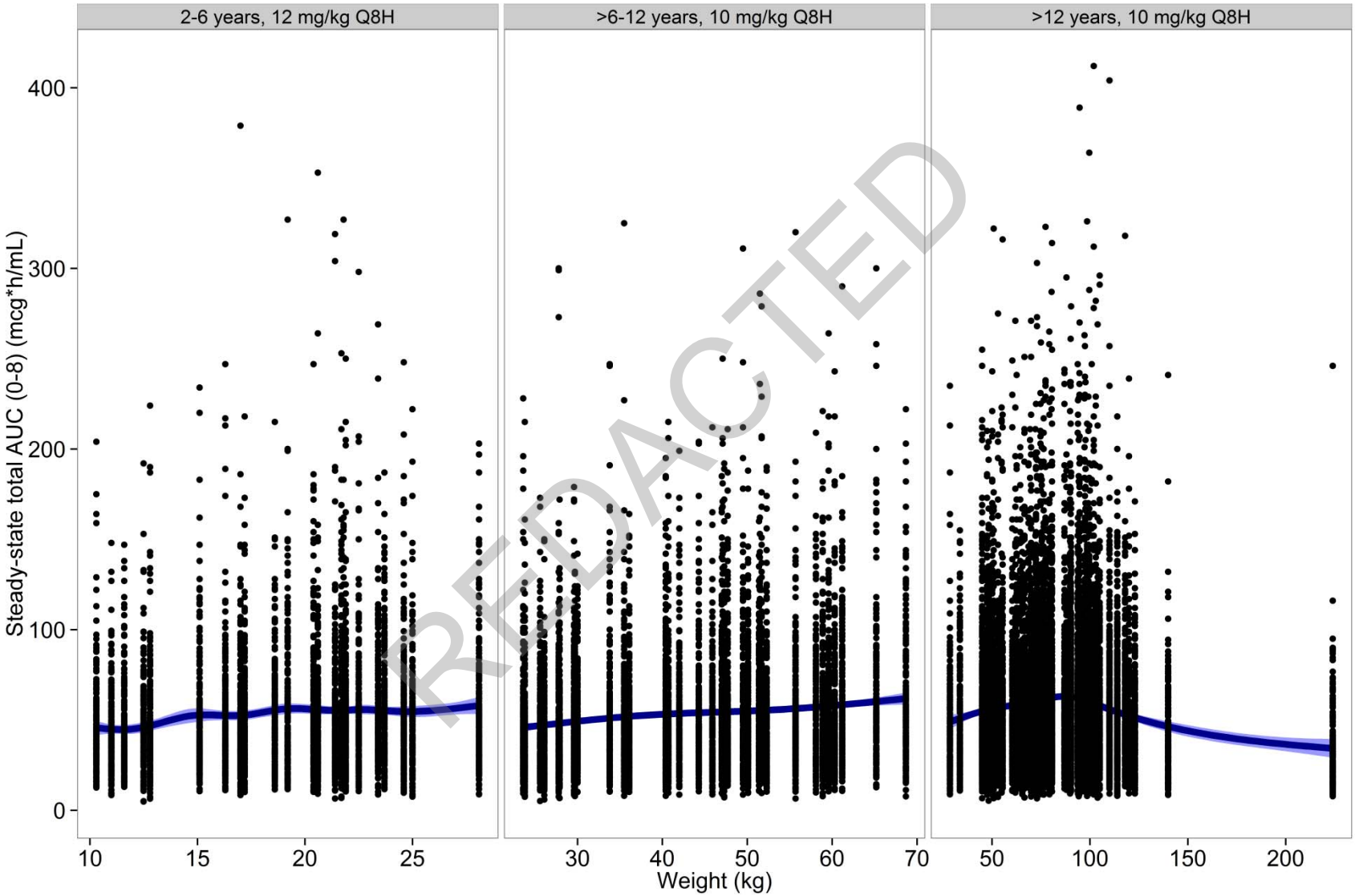


Figure 8. Box plot of $AUC_{0\text{-}8,SS}$ following aged-based clindamycin dosing. The upper and lower whiskers extend to the highest and lowest points that are within 1.5*interquartile range.

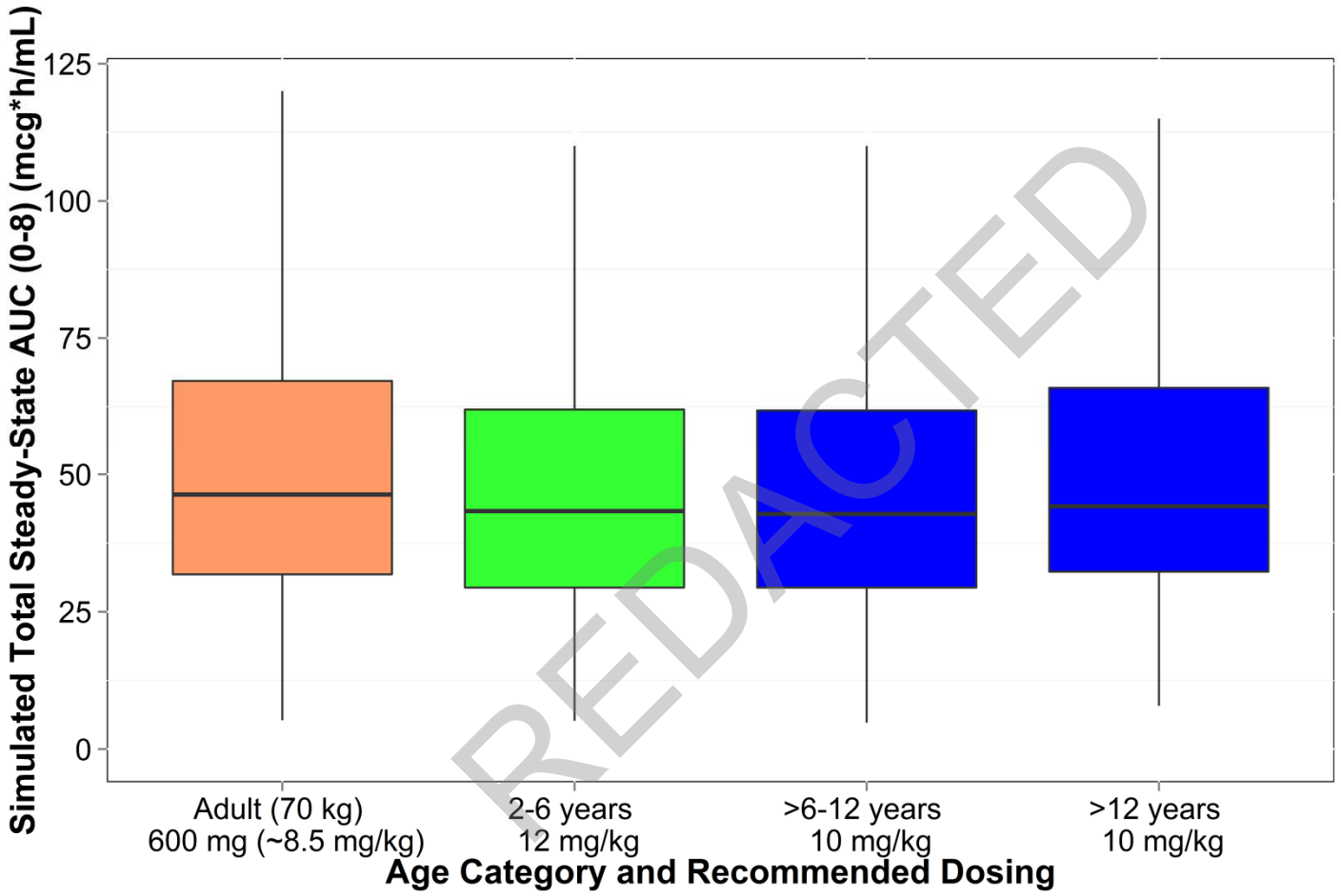


Figure 9. Box plot of $AUC_{0\text{-}8,SS}$ following aged-based clindamycin dosing and stratified by obese status. The upper and lower whiskers extend to the highest and lowest points that are within 1.5*interquartile range.

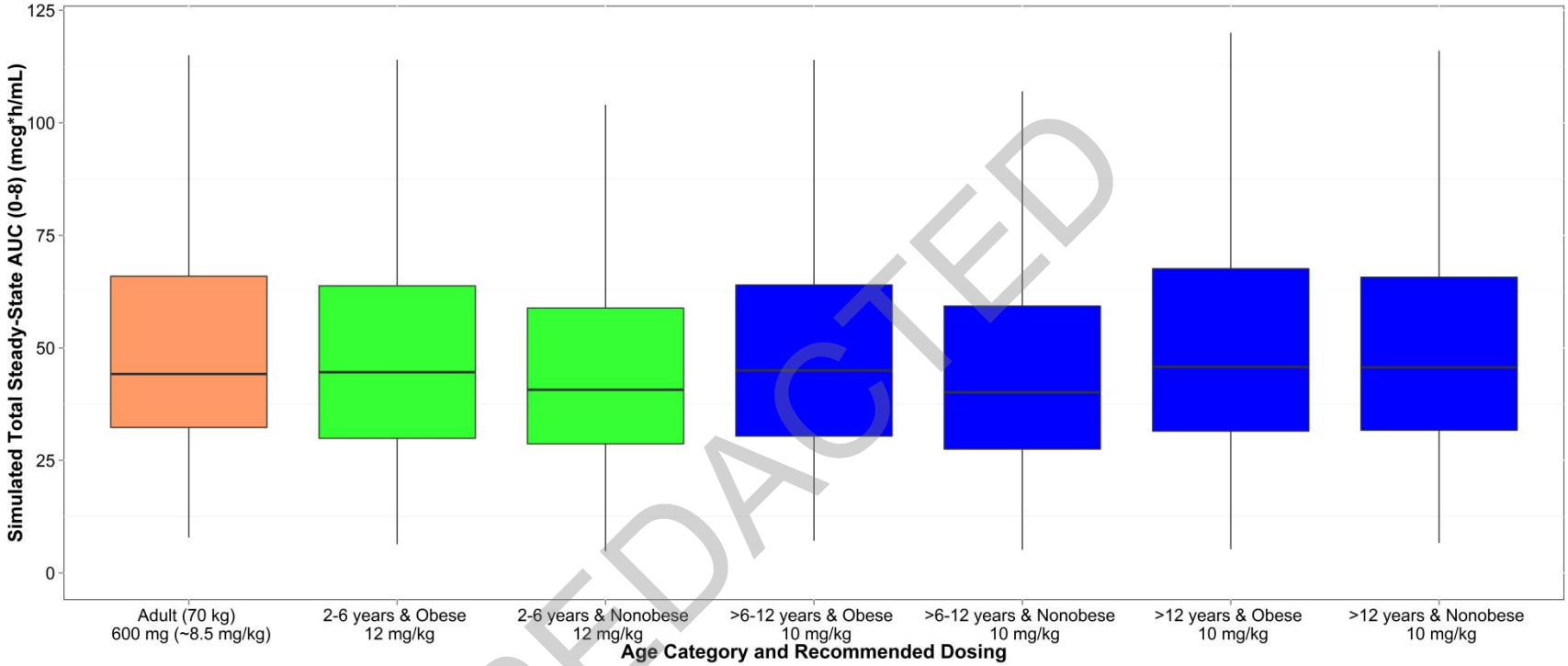


Figure 10. Simulated $C_{MAX,SS}$ vs. weight and stratified by age group. The solid blue line denotes the loess curve.

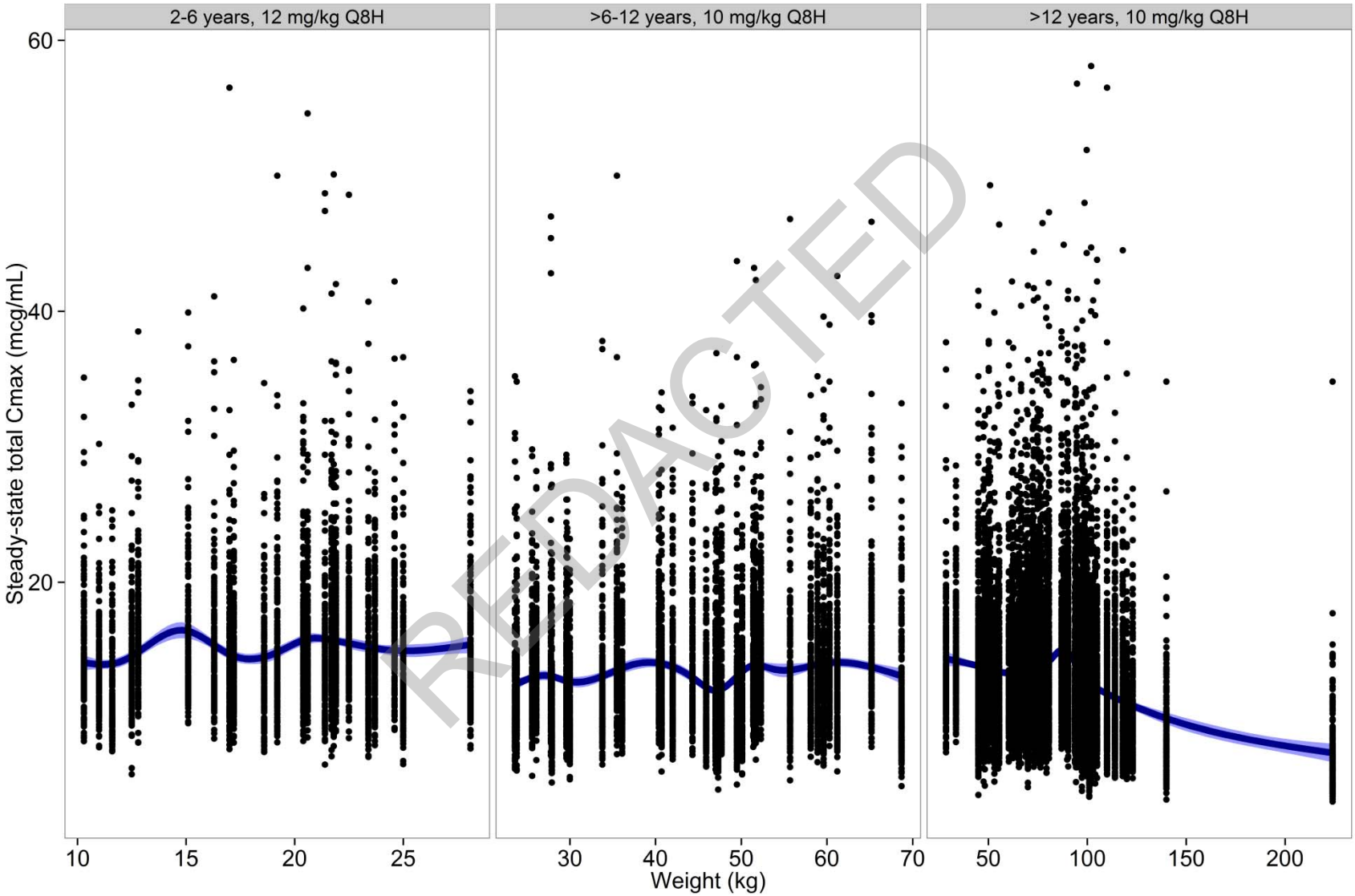


Figure 11. Box plot of $C_{MAX,SS}$ following aged-based clindamycin dosing. The upper and lower whiskers extend to the highest and lowest points that are within 1.5*interquartile range.

