Modeling & Simulation in Pediatric Drug Development: *Application of Pharmacometrics to Define the Right Dose for Children*

小児医薬品開発におけるファーマコメトリックスの活用

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Cincinnati Children's Hospital Medical Center

- Ranked in Top 3 of pediatric programs in the U.S
- 628 beds; >15,000 employees; 822 faculty
- Operations of $2.1 Billion

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- Over 1.4 Million sq.ft. of research space
- $200 Million in Research Funding per year ($140 Million from the NIH)

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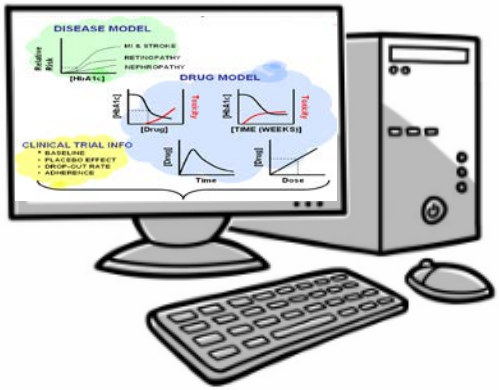
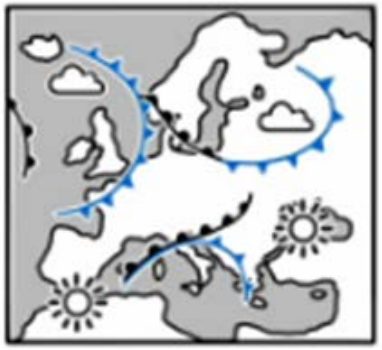
Objectives

- Describe the use of developmental pharmacometrics to design informative pediatric trials
- Present examples of the application of modeling & simulation in pediatric drug studies
- Illustrate the potential of M&S to generate age-appropriate pediatric dosing information

Power of Modeling & Simulation





https://www.youtube.com/watch?v=o2ntCRCgpUM

The benefits of modeling and simulation in drug development: July 27, 2014

Promise of Modeling & Simulation

PK/PD driven decision support

Informative Designs -> Improved Outcomes

https://www.youtube.com/watch?v=o2ntCRCgpUM

The benefits of modeling and simulation in drug development: July 27, 2014

Pediatric Study Decision Tree

Reasonable to assume (pediatrics *vs.* adults)
- **similar disease progression?**
- **similar response to intervention?**

Neonates: birth up to 1 month
Infants: 1 month up to 2 years
Children: 2 years up to 12 years
Adolescents: 12 years up to 16 years

NO

Conduct PK studies
Conduct safety/efficacy trials*

YES TO BOTH

Reasonable to assume ***similar concentration-response*** (C-R) in pediatrics and adults?

NO

Is there a PD measurement** that can be used to predict efficacy?

YES

Conduct PK studies to achieve ***levels similar to adults***
Conduct safety trials

NO

YES

Conduct PK/PD studies to get C-R for PD measurement
Conduct PK studies to achieve target concentrations based on C-R
Conduct safety trials

