

SUPPLEMENTARY TABLES AND FIGURES

SUPPLEMENTARY FIGURE LEGENDS

Figure S1. Population (A) and individual (B) predictions versus observations and conditional weighted residuals (CWRES) versus time (C) and population predictions (D) for the combined dataset

Figure S2. Visual predictive check for the final model using combined dataset (A) and stratified by study (B-D). Dashed lines represent percentiles (5th, 50th, 95th) of observed data. Solid lines represent percentiles (5th, 50th, 95th) of simulated data. The shaded region denotes the 90% prediction interval of the simulated data.

Table S1. PK sampling times in the CLN01 trial^a

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

IV: intravenous.

^aTime starts at end of flush after the 30-minute infusion.

^bPriority samples.

Table S2. Research-only sample collection scheme for clindamycin following intravenous administration for POP01 trial

Sample Name	Dosing Interval (hours)		
	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

^aTime=0: end of infusion; sample collected after flush ends.

^bPre: within 1 hour prior to next administration of study drug.

Table S3. 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 S4. Optimal plasma sampling collection windows for study drug by dosing interval in STA01 trial

Sample #	Dosing Interval (hours)		
	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.

Table S5. Summary of population PK model development

Description	Population Model	OFV	Δ OFV ^a
<i>Univariable analysis</i>			
Base model	$CL = 10.2 \cdot (WT/70)^{0.75}$; $V = 77.1 \cdot (WT/70)$	7157.9	-
Post-menstrual age on CL	$CL = 14.6 \cdot (WT/70)^{0.75} \cdot (PMA^{3.39} / (41.1 + PMA^{3.39}))$	7042.3	-115.6
α -1 acid glycoprotein on V	$V = 66.7 \cdot (WT/70) \cdot (AAG/2.4)^{-0.47}$	7126.2	-31.7
Albumin on V	$V = 73.6 \cdot (WT/70) \cdot (ALB/3.3)^{-1.04}$	7138.1	-19.8
Total bilirubin on CL	$CL = 10.5 \cdot (WT/70)^{0.75} \cdot (TBIL/0.8)^{-0.23}$	7144.8	-13.1
Serum creatinine on CL	$CL = 10.2 \cdot (WT/70)^{0.75} \cdot (SCR/0.5)^{-0.36}$	7145.2	-12.7
Albumin on CL	$CL = 10.7 \cdot (WT/70)^{0.75} \cdot (ALB/3.3)^{0.93}$	7149.2	-8.7
Obese Status ^b on V	$V = 84.3 \cdot (WT/70) \cdot 0.73^{OBESE}$	7149.9	-8.0
α -1 acid glycoprotein on CL	$CL = 10.2 \cdot (WT/70)^{0.75} \cdot (AAG/2.4)^{-0.04}$	7157.7	-0.2
<i>Multivariable analysis –first step</i>			
Post-menstrual age on CL Albumin on V	$CL = 14.3 \cdot (WT/70)^{0.75} \cdot (PMA^{3.26} / (39.7 + PMA^{3.26}))$ $V = 67.1 \cdot (WT/70) \cdot (ALB/3.3)^{-0.79}$	7023.8	-18.5
<i>Multivariable analysis - second step</i>			
Postmenstrual age on CL Albumin and α-1 acid glycoprotein on V	$CL = 13.8 \cdot (WT/70)^{0.75} \cdot (PMA^{2.83} / (39.5 + PMA^{2.83}))$ $V = 63.6 \cdot (WT/70) \cdot (ALB/3.3)^{-0.83} \cdot (AAG/2.4)^{-0.25}$	7014.6	- 9.2
<i>Multivariable analysis – full model</i>			
Postmenstrual age and serum creatinine on CL Albumin and α-1 acid glycoprotein on V	$CL = 14.8 \cdot (WT/70)^{0.75} \cdot (PMA^{1.43} / (51.6^{1.43} + PMA^{1.43})) \cdot (SCR/0.5)^{-0.34}$ $V = 63.6 \cdot (WT/70) \cdot (ALB/3.3)^{-0.77} \cdot (AAG/2.4)^{-0.29}$	7003.0	-11.6
<i>Multivariable analysis – final model</i>			
Postmenstrual age on CL Albumin and α-1 acid glycoprotein on V	$CL = 13.8 \cdot (WT/70)^{0.75} \cdot (PMA^{2.83} / (39.5 + PMA^{2.83}))$ $V = 63.6 \cdot (WT/70) \cdot (ALB/3.3)^{-0.83} \cdot (AAG/2.4)^{-0.25}$	7014.6	-

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

^aChange 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.