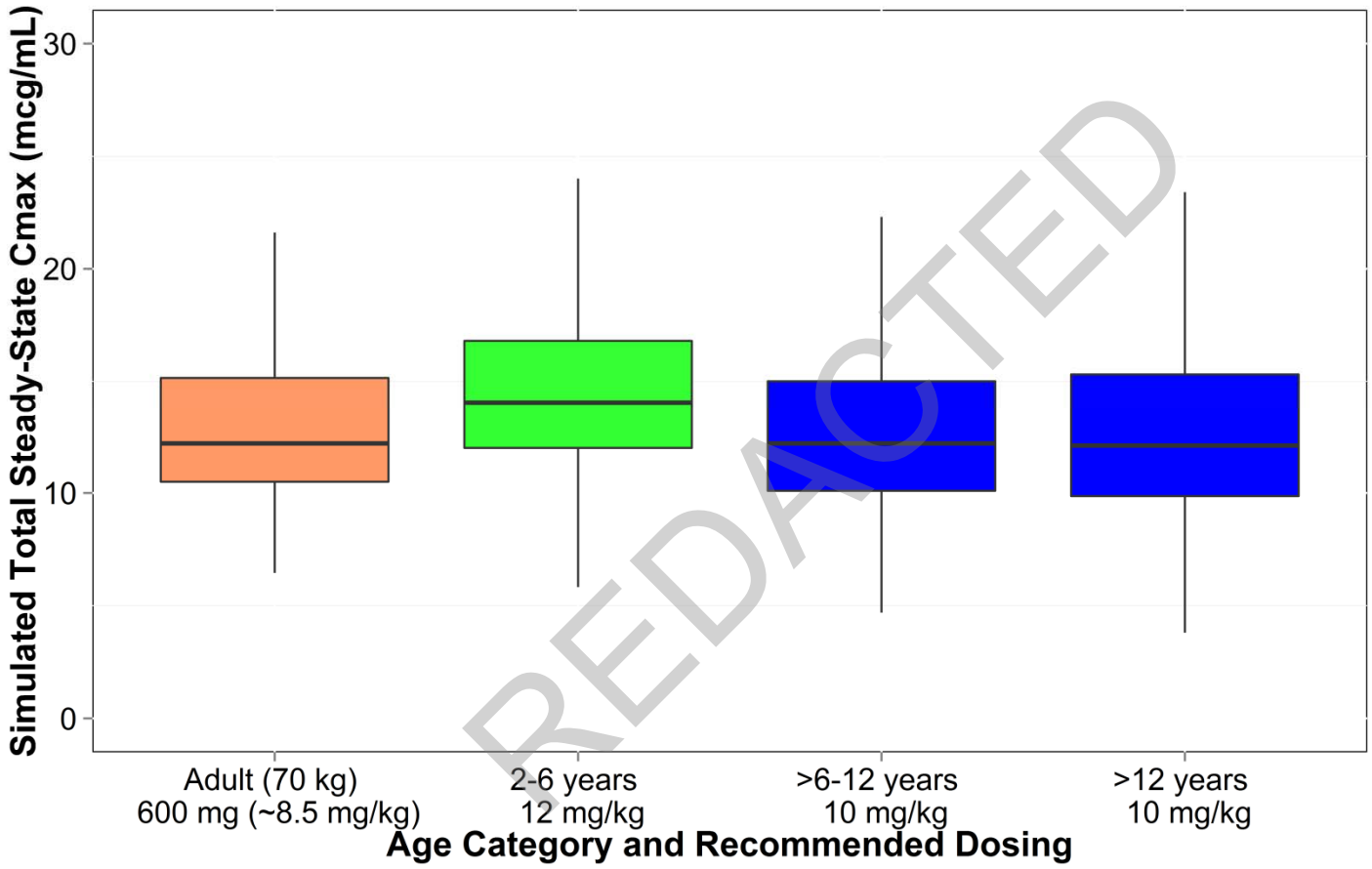


Figure 12. Box plot of $C_{MAX,SS}$ following aged-based clindamycin dosing and stratified by obese status.

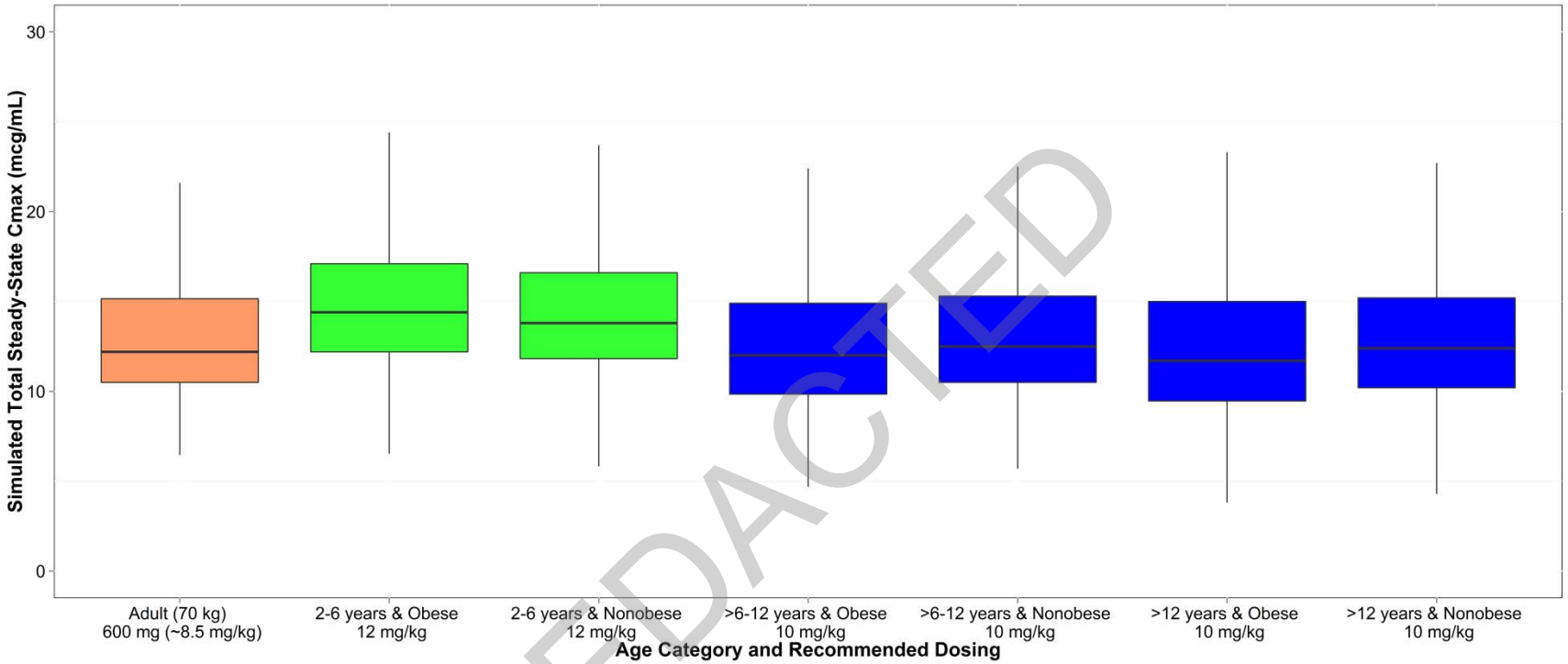


Table 17. Percentage of participants with simulated unbound concentrations above a minimum inhibitory concentration (MIC) of 0.12 µg/mL.

	$fC_{50,SS}$ [a,b]	
	Obese	**Non-Obese**
>12 years	99%	99%
>6-12 years	99%	97%
>2-6 years	97%	96%

[a] Simulated steady-state concentration at time half the dosing interval.

[b] Fraction bound of 83%.[2]

5. Discussion

Clindamycin is widely prescribed in the pediatric population. Its broad spectrum activity and favorable safety profile are among the reasons for its frequent use. MRSA treatment guidelines promote clindamycin as a treatment option in patients with community-acquired infection; in hospitalized children with complicated skin and soft tissue infections when the clindamycin resistance rate is low; and in stable children with pneumonia in the absence of bacteremia (and low resistance rate) (1). The CLN01 trial is designed to assess the PK of clindamycin in overweight and obese children 2 years – <18 years of age.

Limited data suggest that there are important age dependent differences in the disposition of clindamycin. One study evaluated clindamycin PK following intravenous administration (17.9-44 mg/kg/day) in 12 newborn infants (GA 26-39 weeks; PNA 1-24 days; WT 0.8-2.6 kg) (11). In seven of the infants, where an unchanged dose was administered for 2-6 days, mid-interval steady-state concentrations ranged between 12.7 and 40 mcg/mL. The mean (range) weight-normalized V and CL reported for all infants was 0.56 L/kg (0.15-1.1) and 0.06 L/h/kg (0.02-0.13), respectively. In another study, 40 infants (GA 28-40 weeks; PNA 2-27 days; WT 1-9.6 kg) were administered intravenous clindamycin (15-20 mg/kg/day), and the PK was described for three separate groups of patients (Group 1: premature, <28 days; Group 2: term, <28 days; Group 3: all >28 days)(12). No significant differences were noted between maximum (Group 1: 10.92 mcg/mL; Group 2: 10.45 mcg/mL; Group 3: 12.69 mcg/mL) and minimum (Group 1: 5.52 mcg/mL; Group 2: 2.8 mcg/mL; Group 3: 3.03 mcg/mL) concentrations between groups. However, CL was significantly higher in infants > 4 weeks age (1.59 L/h) when compared to premature (0.29 L/h) or term (0.68 L/h) infants (body weights not reported). In older children, one study characterized clindamycin's PK following oral administration (75 mg single-dose) in 11 children 8-11 years of age (6). An oral clearance of ~0.38 L/h/kg and V of ~0.86 L/kg were reported.

In the present study clindamycin data from three trials was combined to describe drug disposition across all pediatric age groups. After accounting for size-based differences in PK parameters using a fixed-exponent allometric relationship (CL: 0.75; V: 1), a sigmoidal maturation function was tested to account for developmental factors in clearance. A sigmoidal E_{MAX} model was selected as it allows for a gradual maturation in drug CL in infants and toddlers, while attaining an adult clearance in older age groups (25). The maturation half-life (i.e., TM_{50}) and slope factor for the POP01 dataset was 39.5 weeks and 2.8, respectively. These estimates

are similar to previously reported estimates for other CYP3A substrates: 39.7 weeks and 1 (HILL factor not estimated) for lopinavir (26); 35.7 weeks and 3.87 for levobupivacaine (27, 28). This estimate is also in line with what is known about the ontogeny of CYP3A4, which appears in the first week of life and reaches adult levels by early childhood (1-10 years) (29).

Data collected from 76 obese pediatric participants were used to characterize drug disposition in the presence of excess body weight. When developing the base model, various indirect measures of body size (e.g., FFM, NFM, and LBW) were evaluated and compared with the use of total body weight. Of these three indirect body size measures, all increased the objective function relative to use of total body weight. This may indicate that accounting for a patient's total body weight may be the most robust measure of accounting for differences in CL and/or V. Thus, all additional covariate relationships were assessed after inclusion of total body weight. In addition to PMA, other covariates that reached statistical significance and were included in the final model were albumin and AAG on volume of distribution. The latter is known to be the predominant binding protein for clindamycin (23), and both may contribute to variable protein binding in children. Although serum creatinine on CL also reached statistical significance, it was not included in the model because the association appeared to be most pronounced due to one influential individual, and a significant fraction of participants in the POP01 study lacked a measure of this covariate.

To assess which measure is optimal for drug dosing, individual empirical Bayesian estimates from the final model were compared between obese and non-obese participants, and further stratified by age. Statistically significant differences were only observed between obese and non-obese children for absolute V (>6-12 years and >12 years) and half-life of elimination (>6-12 years). The prolongation in half-life observed in the >6-12 years age group is likely due to an increase in V because CL was not significantly different between obese and non-obese children. When weight-scaled PK parameter estimates (CL, V) were compared, no clinically (or statistically) significant differences were noted. For V, a measure of drug distribution, this indicates that clindamycin exhibits significant uptake into excess body fat (30). This is consistent with clindamycin's log P value (2.1), which indicates preferential distribution into a more lipophilic organic phase. For CL, which is important for maintenance dosing, there was a lack of clinically (and statistically) significant differences in weight-scaled estimates between obese and non-obese patients, regardless of which body size measure was used.

Simulations were performed using the final model to assess optimal dosing in obese and non-obese children. Previously recommended intravenous dosing regimens were simulated (13): 2-6 years, 12 mg/kg every 8 hours; >6-18 years, 10 mg/kg every 8 hours. A maximum daily dose of 2700 mg/day (900 mg intravenously every 8 hours) was selected as this is the largest dose recommended in the product label for severe infections. Exposure was also simulated for a 70 kg adult receiving 600 mg intravenously every 8 hours, which was comparable to those previously reported in the literature (10). The simulations demonstrated that dosing using total body weight and a maximum dose of 900 mg resulted in comparable (20-25%) exposure to that of an adult receiving 600 mg every 8 hours. Also, there were no trends in differences in $AUC_{0\text{-}8,SS}$ as a function of albumin or AAG (Appendix Figures 36 and 37). Last, >95% of participants had simulated unbound, steady-state clindamycin concentrations that were above a minimum inhibitory concentration of 0.12 mcg/mL for at least half the dosing interval following optimal dosing.

6. Conclusions

Statistically significant differences between obese and non-obese children were only observed for volume of distribution (>6 years) and half-life of elimination (2-6 years). After volume of distribution was normalized by body weight, these differences were no longer significant. Thus, after accounting for size-based differences using total body weight, physiologic differences using age, and plasma protein concentrations, the PK of clindamycin are not further affected by obesity. Clindamycin should be dosed using total body weight in obese and non-obese children.

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APPENDIX

Table A1. Participants dropped from PK analysis.

Study	SUBJID	Reason for Dropping
POP01	Redact	Oral administration
POP01	Redact	Oral administration
POP01	Redact	Oral administration
POP01	Redact	Oral and intravenous administration
POP01	Redact	Oral administration
POP01	Redact	Oral and intravenous administration
POP01	Redact	Oral administration
POP01	Redact	Oral and intravenous administration
POP01	Redact	Oral and intravenous administration
POP01	Redact	Oral and intravenous administration
POP01	Redact	Oral administration
POP01	Redact	Oral administration
POP01	Redact	Oral administration
POP01	Redact	Oral administration
POP01	Redact	Oral and intravenous administration
POP01	Redact	Oral and intravenous administration
POP01	Redact	Oral and intravenous administration

POP01	Redact	Oral administration
POP01	Redact	Oral administration
POP01	Redact	Oral administration
POP01	Redact	Oral administration
POP01	Redact	Oral administration
POP01	Redact	Oral and intravenous administration
POP01	Redact	Oral administration
POP01	Redact	Oral and intravenous administration
POP01	Redact	Oral and intravenous administration
CLIN01	Redact	Participant does not contribute any PK data

Table A2. Samples dropped from PK analysis.