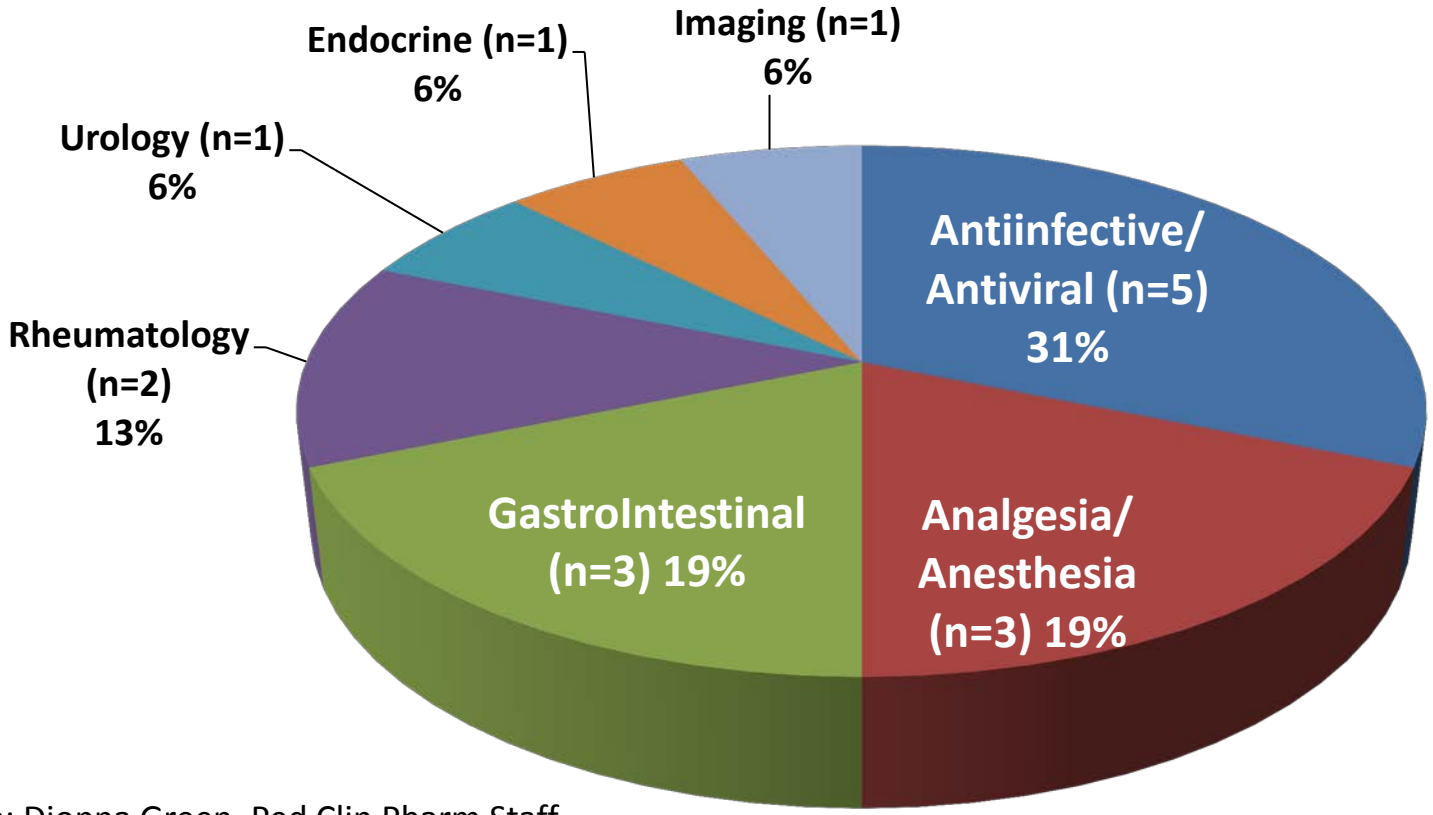
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425885.pdf

Advisory Committee for Pharmaceutical Science and Clinical Pharmacology – March 2012

- Should modeling and simulation methods be considered in **all** pediatric drug development programs? - **(VOTE) YES: 13; NO: 0; ABSTAIN: 0**
- Can dose(s) for the adolescent (>12 years) population be derived using adult data without the need for a dedicated PK study? – **(VOTE) YES: 12; NO: 1**
- Should the routine use of PBPK in pediatric drug development, when possible, be recommended at the present time? – **(VOTE) YES: 7; NO: 6**

