POPULATION PHARMACOKINETICS OF FLUCONAZOLE IN EXTREMELY LOW BIRTH WEIGHT INFANTS

Jeremiah D Momper, PharmD, PhD[1], Edmund V Capparelli, PharmD[1], Kelly C Wade, MD, PhD[2], Girija Natarajan, MD[3], Jamie Gao[4], Matt Laughon, MD, MPH[5], P Brian Smith, MD, MPH[4], and Daniel K Benjamin Jr, MD, PhD[4]

1. University of California, San Diego, La Jolla, CA
2. Children's Hospital of Philadelphia, Philadelphia, PA
3. Wayne State University, Detroit, MI
4. Duke University, Durham, NC,
5. University of North Carolina, Chapel Hill, NC

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A project of the Best Pharmaceuticals for Children Act

DISCLOSURE STATEMENT
JEREMIAH MOMPER (Presenter)

Dr. Momper has disclosed the following financial relationships. Any real or apparent conflicts of interest related to the content of this presentation have been resolved.

Affiliation / Financial Interest	Organization
Consultant	Omnitura Therapeutics, Epocrates, Genyous Biomed, Athenahealth
Ownership interest	Illumina

Background

- Knowledge of fluconazole pharmacokinetics (PK) is necessary to determine optimal dosing that takes into consideration the rapid maturation in extremely premature infants.

- The objective of this study was to characterize the population PK and dosing requirements of fluconazole in infants <750 g birth weight.
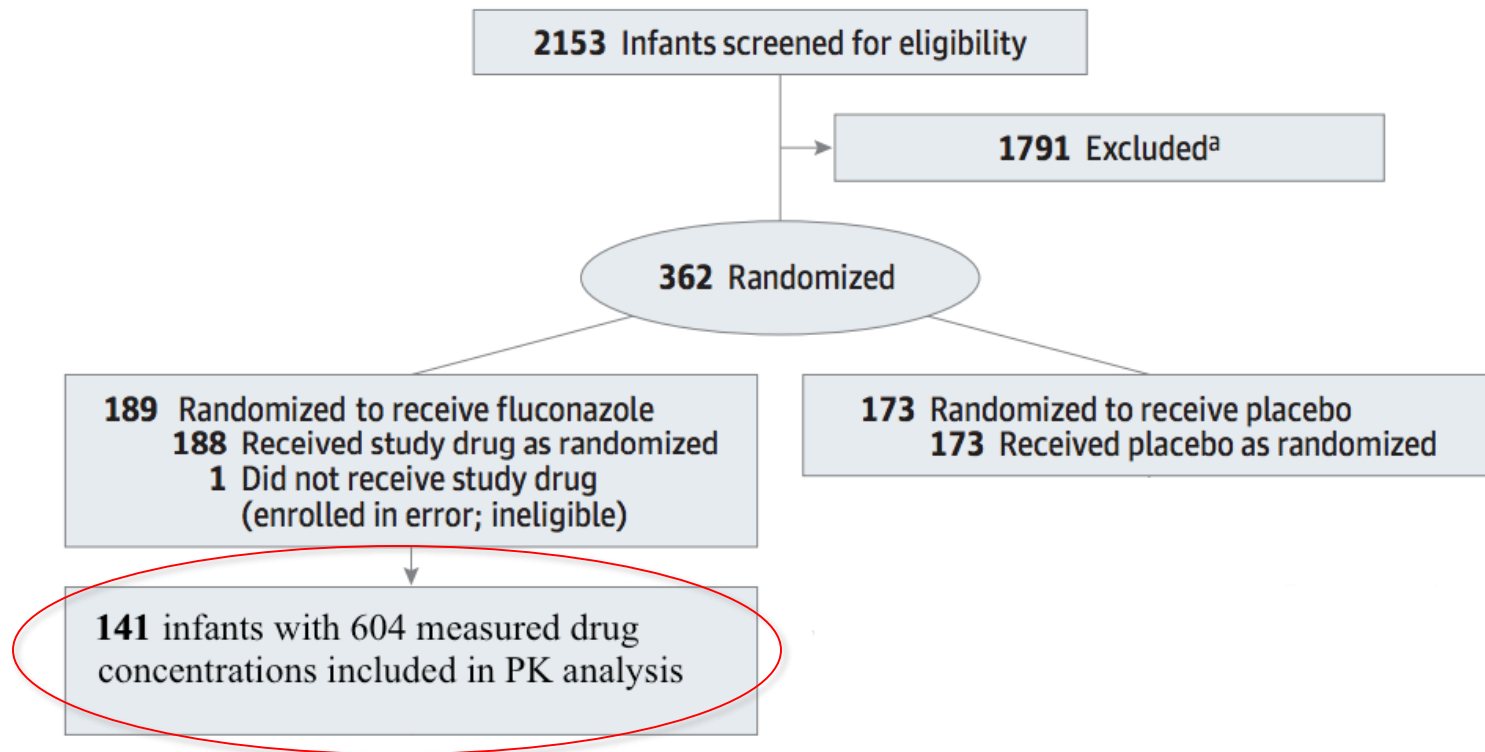
Multi-center, randomized, placebo-controlled trial that evaluated the efficacy and safety of fluconazole in premature infants weighing < 750 g at birth[1]