Study	SUBJID	TALD	DV	Reason for Dropping
POP01	Redacted	10.38	14775.2	Unlikely sample timing
STA01	Redacted	90.32	1688.55	Unlikely sample timing
STA01	Redacted	1.17	10066.1	Scavenged sample
STA01	Redacted	4.58	6277.7	Scavenged sample
STA01	Redacted	12.47	2931.7	Scavenged sample
STA01	Redacted	44.15	334.4	Scavenged sample
STA01	Redacted	10.25	1933.1	Scavenged sample
STA01	Redacted	10.25	1801.05	Scavenged sample
STA01	Redacted	7.58	3824.75	Scavenged sample
STA01	Redacted	0.5	3274.43	Scavenged sample
CLN01	Redacted	4.25	14366.9	Scavenged sample
CLN01	Redacted	12.43	1621.1	Scavenged sample

Figure A1. Histogram of gestational age in merged dataset. Gestational age set to 40 weeks for all patients in POP01 with a postnatal age >120 days.

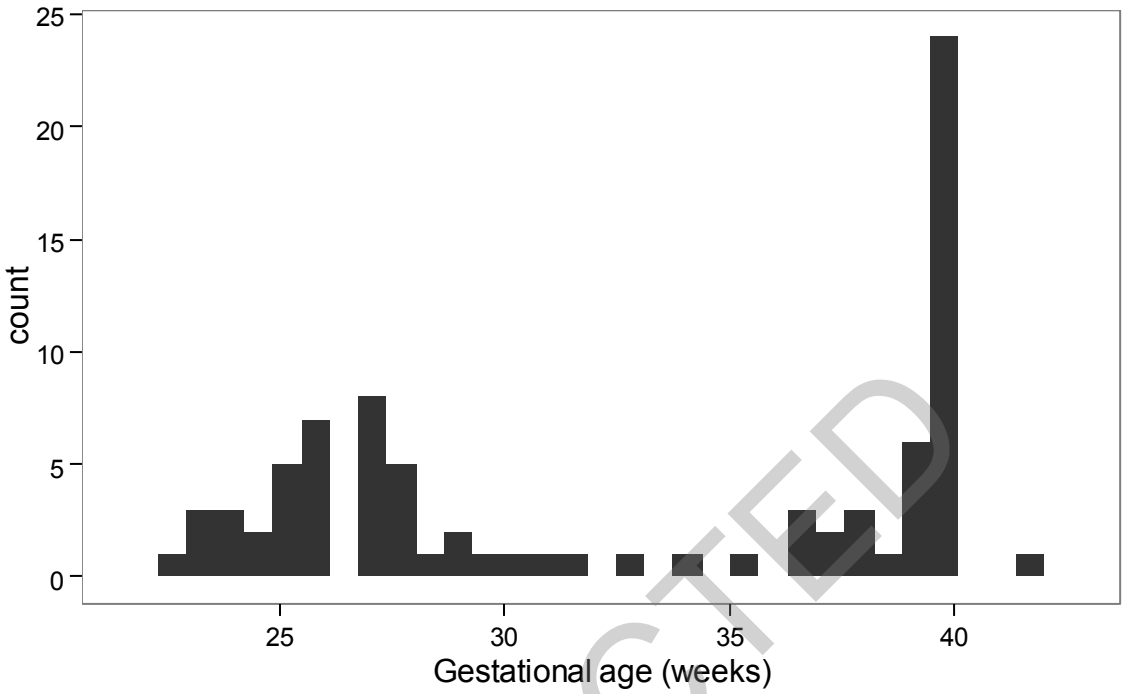

Figure A2. Histogram of postnatal age in the merged dataset.

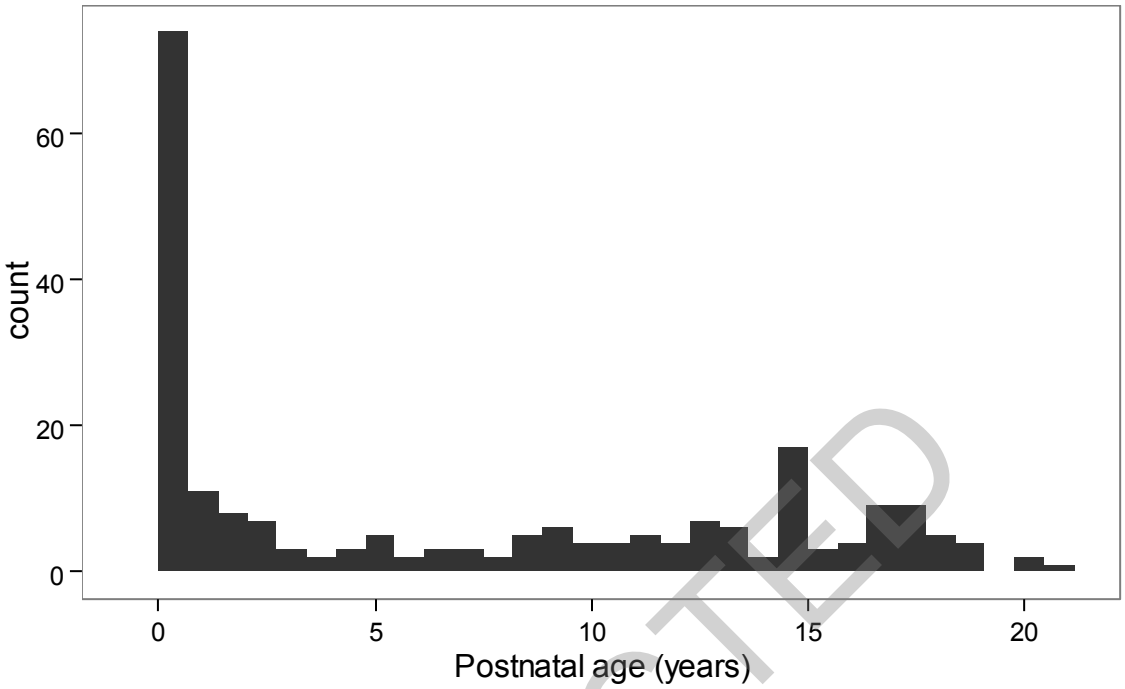

Figure A3. Histogram of weight in the merged dataset.

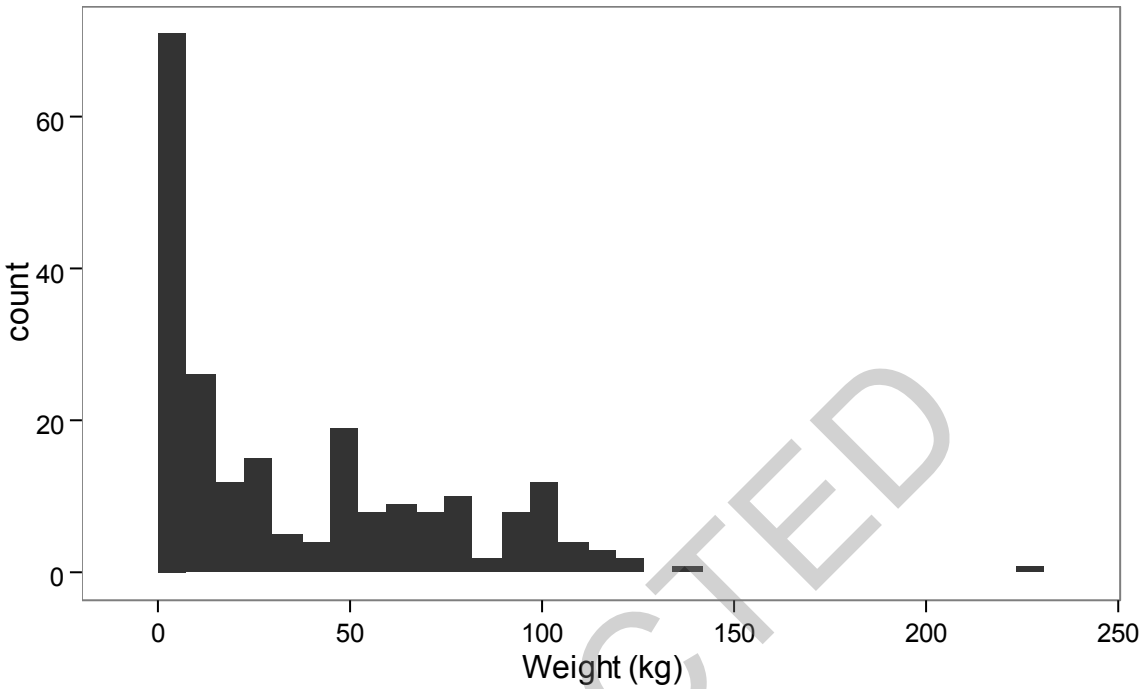

Figure A4. Histogram of albumin in the merged dataset.

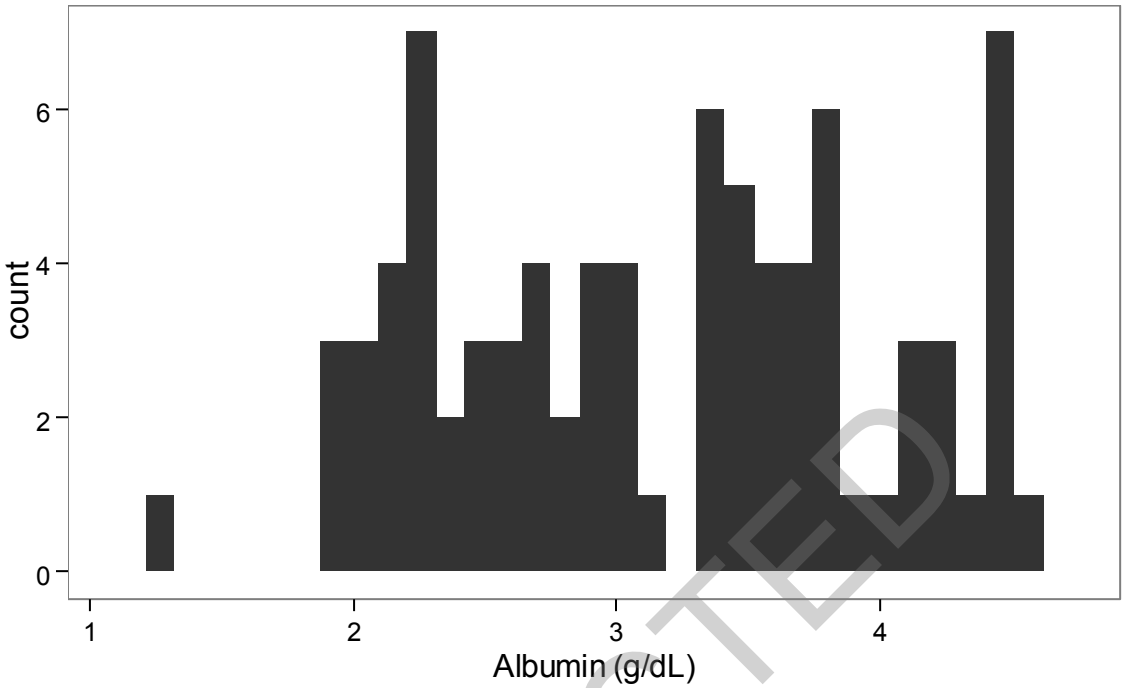

Figure A5. Histogram of α-1 acid glycoprotein in the merged dataset.

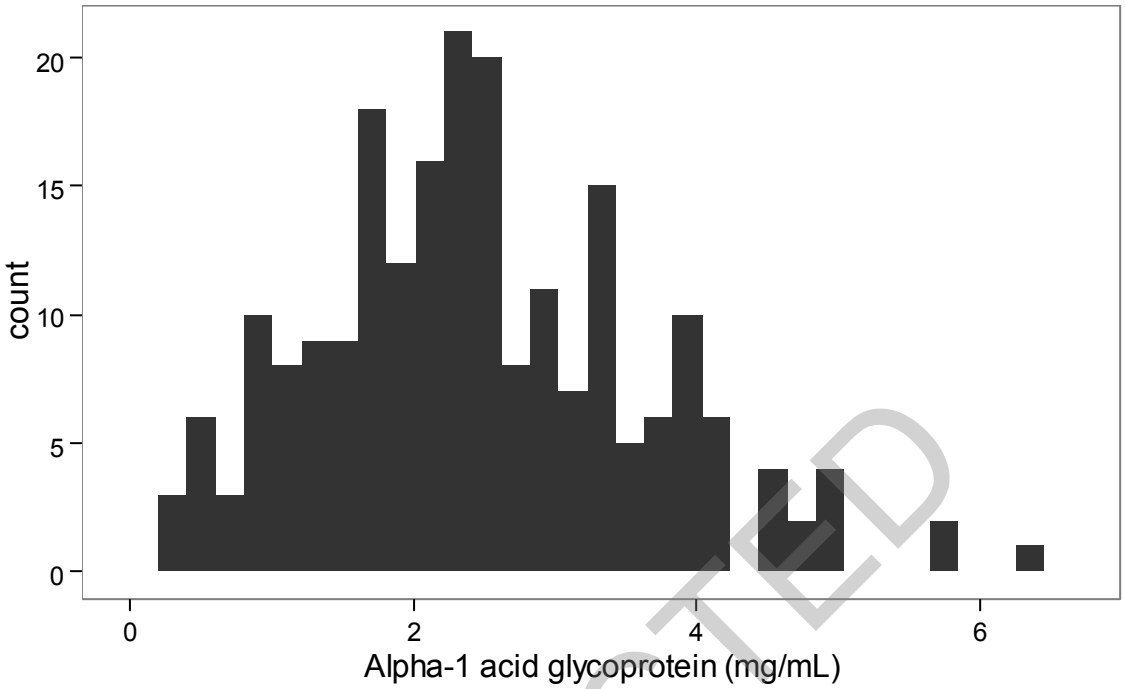

Figure A6. Histogram of serum creatinine in the merged dataset.

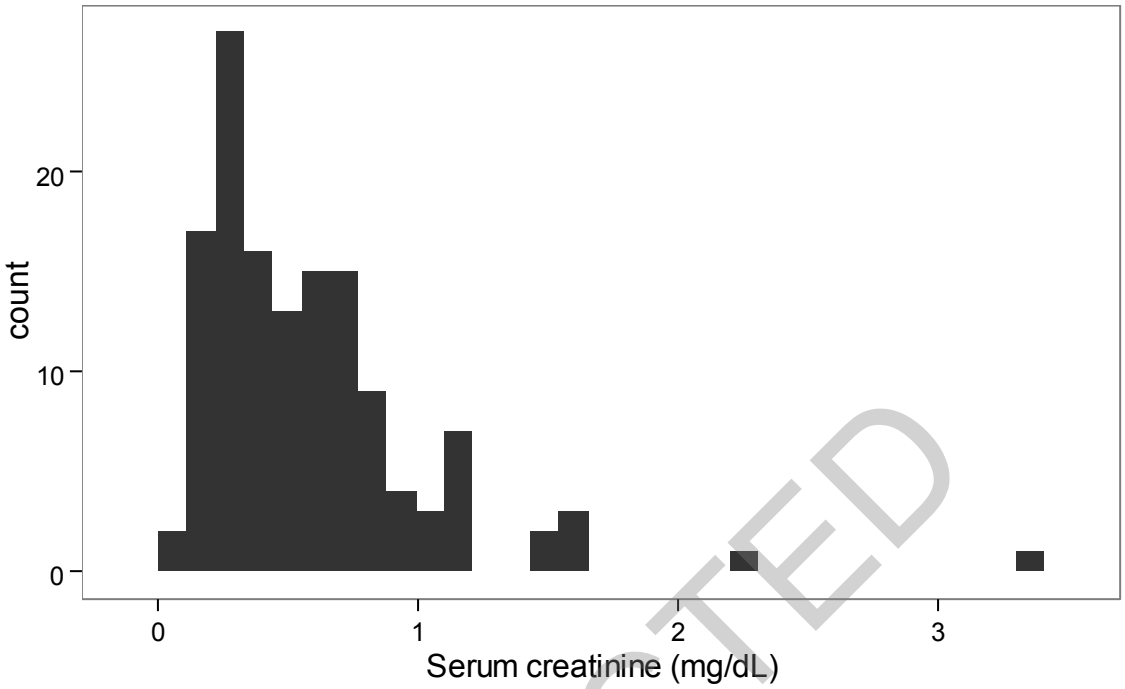

Figure A7. Histogram of alanine aminotransferase in the merged dataset.