http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/ucm286697.htm

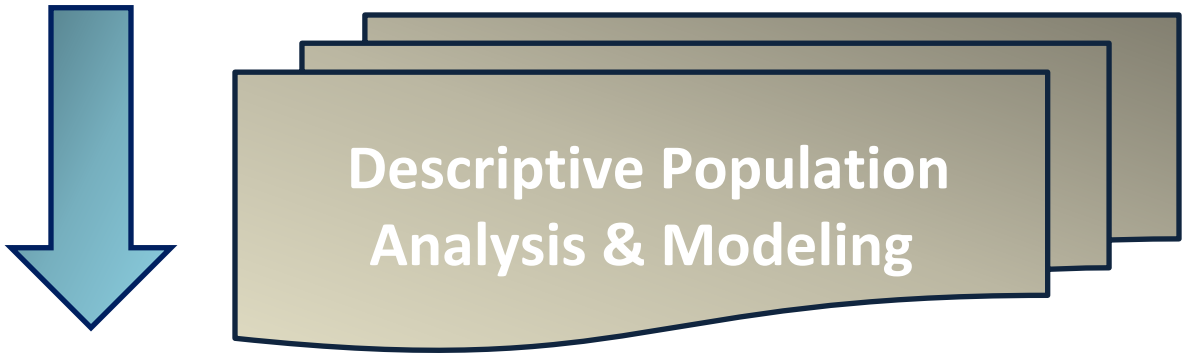
36% (16/45) of partial extrapolation product reviews describe the use of M&S in the development program



Source: Dionna Green, Ped Clin Pharm Staff
Adapted from Dr. Gilbert Burckart, PBPK Workshop FDA-CERSI, 2014

Dunne J. et al. Pediatrics 2011; 128: e1242-e1249
http://pediatrics.aappublications.org/content/128/5/e1242

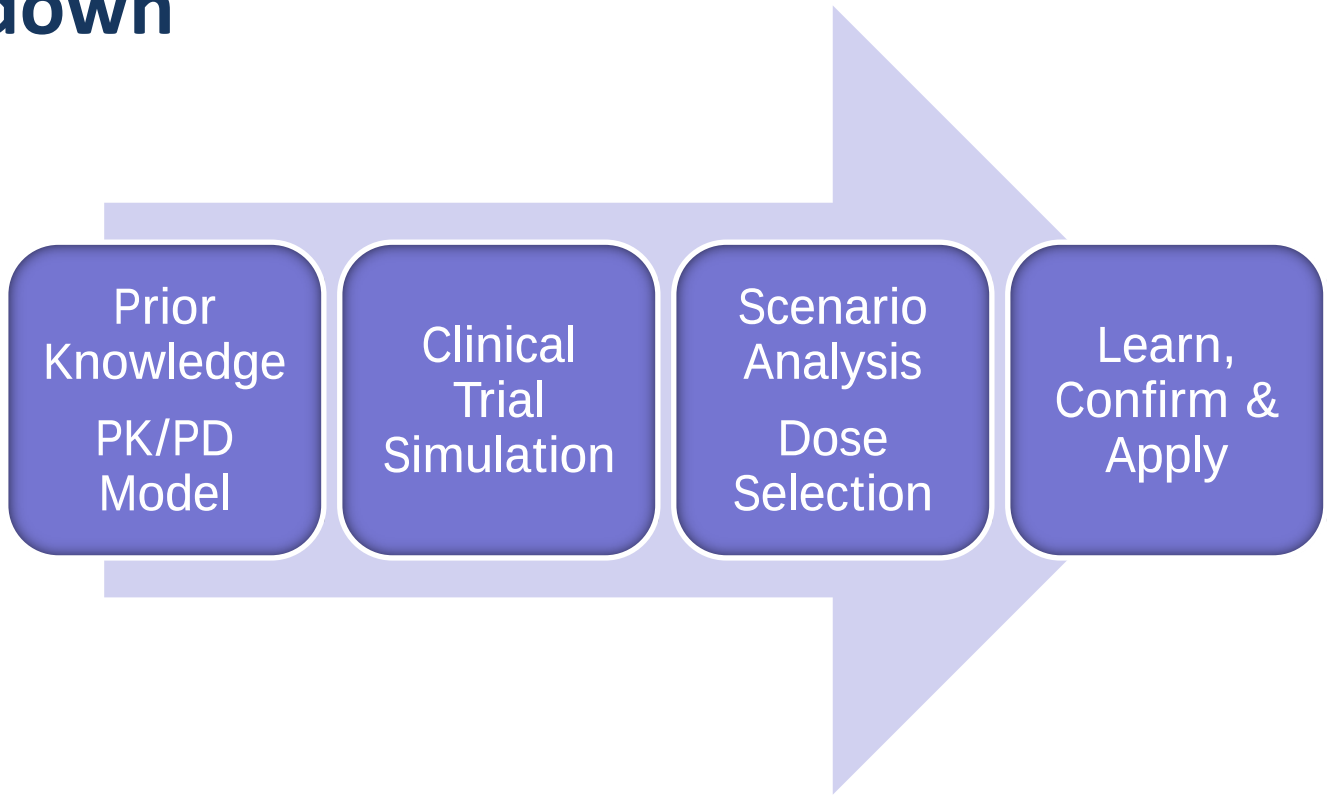
Applying Pharmacometrics in Adults & Children