- Infants received IV or oral fluconazole 6 mg/kg twice weekly for up to 42 days
- Plasma fluconazole concentrations from scheduled and scavenged samples were determined using a validated LC-MS/MS assay

1. *JAMA*. 2014 May 7;311(17):1742-9.

Methods: PK Sampling

Scheduled PK samples collected according to 1of 8 sampling schemes with 3 samples taken around doses 3, 5, 7 or 9 and the final dose
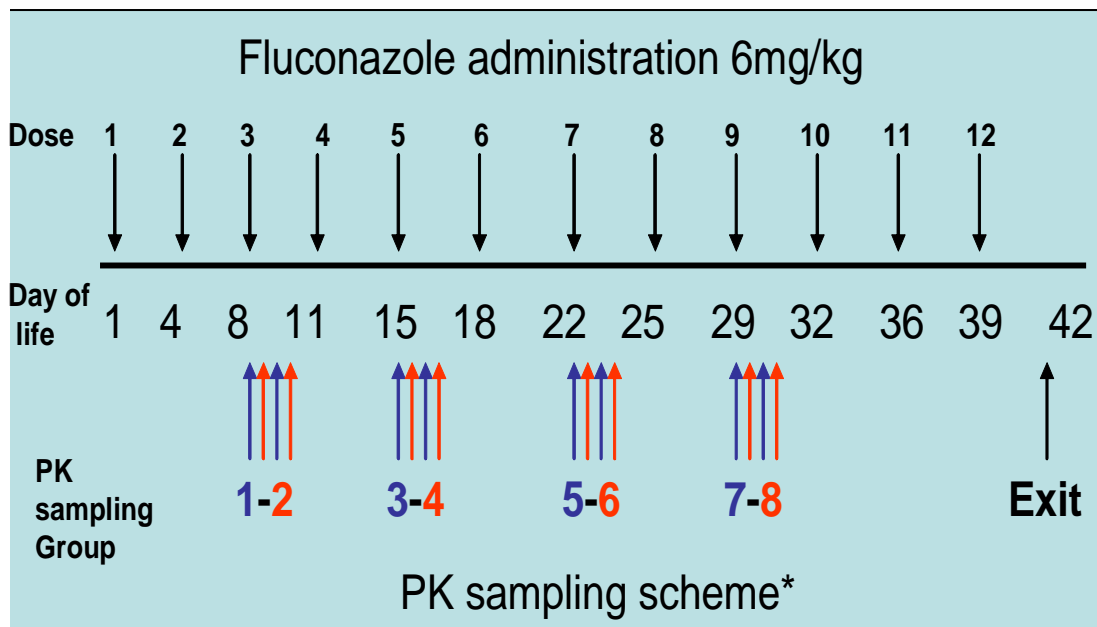
Scavenged PK samples were also collected according to a preferred collection schedule
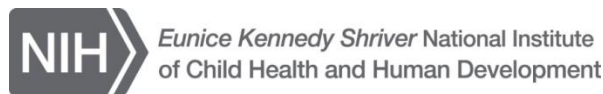
Methods: Population PK Analysis