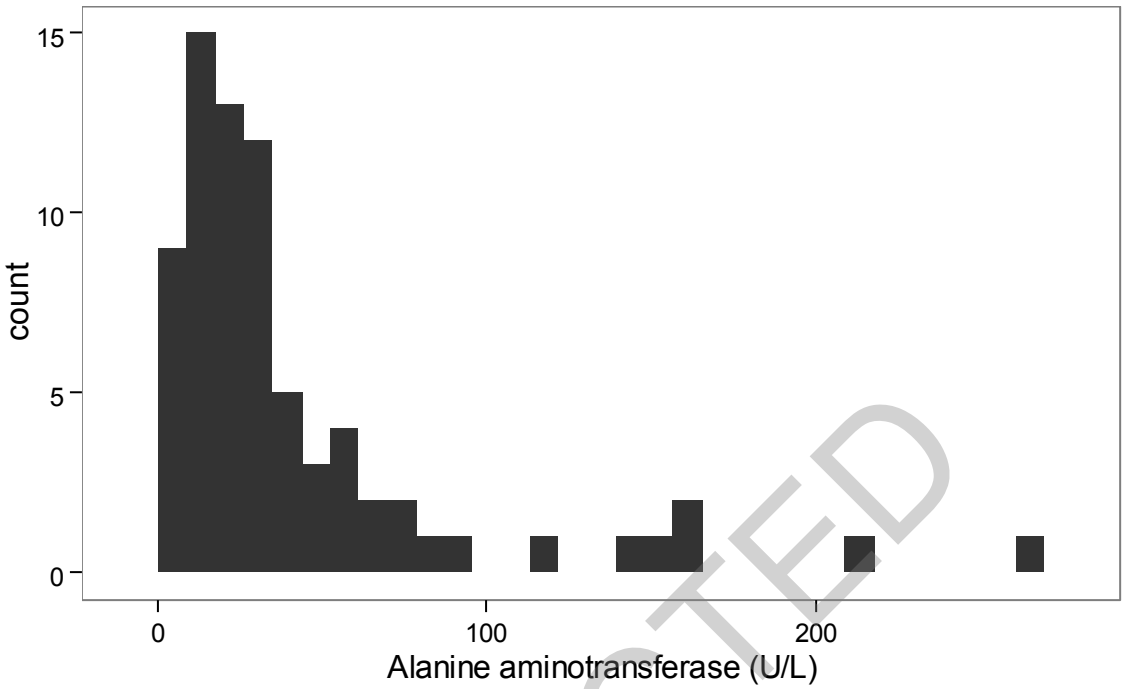

Figure A8. Histogram of aspartate aminotransferase in the merged dataset.

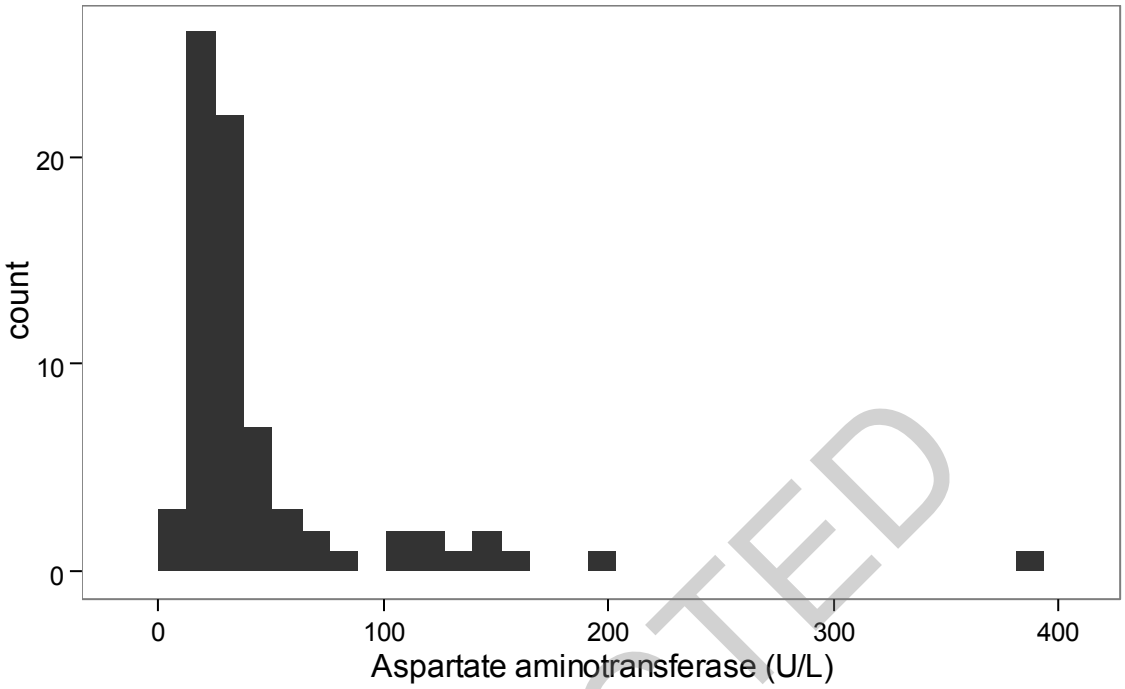

Figure A9. Concentration versus time data for the POP01 data only.

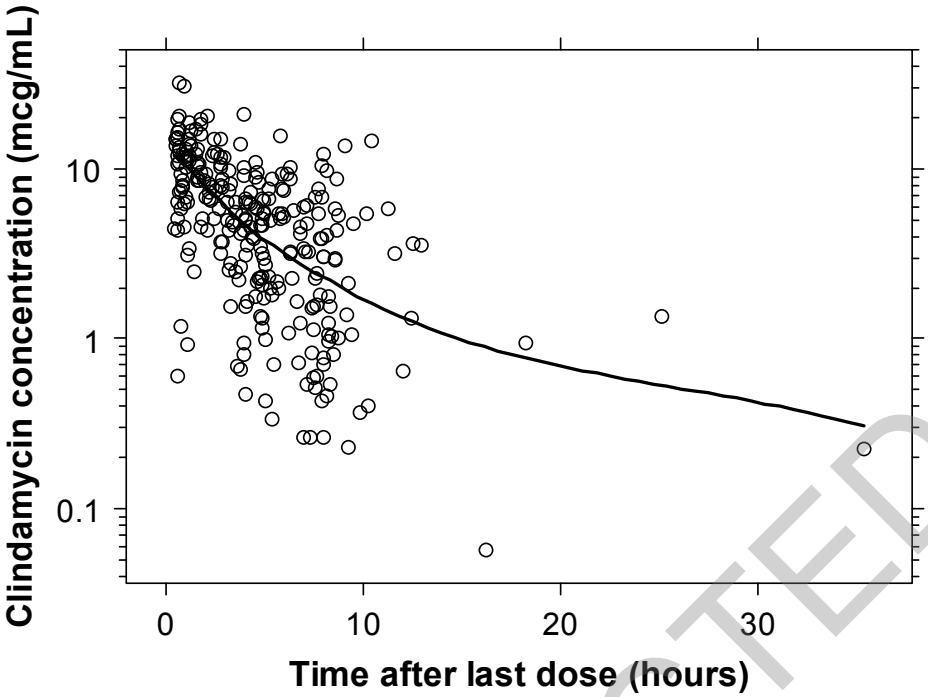

Figure A10. Concentration versus time data for the STA01 data only.

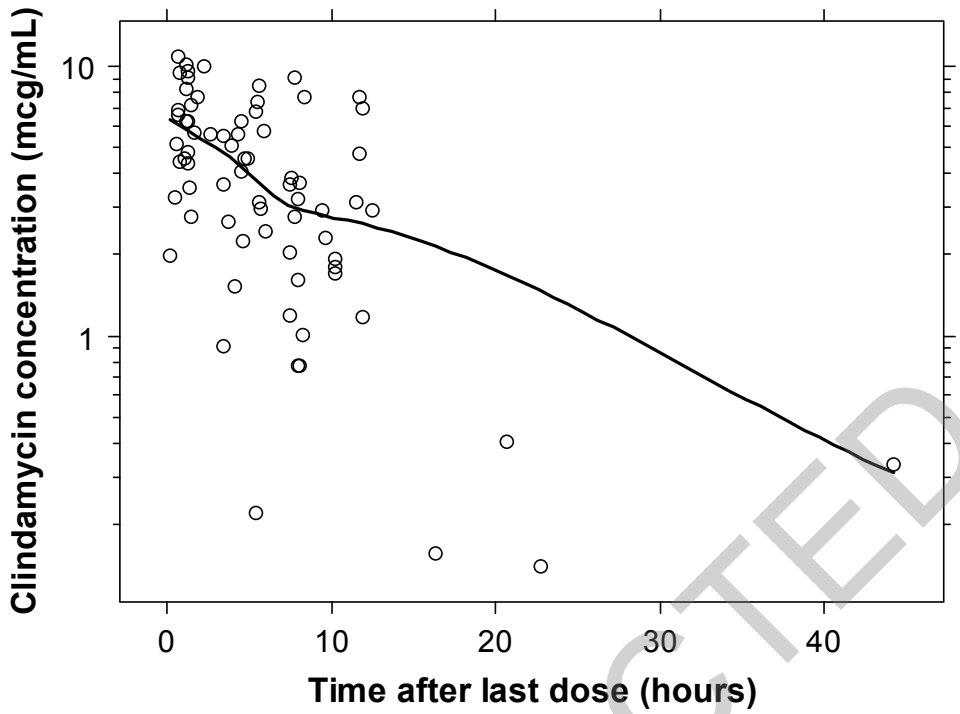

Figure A11. Concentration versus time data stratified by participant number from the CLN01 trial.

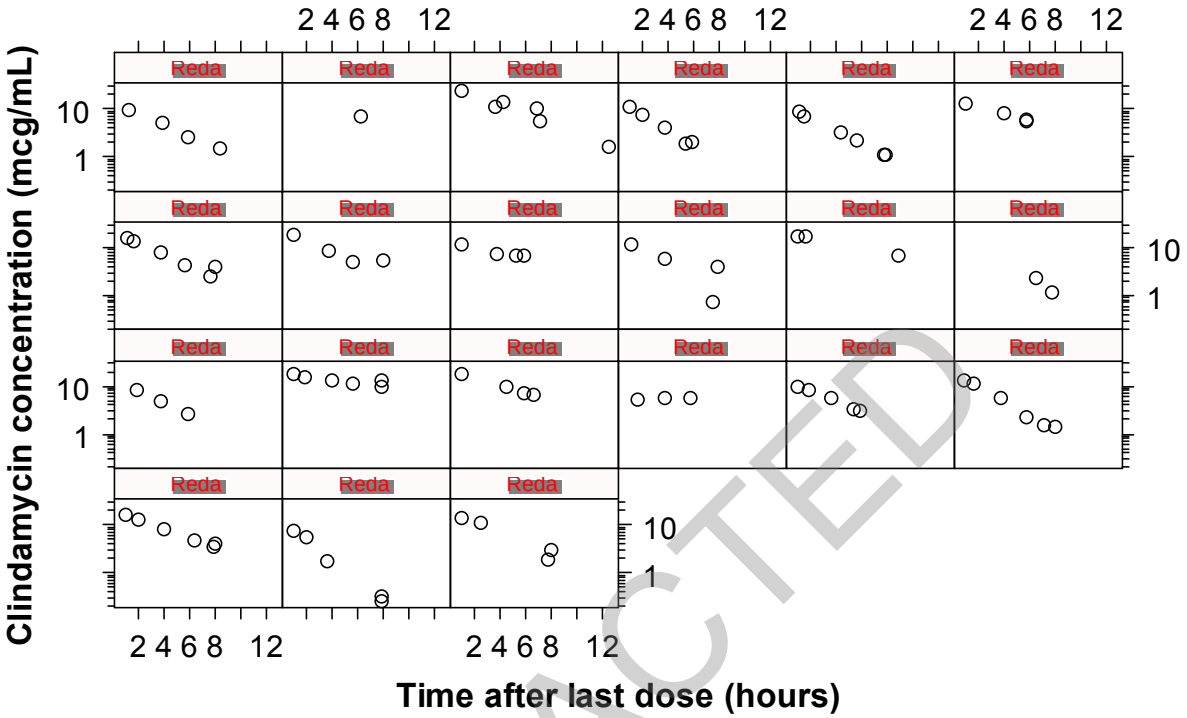

Figure A12. Population and individual predictions vs. observation for the base model.

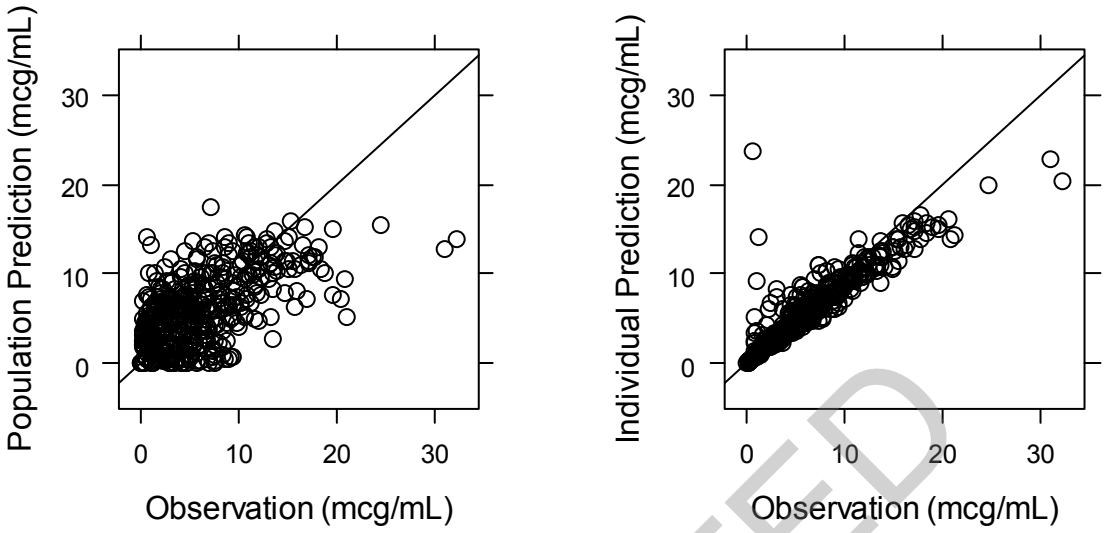

Figure A13. Conditional weighted residuals vs. time and population predictions for the base model.