Clinical data

Population PK/PD & covariate exploration

Top-down



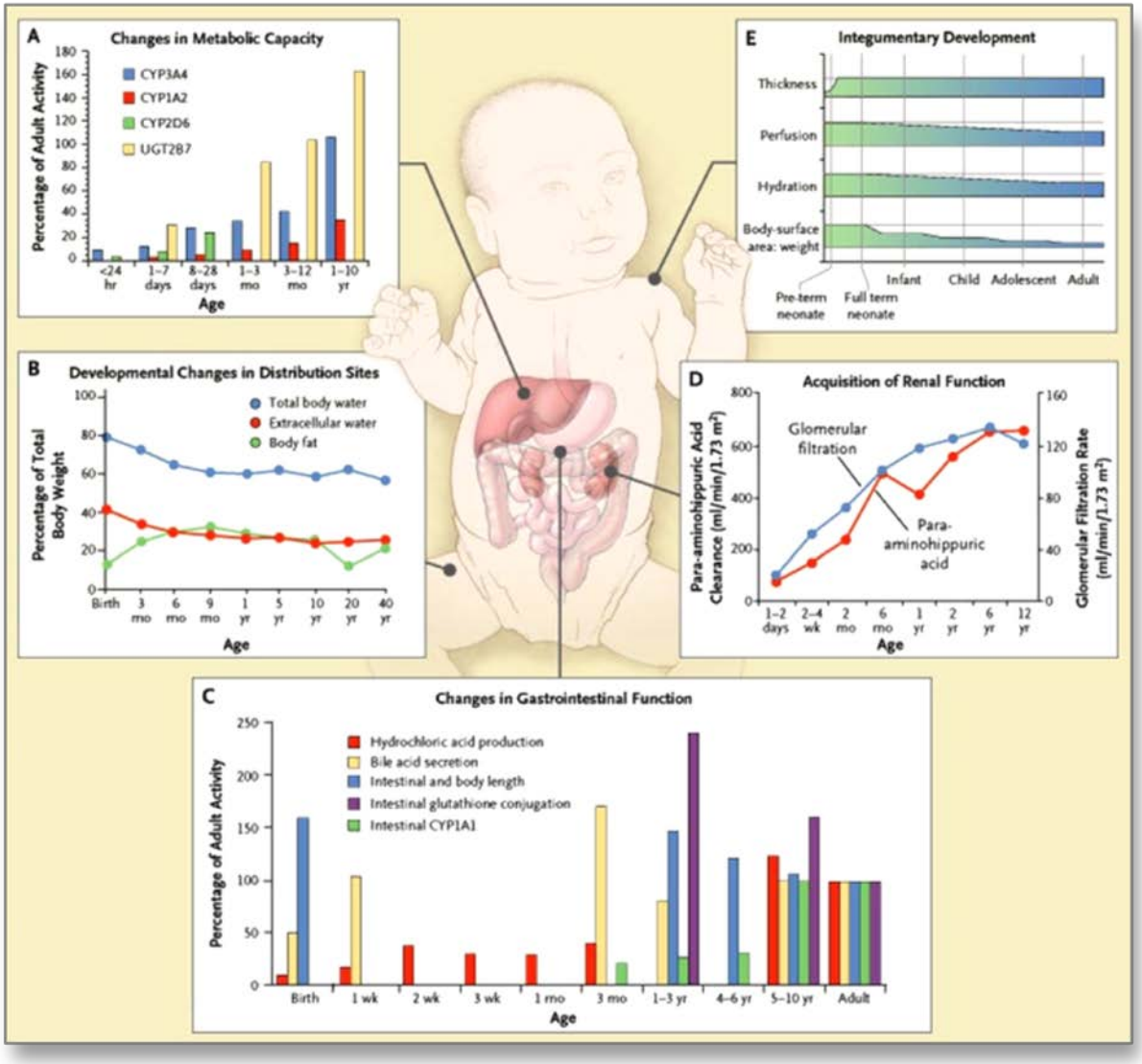
Vinks AA, Emoto C, Fukuda T. Clin Pharmacol Ther. 2015 Sep;98(3):298-308.