^bOBESE: If obese (BMI \geq 95th percentile) equal to 1; if not assessed (<2 years age) or non-obese, then equal to 0.

Table S6. Population PK parameter estimates for the full model and limited dataset excluding maturational effect of PMA

	Final Model – All Data	Final Model - ≥ 2 years only and maturation function dropped
Parameter	Estimates	
CL_{70KG} (L/H)	13.8	13.4
V_{70KG} (L)	63.6	57
TM₅₀ (weeks)	39.5	-
HILL	2.8	-
Albumin on V exponent	-0.8	-0.6
α-1 acid glycoprotein on V exponent	-0.3	-0.3
BSV (CL, %)	58.5	53.6
BSV (V, %)	11.6	8.6
p CL-V	0.8	1.0
Prop., POP01 (%)	33.6	32.9
Prop., STA01 (%)	32.1	-
Prop., CLN01 (%)	20.3	19.7

CL_{70KG}: population clearance estimate scaled to a 70-kg adult; V_{70KG}: population volume of distribution estimate scaled to a 70-kg adult; TM₅₀: 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.

Table S7. Comparison of empirical Bayesian estimates for the final model using TBW to correct for body size excluding children <2 years and the maturation function^a

Age Categories	>2–6 Years ^b		>6–12 Years		>12 Years ^c	
	Non-Obese (N=8)	Obese (N=12)	Non-Obese (N=15)	Obese (N=20)	Non-Obese (N=26)	Obese (N=44)
CL (L/h)	4.24 (0.92-8.53)	5.33 (1.72-7.86)	11.80 (3.41-31.90)	10.24 (4.54-25.0)	13.35 (5.72-35.30)	18.65 (4.04-32.40)
CL (L/h/kg)	0.23 (0.084-0.74)	0.26 (0.11-0.39)	0.32 (0.12-0.72)	0.21 (0.088-0.60)	0.23 (0.066-0.48)	0.18 (0.043-0.61)
CL (L/h/70 kg)	10.88 (3.69-32.84)	14.18 (5.13-19.82)	19.64 (6.80-44.96)	14.04 (5.72-36.67)	15.73 (4.86-32.74)	14.26 (3.22-35.47)
V (L)	14.05 (6.66-18.30)	16.25 (7.29-22.50)	26.30 (16.10-54.10)	42.40 (26.30-81.20)*	53.8 (20.60-86.0)	75.55 (25.7-138.0)*
V (L/kg)	0.75 (0.61-1.15)	0.75 (0.57-0.88)	0.82 (0.62-0.97)	0.90 (0.58-1.19)	0.80 (0.63-1.11)	0.80 (0.61-1.25)
Half-life (h)	2.23 (1.09-5.0)	2.04 (1.52-4.07)	2.02 (0.91-4.71)	2.83 (1.17-5.47)*	2.65 (1.13-6.67)	3.33 (0.87-9.97)

^aValues are median (range).

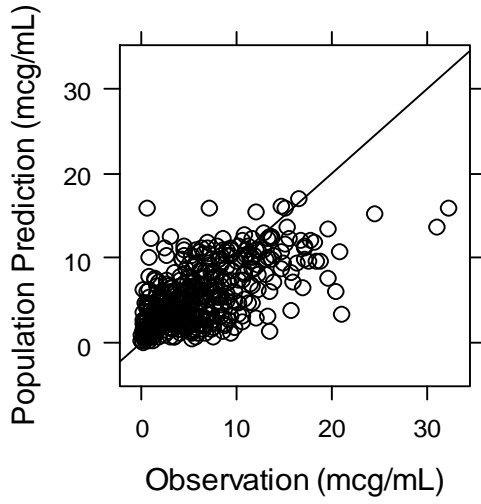
^bThree participants with missing height (and BMI) were not included in this parameter summary.

^cTen participants (6 non-obese, 4 obese) who were >18 years of age were included in the parameter summary.