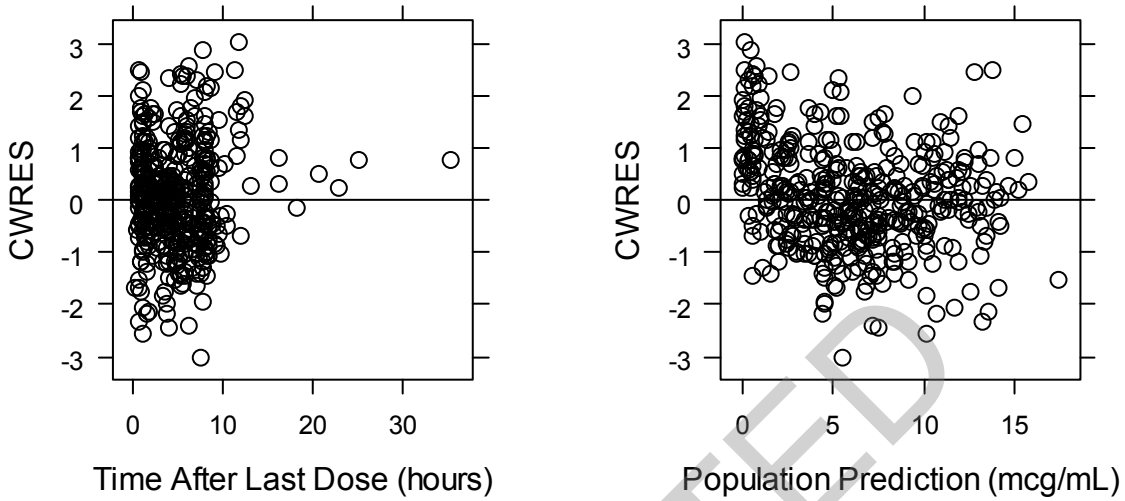

Figure A14. ETA (CL) vs. serum creatinine for the base model.

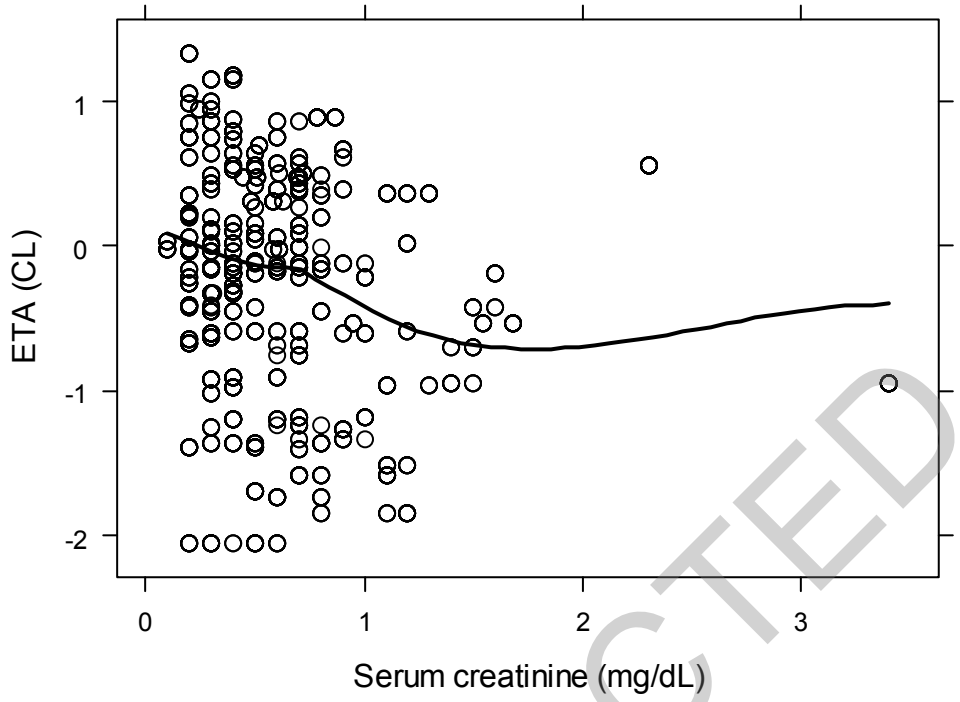

Figure A15. ETA (CL) vs. alanine aminotransferase for the base model.

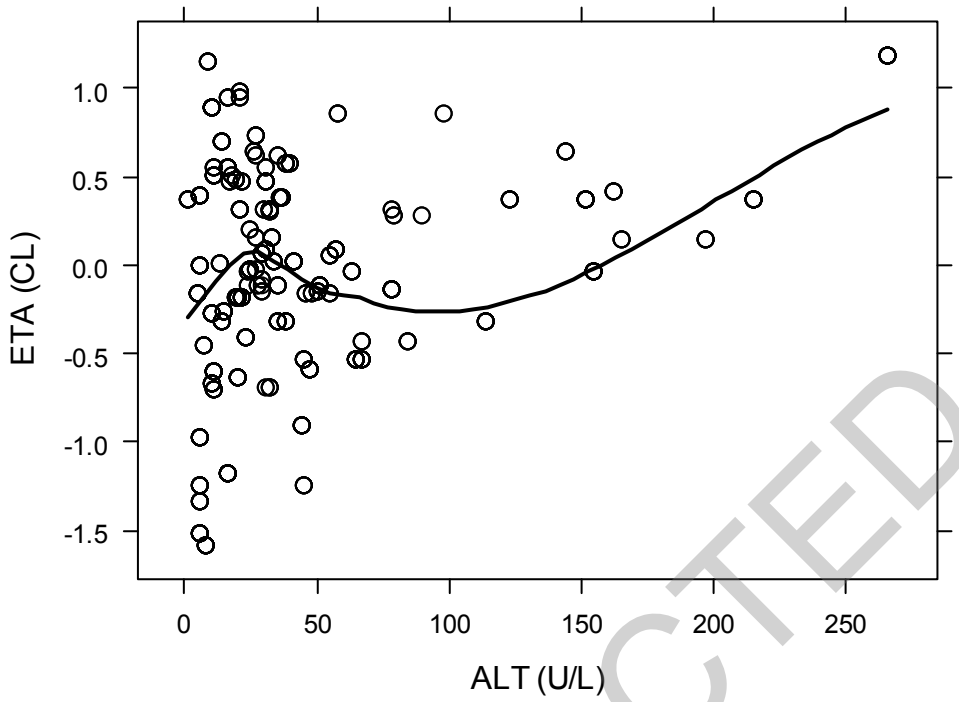

Figure A16. ETA (CL) vs. aspartate aminotransferase for the base model.

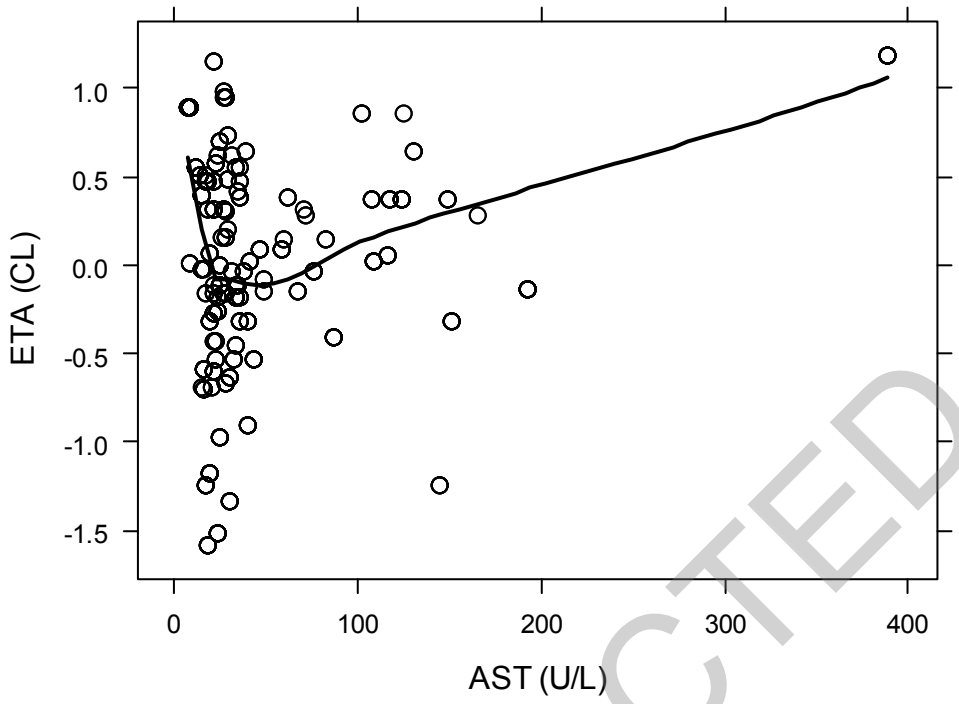

Figure A17. ETA (CL) vs. alpha-1 acid glycoprotein for the base model.

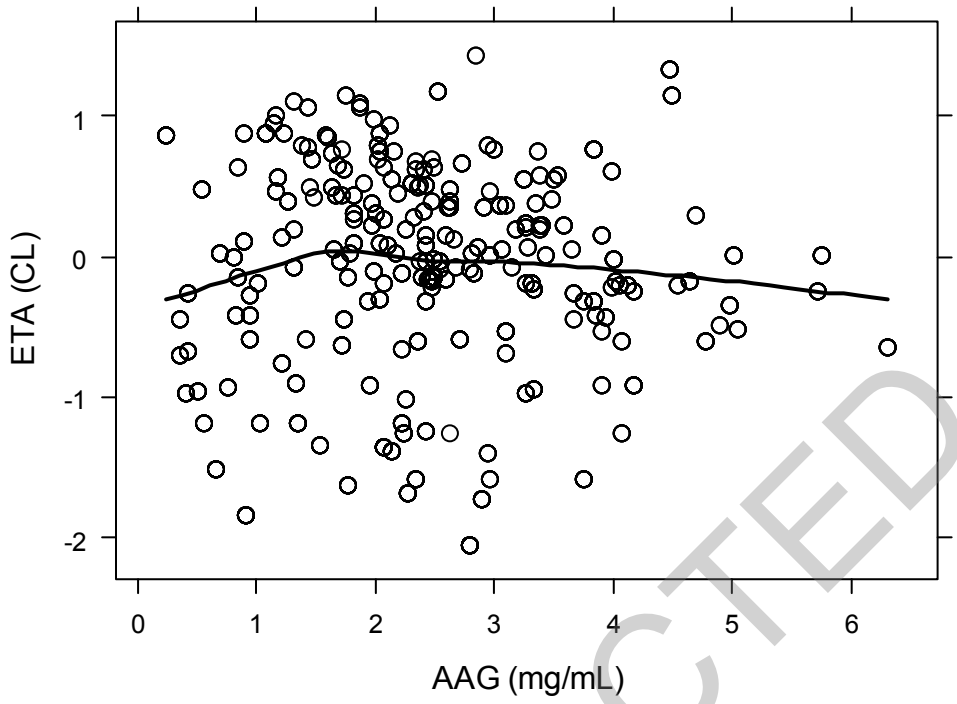

Figure A18. ETA (CL) vs. albumin for the base model.

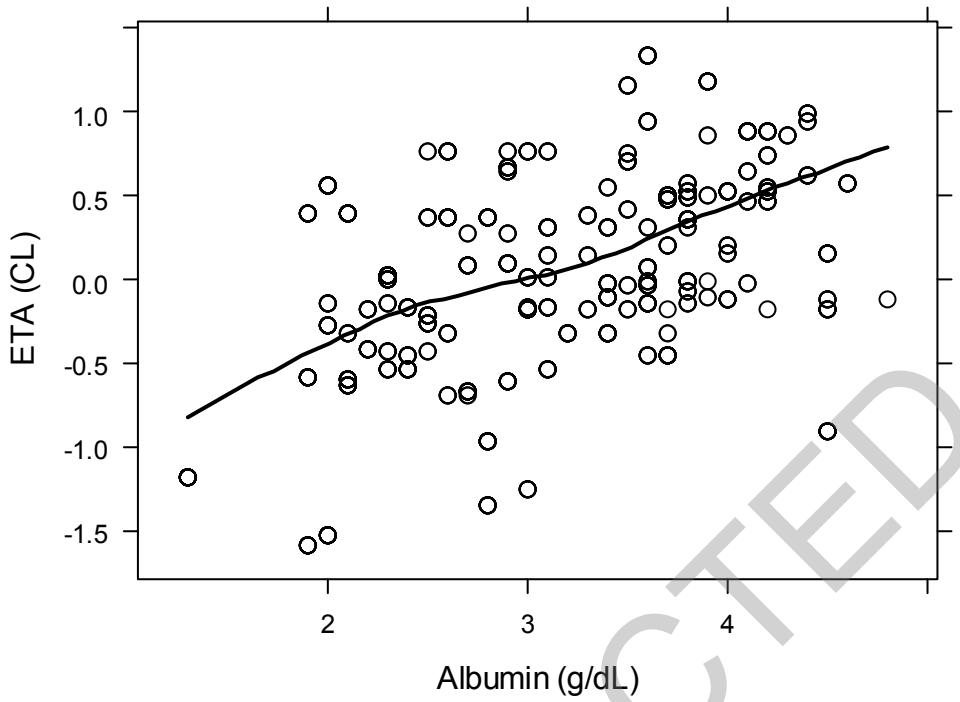

Figure A19. ETA (V) vs. serum creatinine for the base model.

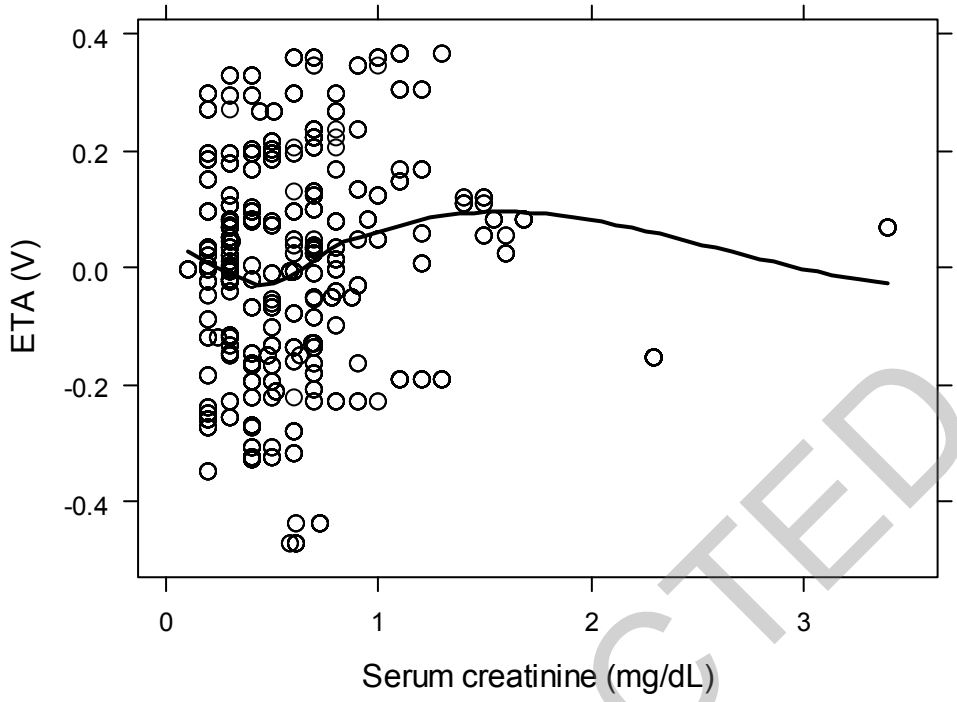

Figure A20. ETA (V) vs. alanine aminotransferase for the base model.