Impact of Development on Drug Disposition

Metabolic capacity

Water distribution

GI function



Body composition

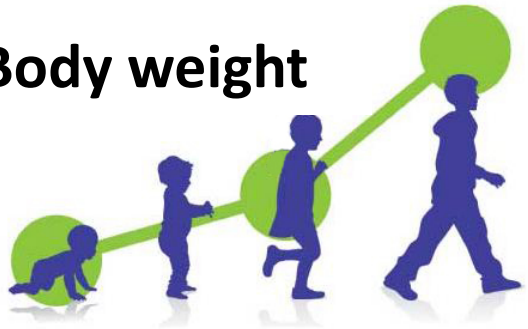
Renal function

Kearns GL et al. *N Engl J Med.* 2003;349:1157-67

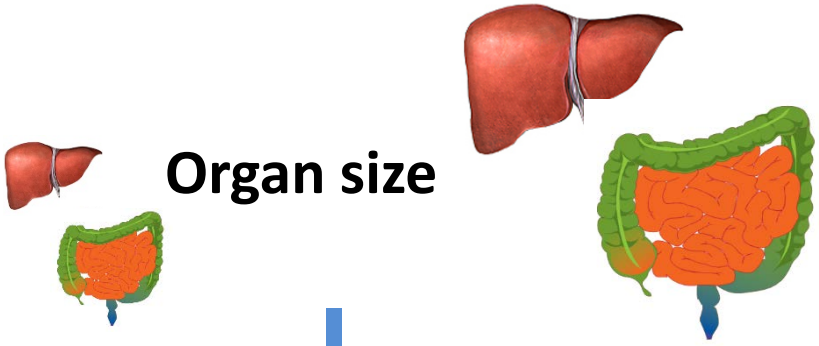
Impact of Size and Maturation

Size Increases

Body weight

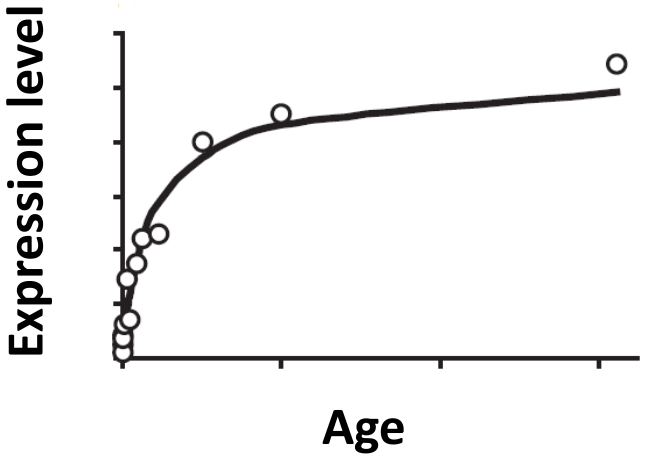


Organ size



Developmental Changes

CYP3A & transporter protein expression



Population PK PBPK model

Emoto C, Fukuda T, Vinks AA et al. CPT: Pharmacometrics Syst Pharmacol. 2015 Feb;4(2):e17.