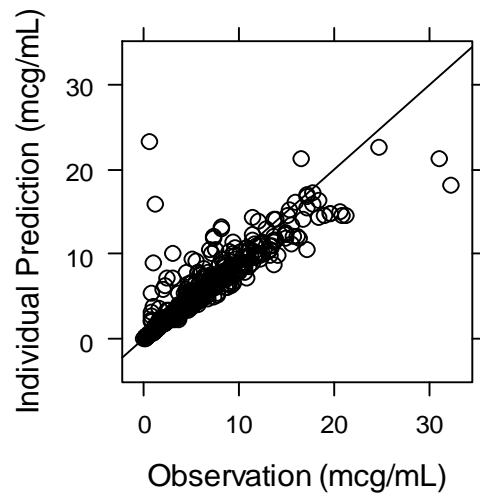
*Statistically significant differences were observed using a rank sum test.

Figure S1

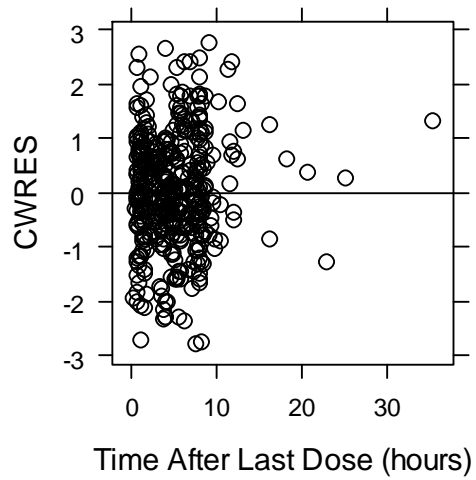
A



B



C



D

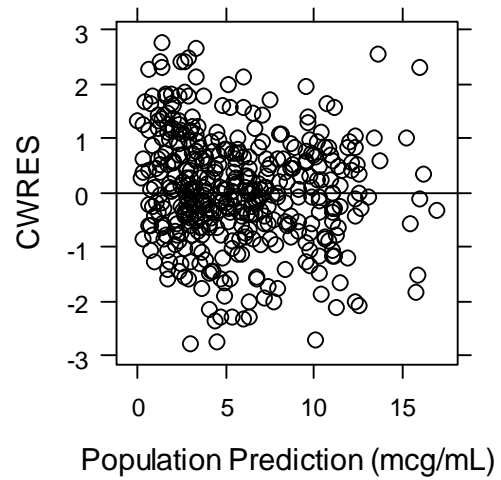
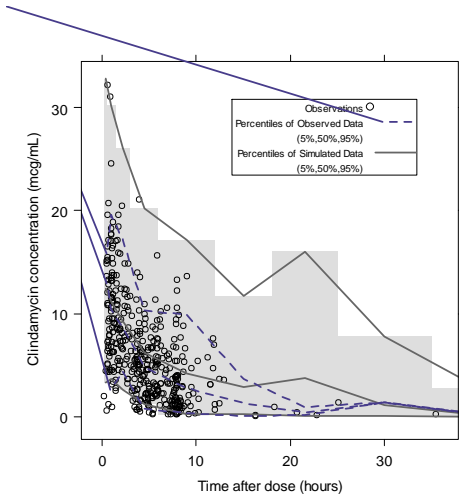
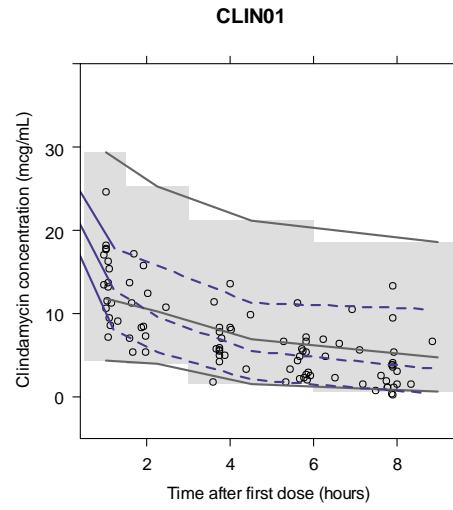


Figure S2

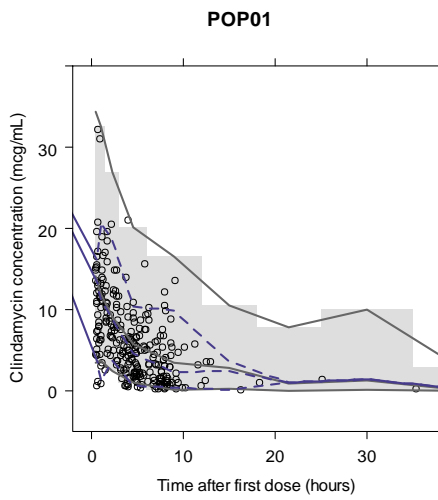
A



B



C



D