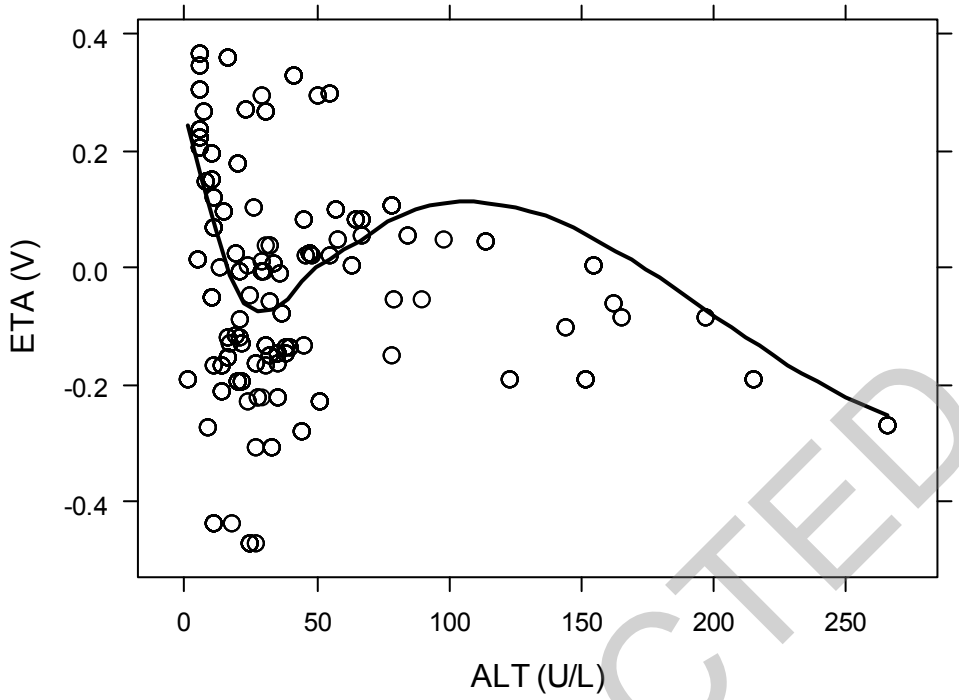

Figure A21. ETA (V) vs. aspartate aminotransferase for the base model.

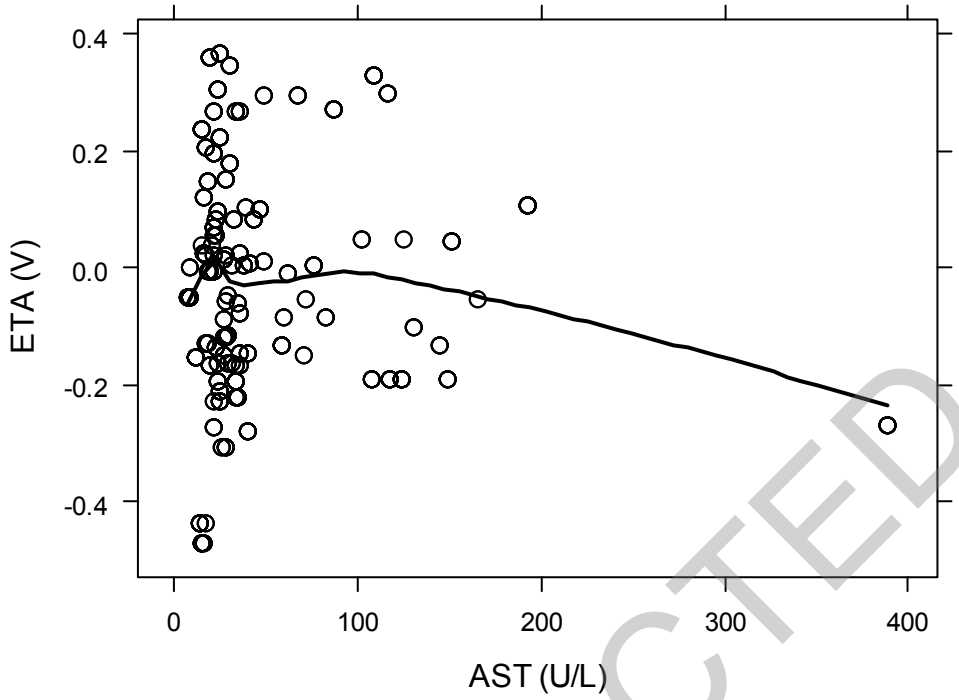

Figure A22. ETA (V) vs. alpha-1 acid glycoprotein for the base model.

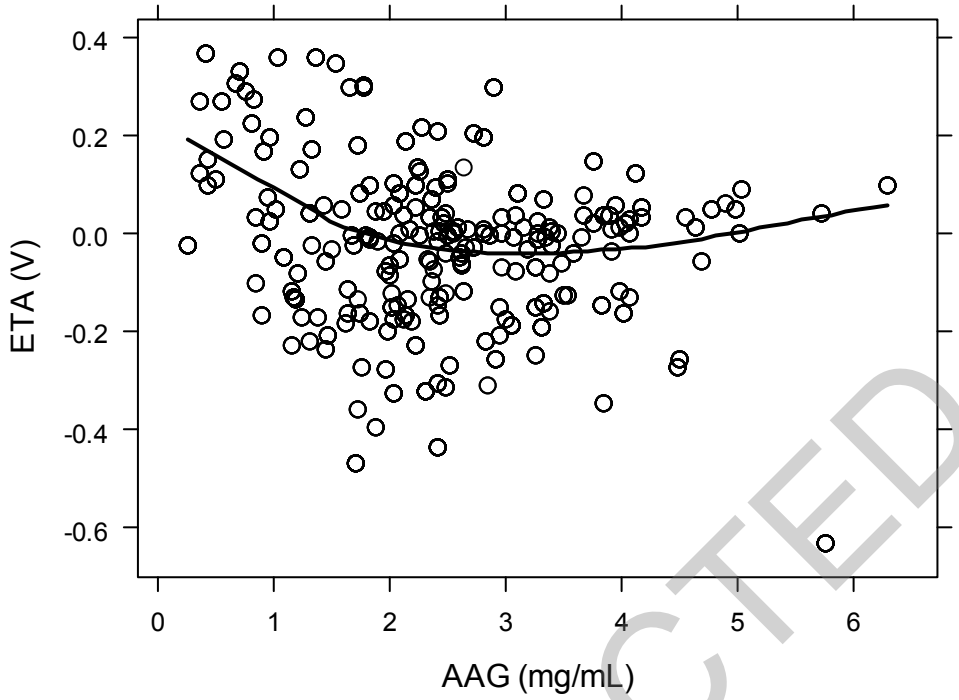

Figure A23. ETA (V) vs. albumin for the base model.

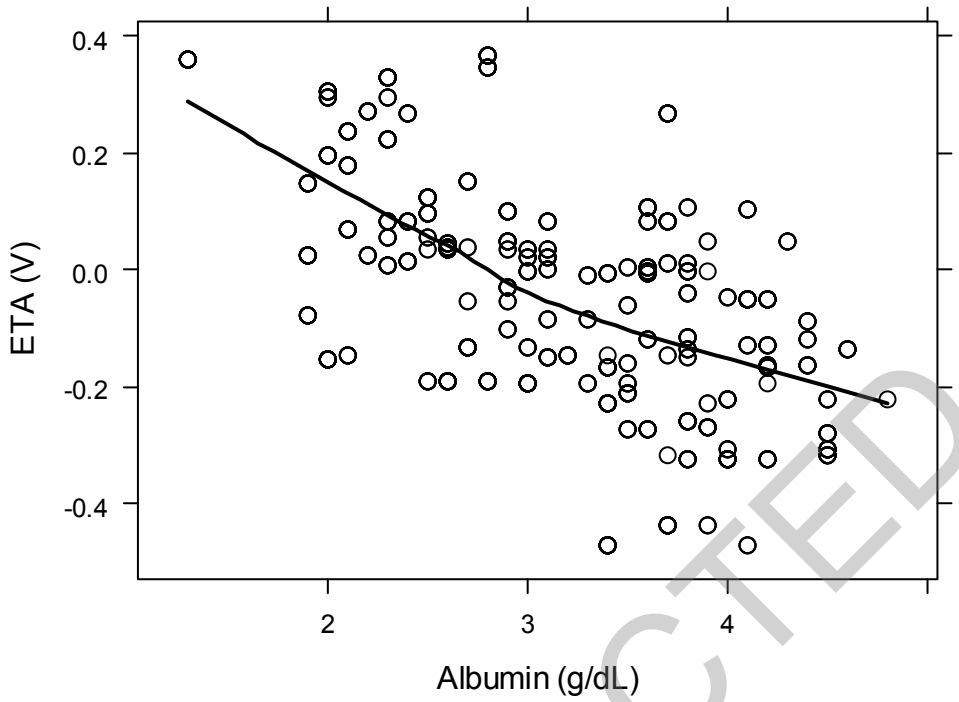

Figure A24. CL vs. albumin for the base model.

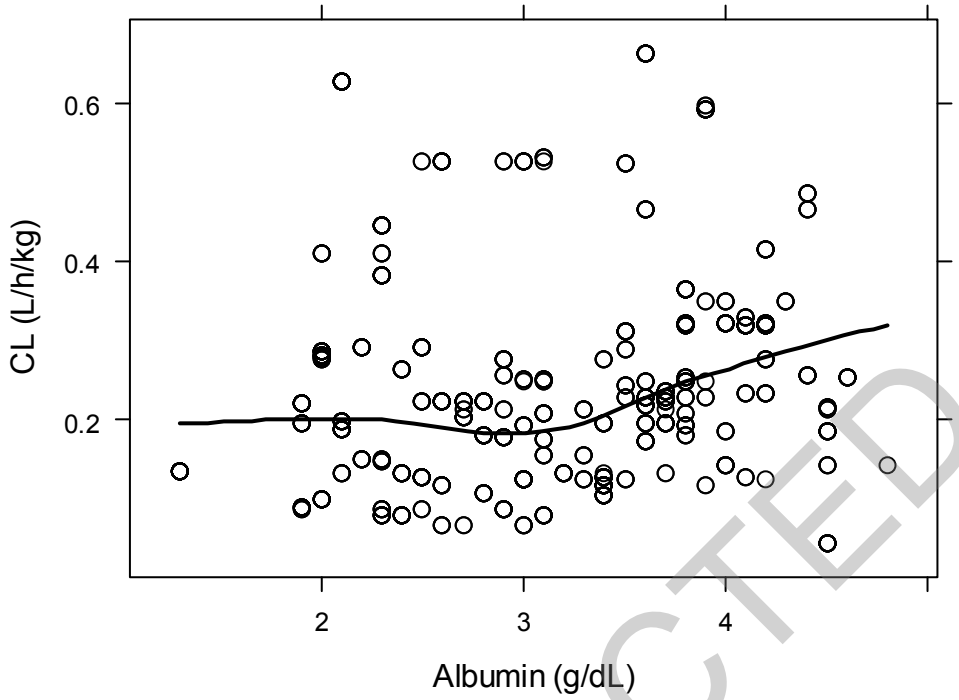

Figure A25. CL vs. alpha-1 acid glycoprotein for the base model.

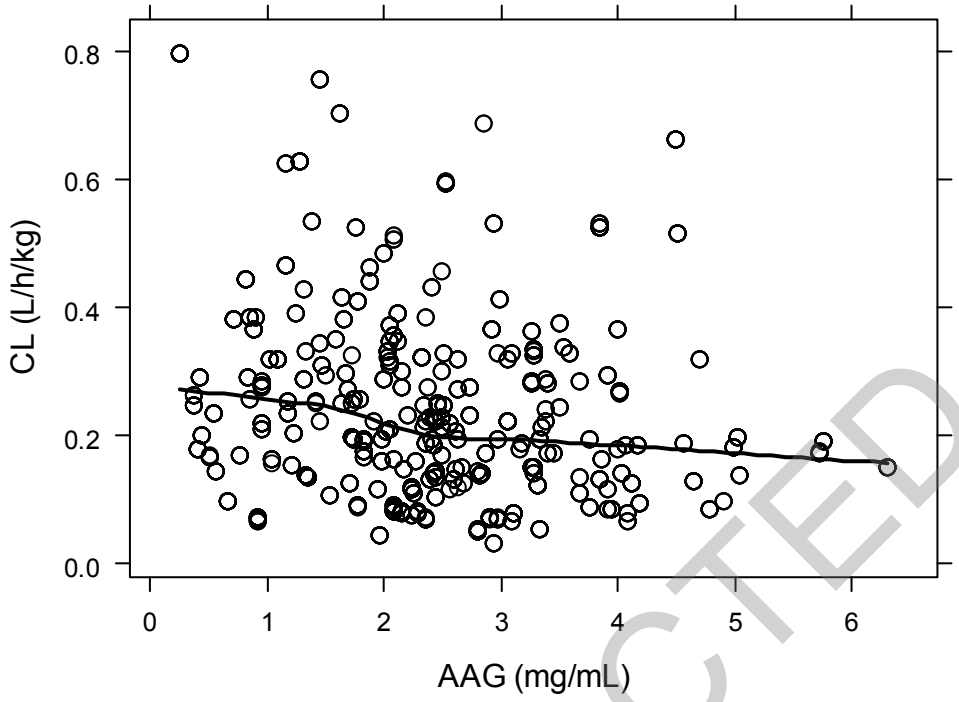

Figure A26. V vs. albumin for the base model.

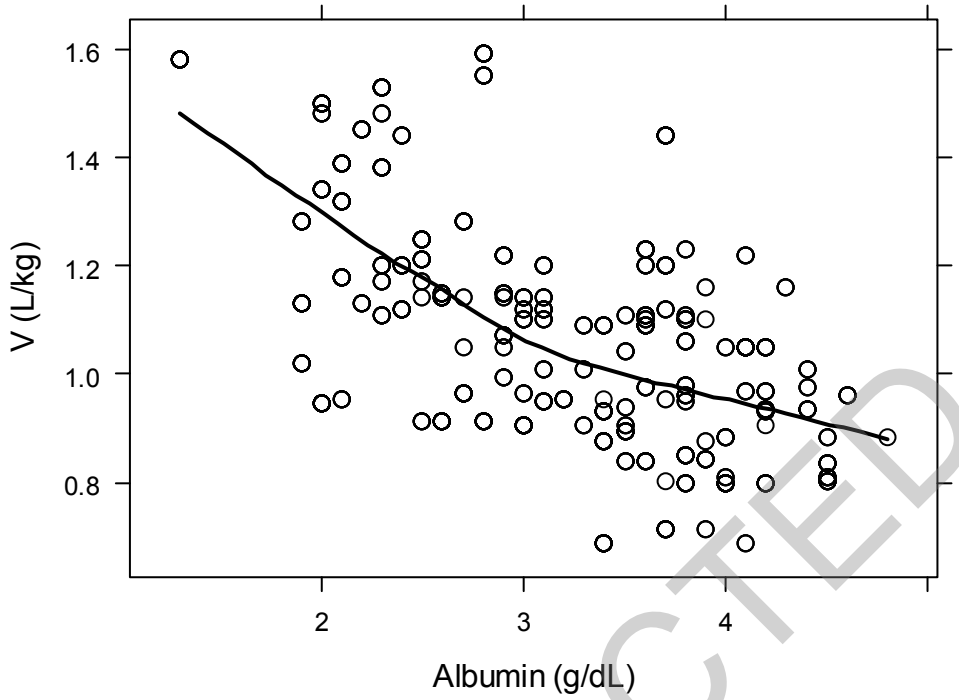

Figure A27. V vs. alpha-1 acid glycoprotein for the base model.