- Concentration-time data were analyzed with nonlinear mixed-effect modeling using NONMEM version 7.2.
- Clearance was scaled by allometric weight ($WT^{0.75}$), and volume of distribution was scaled by weight ($WT^{1.0}$) prior to evaluation of potential covariates.
- Continuous covariates evaluated were PNA, GA, PMA, serum creatinine, and albumin.
- Categorical covariates evaluated were race and ethnicity, intubation status, and birth by Caesarean section.
- Final PK model was used to perform Monte Carlo simulations with a pharmacodynamic target trough concentration of 2 µg/mL.
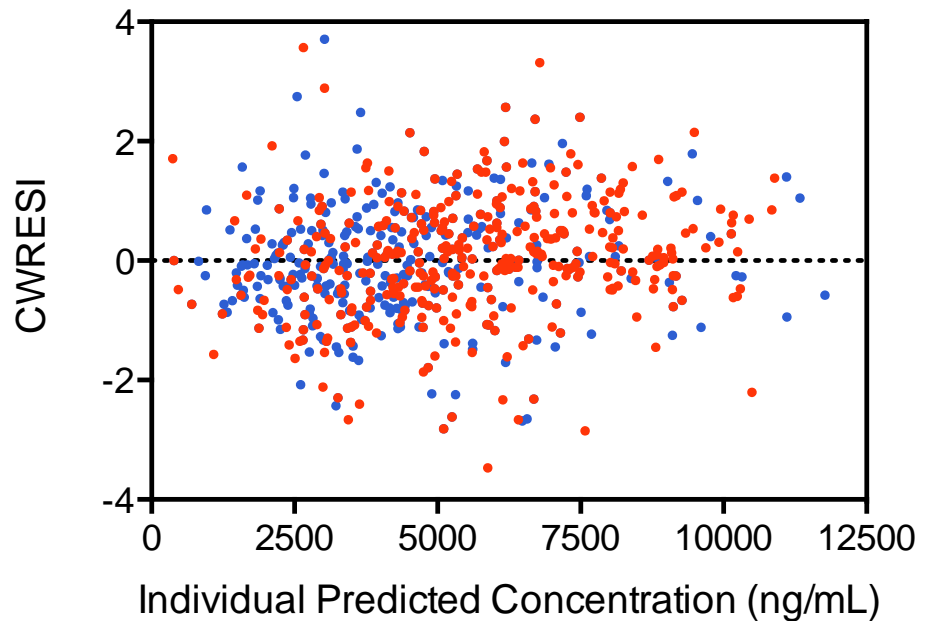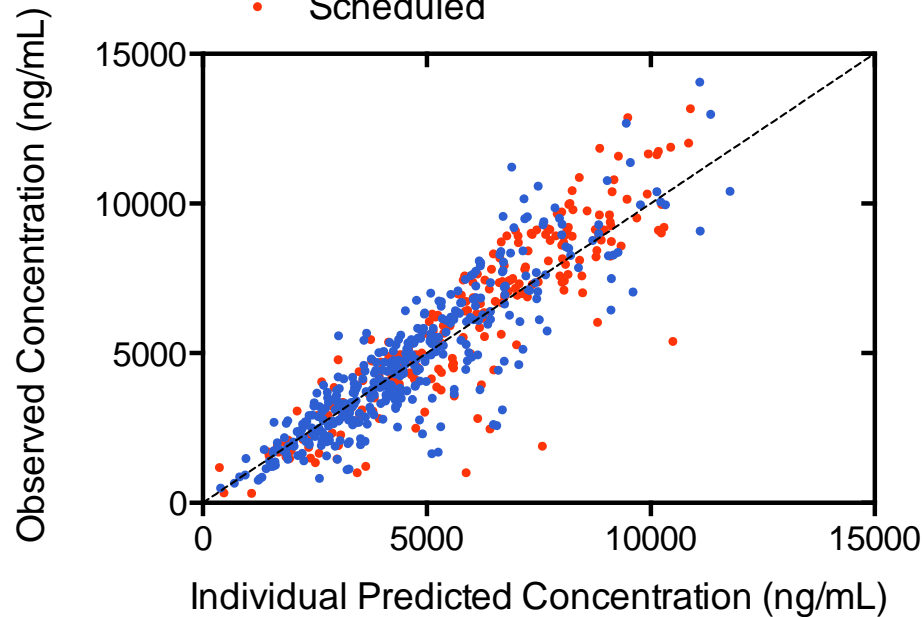
Demographic and Clinical Data at First PK Evaluation

	Median (IQR)
Postnatal age (days)	17 (10 – 25)
Gestational age (weeks)	25 (24 – 26)
Postmenstrual age (weeks)	27.4 (26.2 – 29.1)
Serum creatinine (mg/dL)	0.90 (0.6 – 1.2)
Albumin (g/dL)	2.7 (2.2 – 3.1)

Fluconazole Concentrations: Measured vs. Predicted from the Final PK Model

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Key Steps in Population PK Analysis

Model description	Population model	Objective function value (OFV)	Change in OFV from base model
CL (base model)	$CL = \theta_{CL} * (WT)^{0.75}$	9624	---
PNA	$CL = \theta_{CL} * (WT)^{0.75} * (PNA/25)^{\theta CL\text{-}PNA}$	9492	-132
GA	$CL = \theta_{CL} * (WT)^{0.75} * (GA/25)^{\theta CL\text{-}GA}$	9599	-25
PMA	$CL = \theta_{CL} * (WT)^{0.75} * (PMA/28)^{\theta CL\text{-}PMA}$	9450	-174
SCR	$CL = \theta_{CL} * (WT)^{0.75} * (SCR/0.8)^{\theta CL\text{-}SCR}$	9405	-219
CSCT	$CL = \theta_{CL} * (WT)^{0.75} * \theta CL\text{-}CSCT^{CSCT}$	9617	-7
V (base model)	$V = \theta_V * (WT)^{1.0}$	9624	---
PMA	$V = \theta_V * (WT)^{1.0} * (PMA/28)^{\theta V\text{-}PMA}$	9620	-4
SCR	$V = \theta_V * (WT)^{1.0} * (SCR/0.8)^{\theta V\text{-}SCR}$	9600	-24