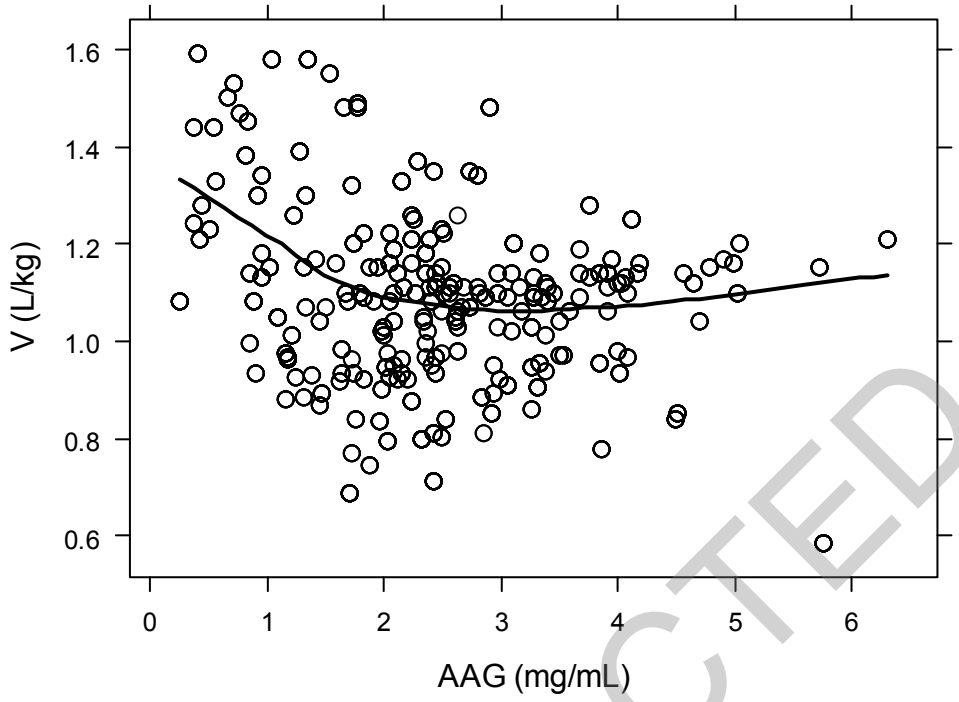

Figure A28. Postmenstrual age vs. albumin in the merged dataset.

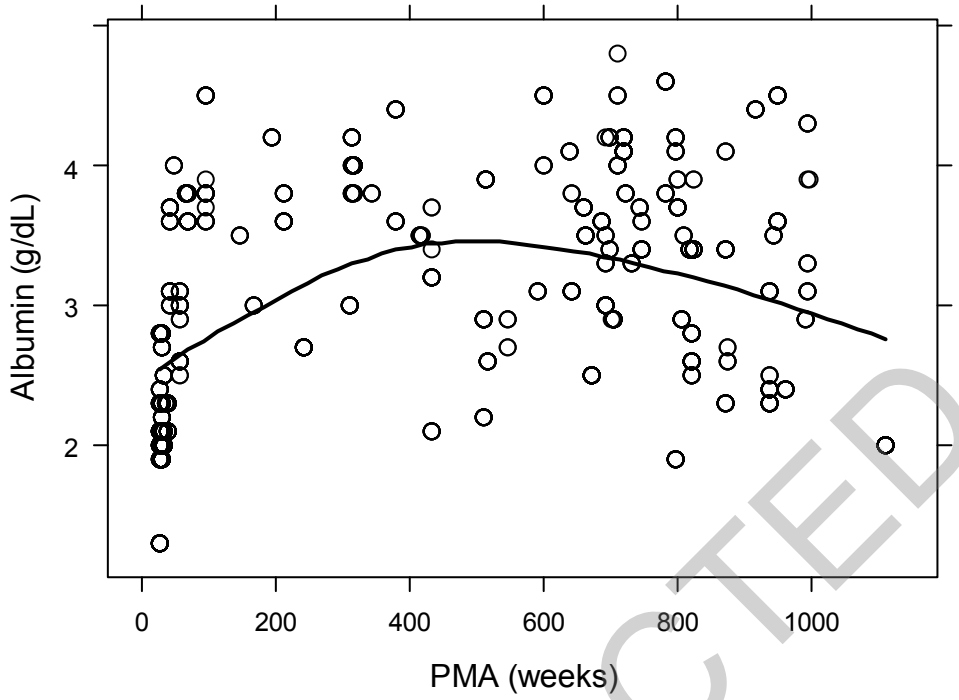

Figure A29. Postmenstrual age vs. alpha-1 acid glycoprotein in the merged dataset.

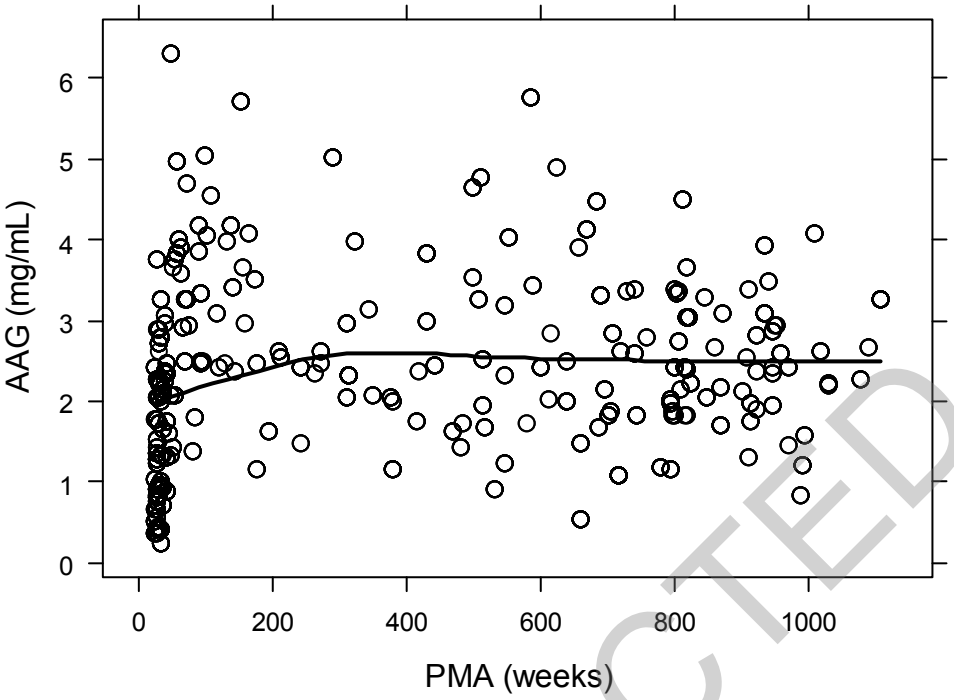

Figure A30. ETA (CL) vs. postmenstrual age for final model.

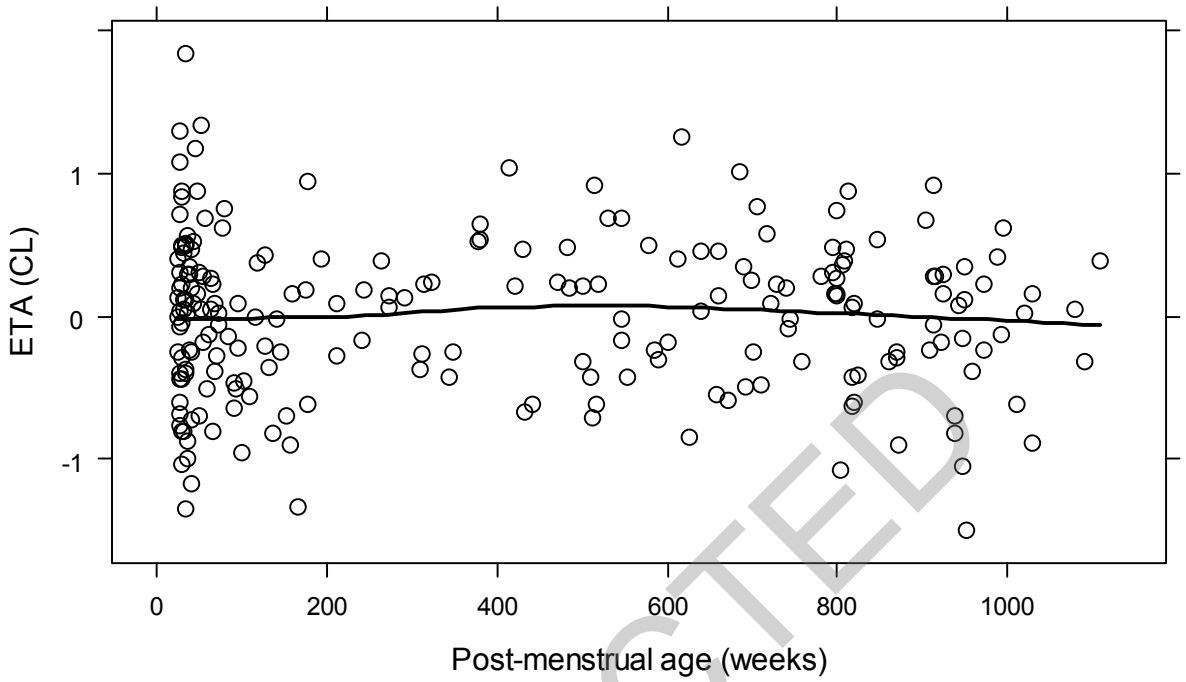

Figure A31. V (L/kg) vs. alpha-1 acid glycoprotein (mg/mL) for final model.

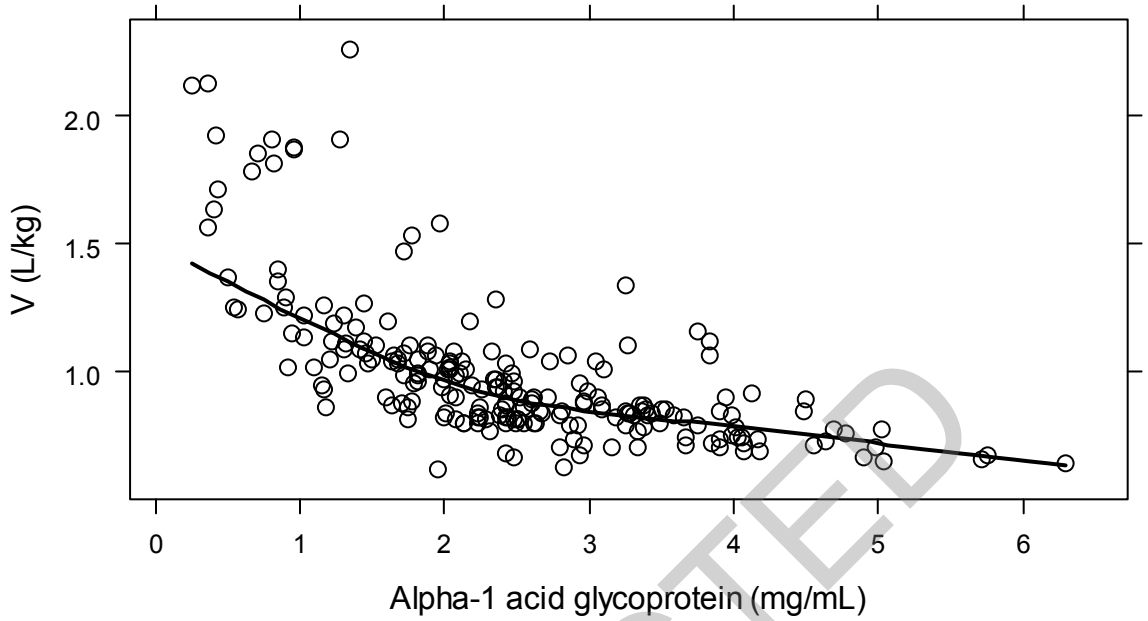

Figure A32. V (L/kg) vs. albumin (g/dL) for final model.

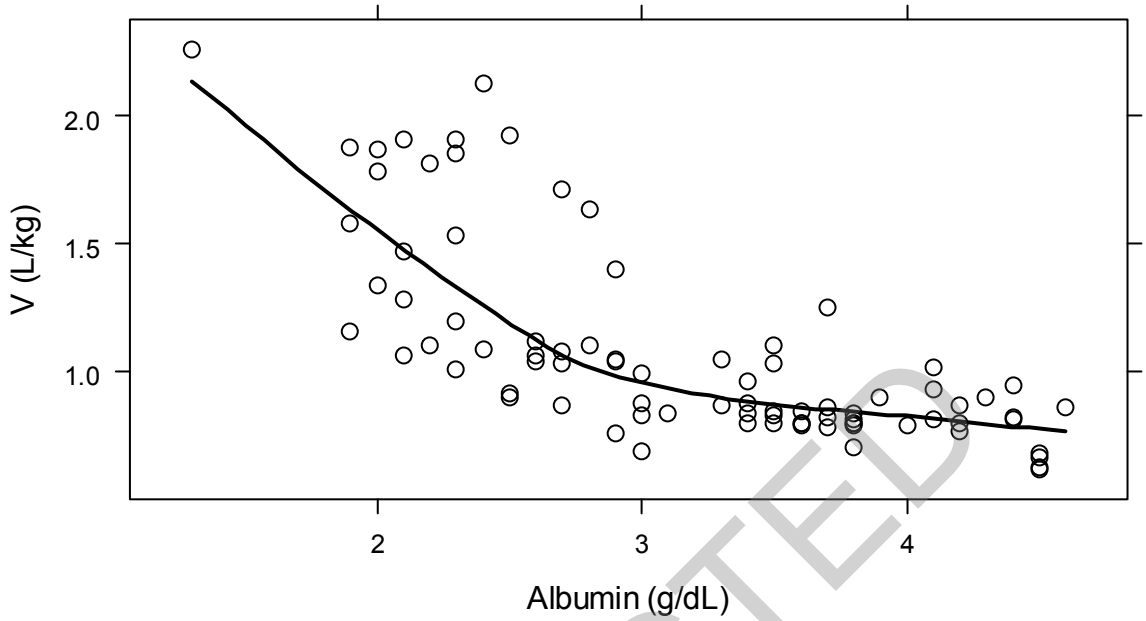

Figure A32. Dose amount in virtual participants >2-6 years of age receiving 12 mg/kg. Each participant is plotted only once.