CL, clearance; V, volume of distribution; PNA, postnatal age; GA, gestational age; PMA, postmenstrual age; SCR, serum creatinine; CSCT, birth by Caesarean section
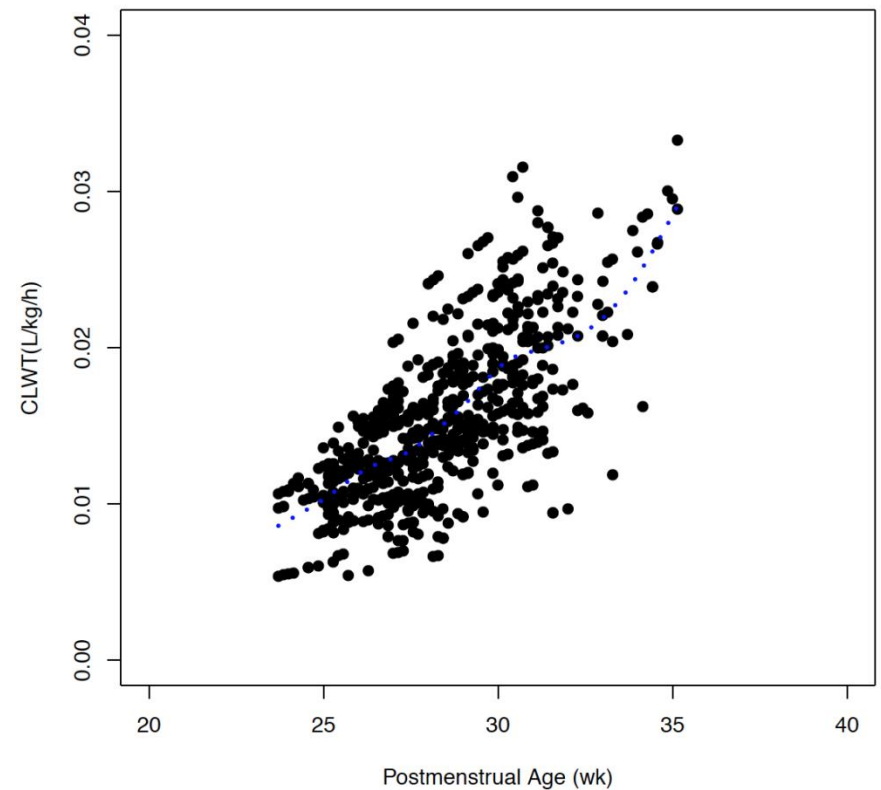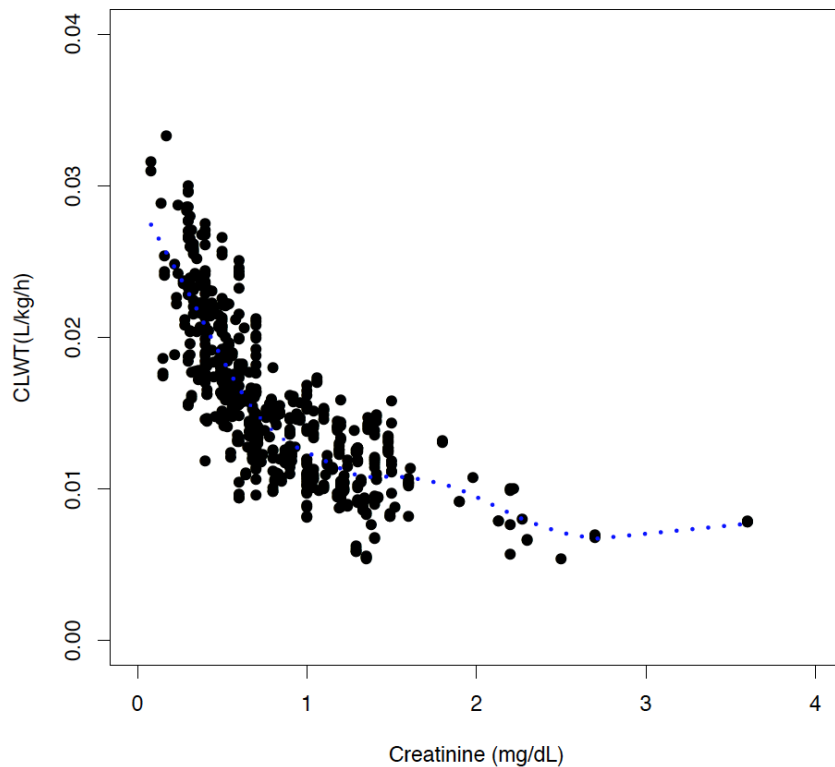
Fluconazole Clearance is Correlated with Serum Creatinine and Postmenstrual Age

CL increases with PNA:
Potential for under-dosing at older ages

PNA is correlated with SCR and is not a significant independent covariate for CL

Fluconazole Final Population PK Parameters

| Parameter	Symbol	Point Estimate	SEE	Bootstrap CI 2.5%	Bootstrap CI Median	Bootstrap CI 97.5%
V	θ_V	1.00	0.0378	0.93	1.00	1.08
CL	θ_{CL}	0.0127	0.00033	0.0120	0.0127	0.0133
F1	θ_{F1}	1.00	0.065	0.86	1.00	1.13
KA	θ_{KA}	0.96	0.25	0.52	0.96	1.81
SCR	θ_{SCR}	-0.410	0.0498	-0.53	-0.41.	-0.32
PMA	θ_{PMA}	2.05	0.35	1.23	2.05	2.62

$$V \ (L) = \theta_{(V)} * WTKG$$
$$CL \ (L/h) = \theta_{(CL)} * WTKG^{0.75} * (SCR/0.8)^{\theta SCR} * (PMA/28)^{\theta PMA}$$
$$F1 \ (\%) = \theta_{(F1)}$$
$$KA \ (1/h) = \theta_{(KA)}$$