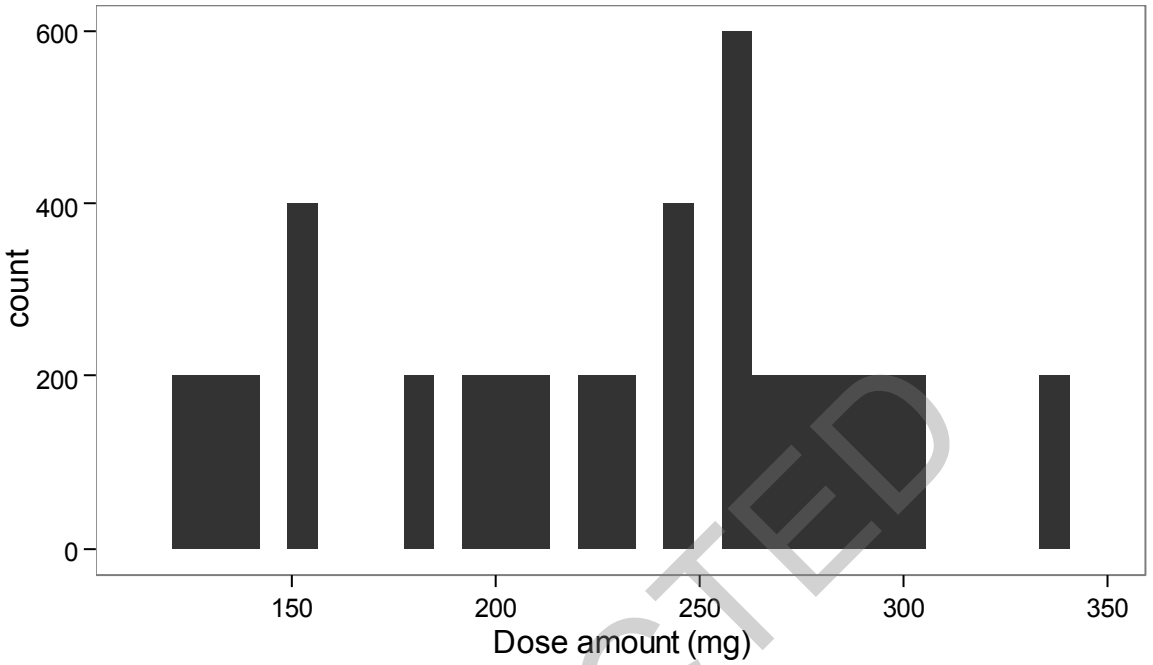

Figure A33. Dose amount in virtual participants >6-12 years of age receiving 10 mg/kg. Each participant is plotted only once.

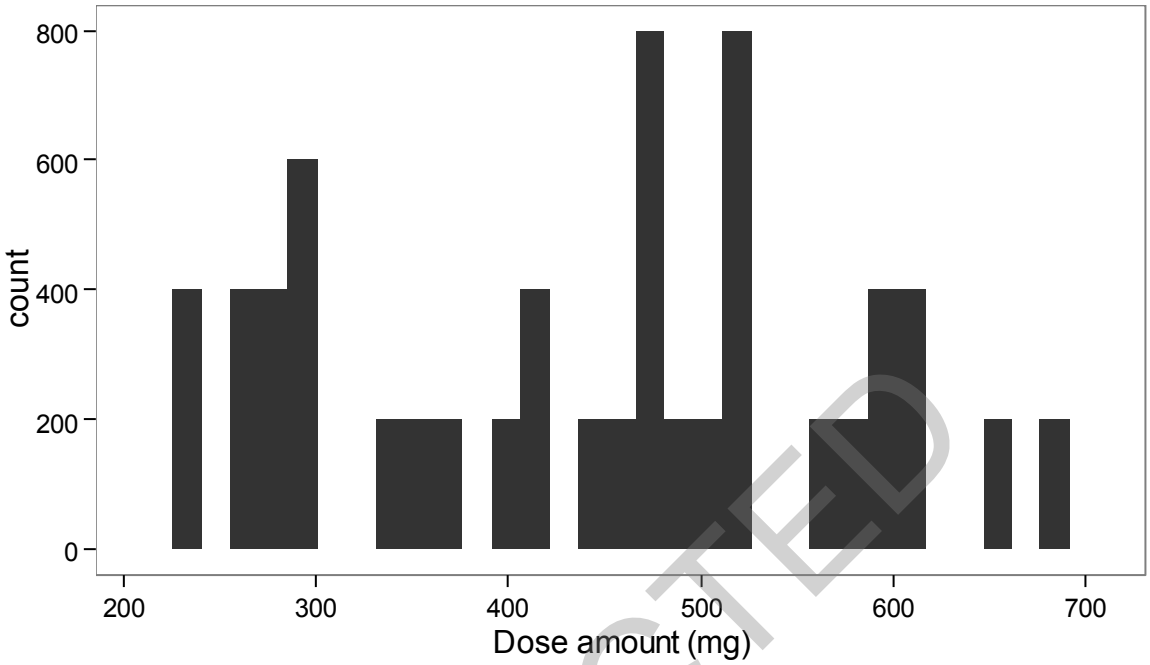

Figure A34. Dose amount in virtual participants >12 years of age receiving 10 mg/kg. Each participant is plotted only once.

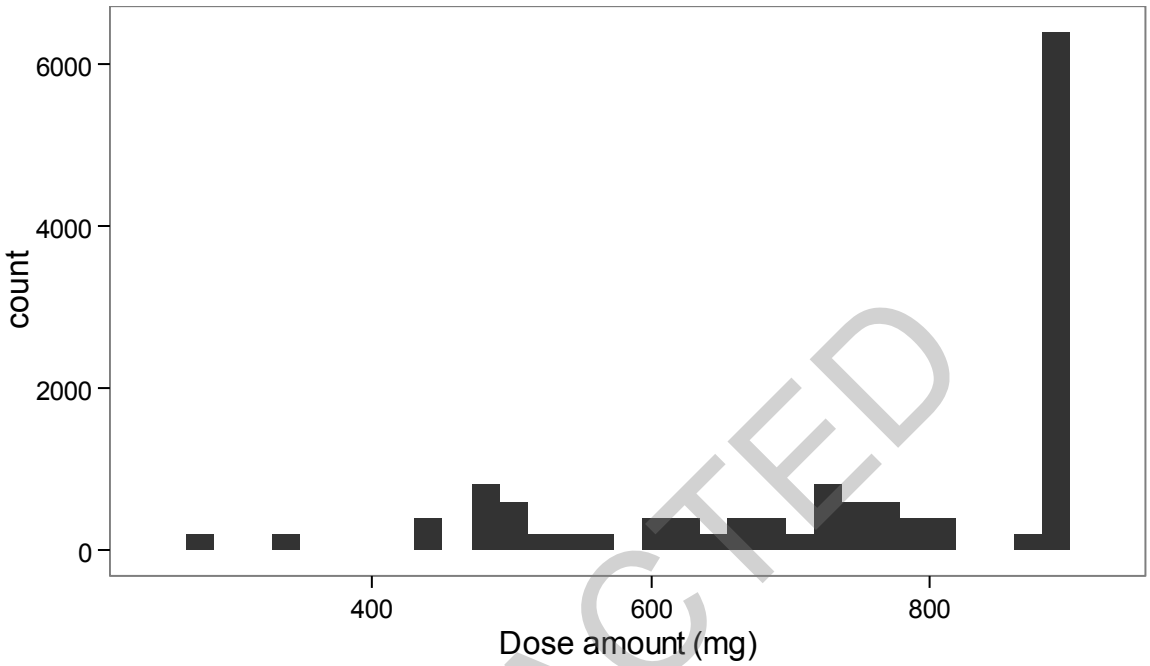

Figure A35. Simulated steady-state $C_{MIN,SS}$ vs. weight and stratified by age group. The solid blue line denotes the loess curve.

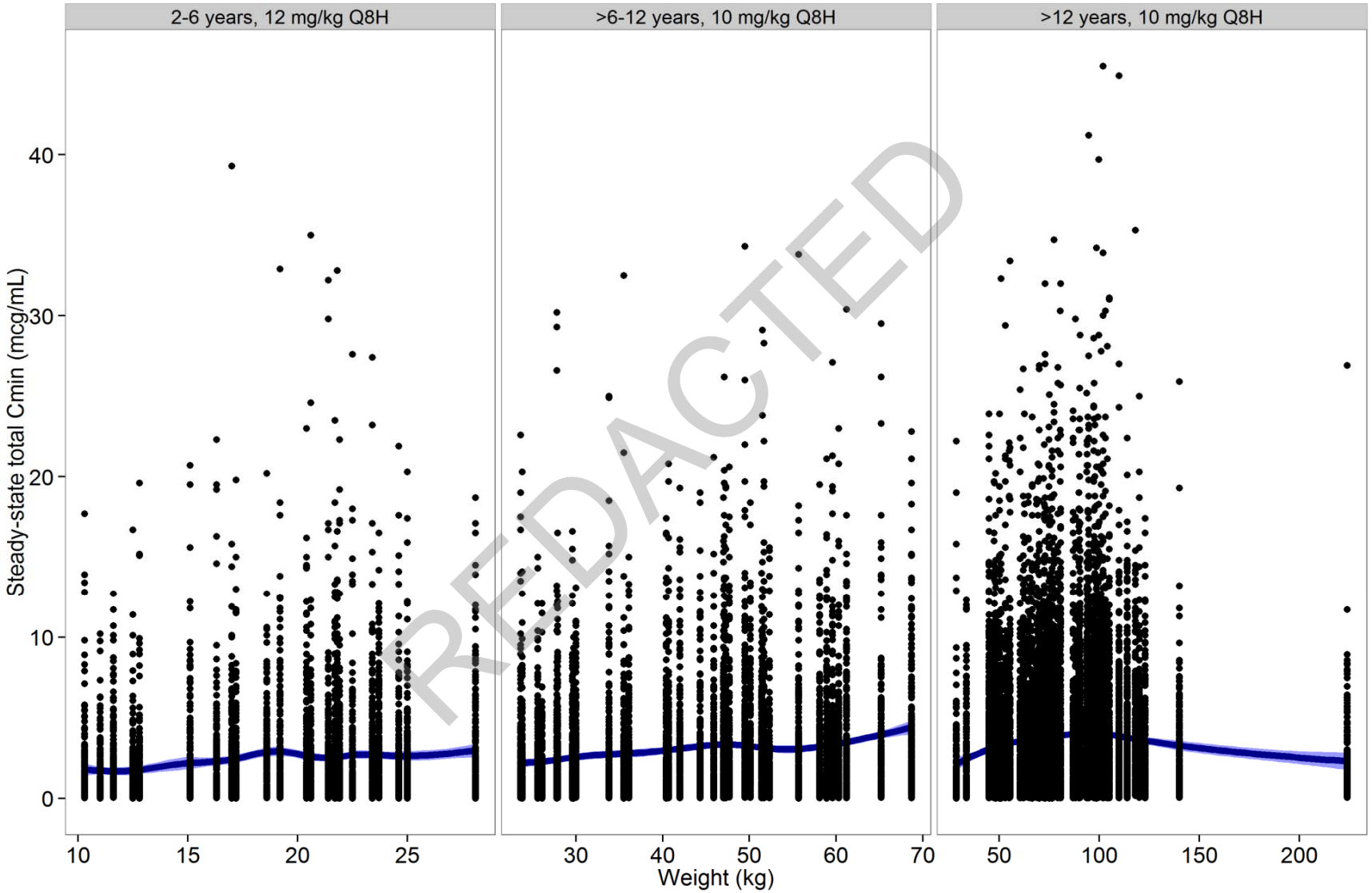

Figure A36. Simulated steady-state $AUC_{0\text{-}8,SS}$ as a function of albumin. The solid blue line denotes the loess curve.

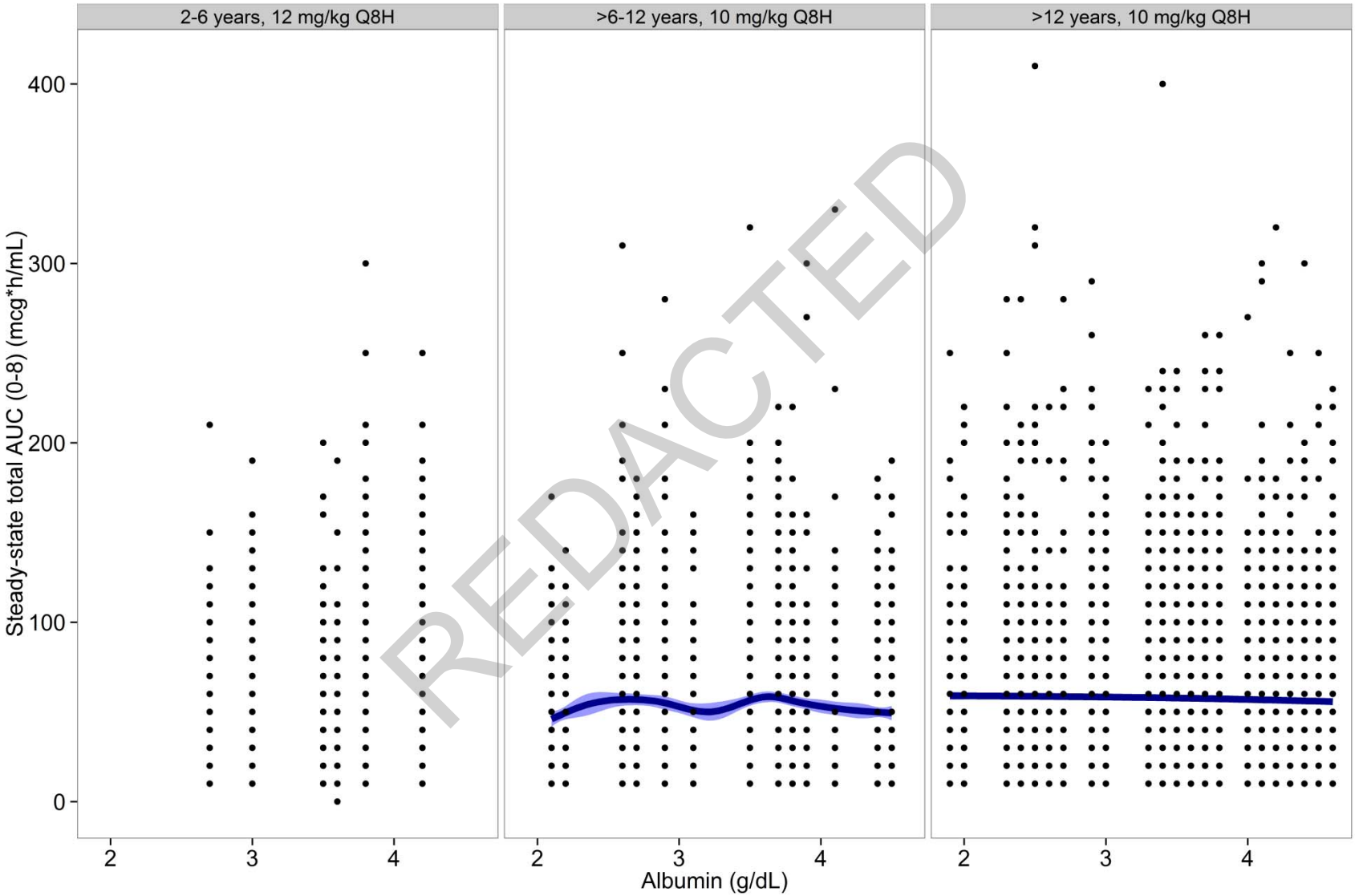

Figure A37. Simulated steady-state $AUC_{0\text{-}8,SS}$ as a function of AAG. The solid blue line denotes the loess curve.