Monte Carlo simulations demonstrate that fluconazole dosed at 6 mg/kg twice weekly results in 89.9% of concentrations above the pharmacodynamic target of 2 µg/mL
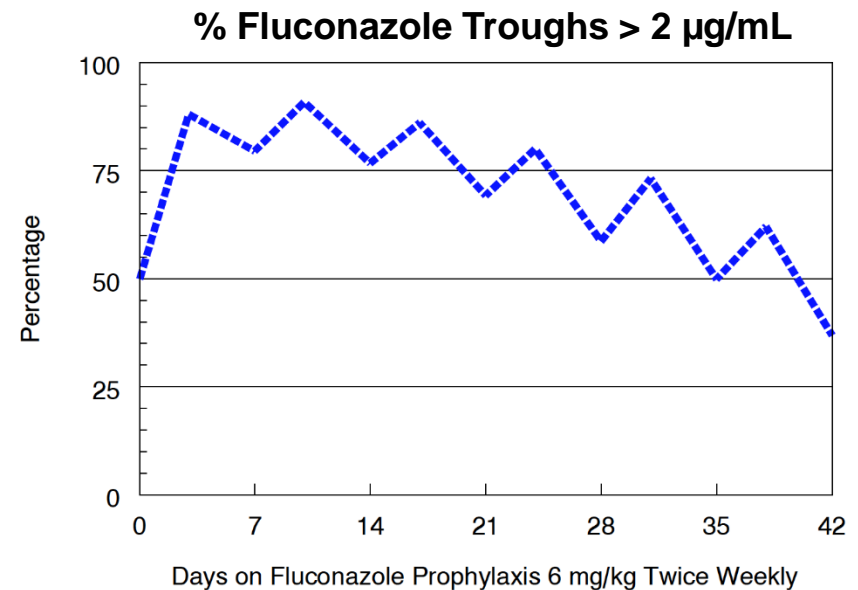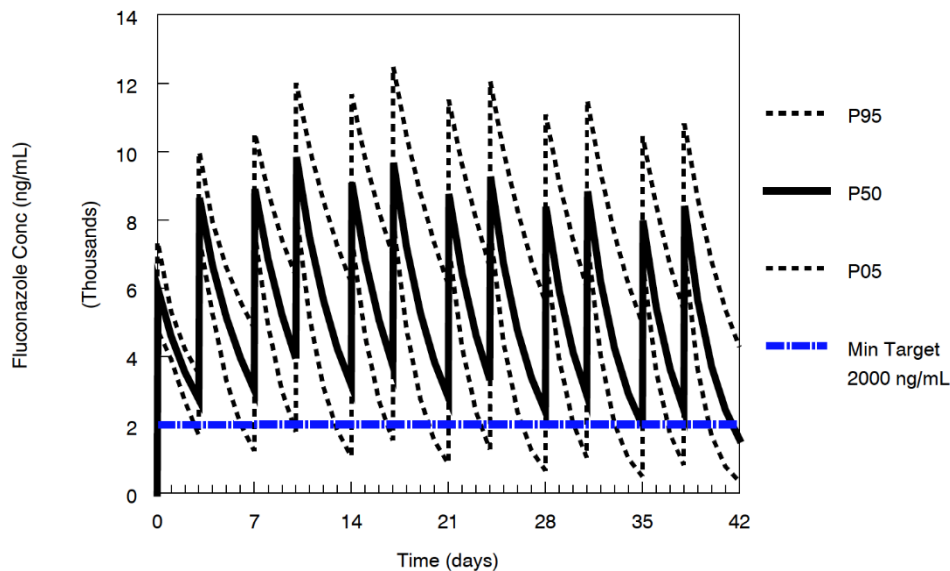
Conclusions

- We successfully characterized the PK of fluconazole using population PK techniques with data across 6 weeks of therapy.
- Serum creatinine best predicts developmental changes in fluconazole clearance.
- A twice-weekly dose of 6 mg/kg given orally or intravenously achieves appropriate plasma concentrations for *Candida* prophylaxis in infants <750 g birth weight.
- Scavenged PK sampling is a minimal-risk approach that will facilitate drug studies in difficult populations.