Case study - Application of M&S to study design

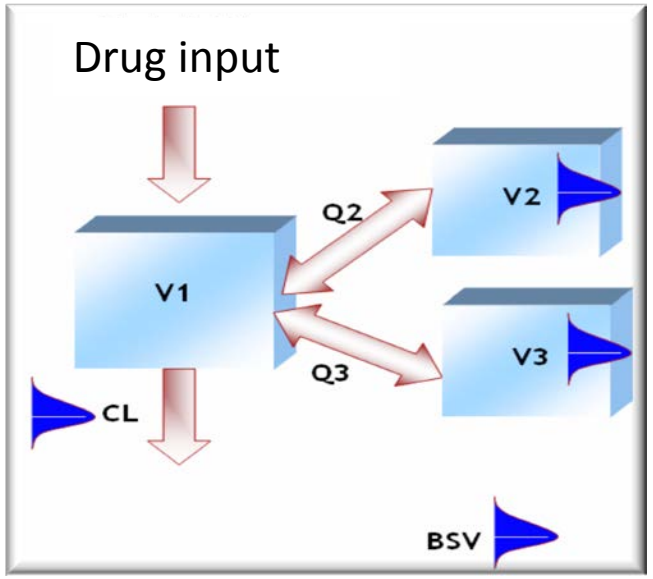
Teduglutide PK/PD in Neonates with Short Bowel Syndrome

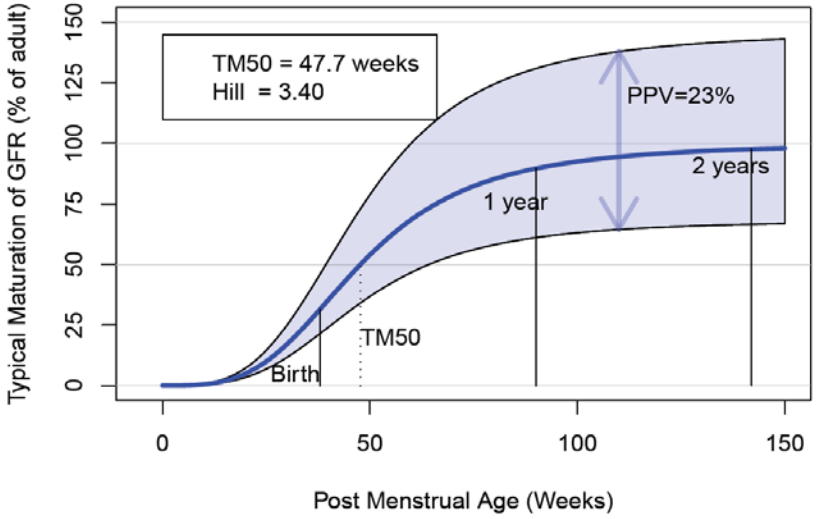
- Teduglutide - a synthetic glucagon-like peptide-2 analog
  - evaluated for treatment of short-bowel syndrome (SBS)
- Design Pediatric multiple-dose Phase-I clinical study
  - determine safety, efficacy and PK of teduglutide in pediatric patients with SBS aged 0-12 months
- Application of clinical trial simulations
  - Assume similar exposure-response (E-R) in pediatrics and adults (FDA pediatric decision tree)
  - Modeling approach for age-weight distribution across age categories
- Goal was to optimize likelihood of achieving target exposure and therapeutic effect
  - based on observations in adult patients

Mouksassi S, et al. Clin. Pharmacol. Ther. 2009, 86:667-71

Development of Pediatric Population Model

- Structural PK model
  - Based on adult, healthy subject, andr pediatric data
- Size component
  - allometric scaling of clearance (CL) and volume of distribution (V)
- Maturation function:
  - include glomerular filtration rate maturation as part of clearance change over time
  - And/or drug metabolizing enzyme maturation function(s)

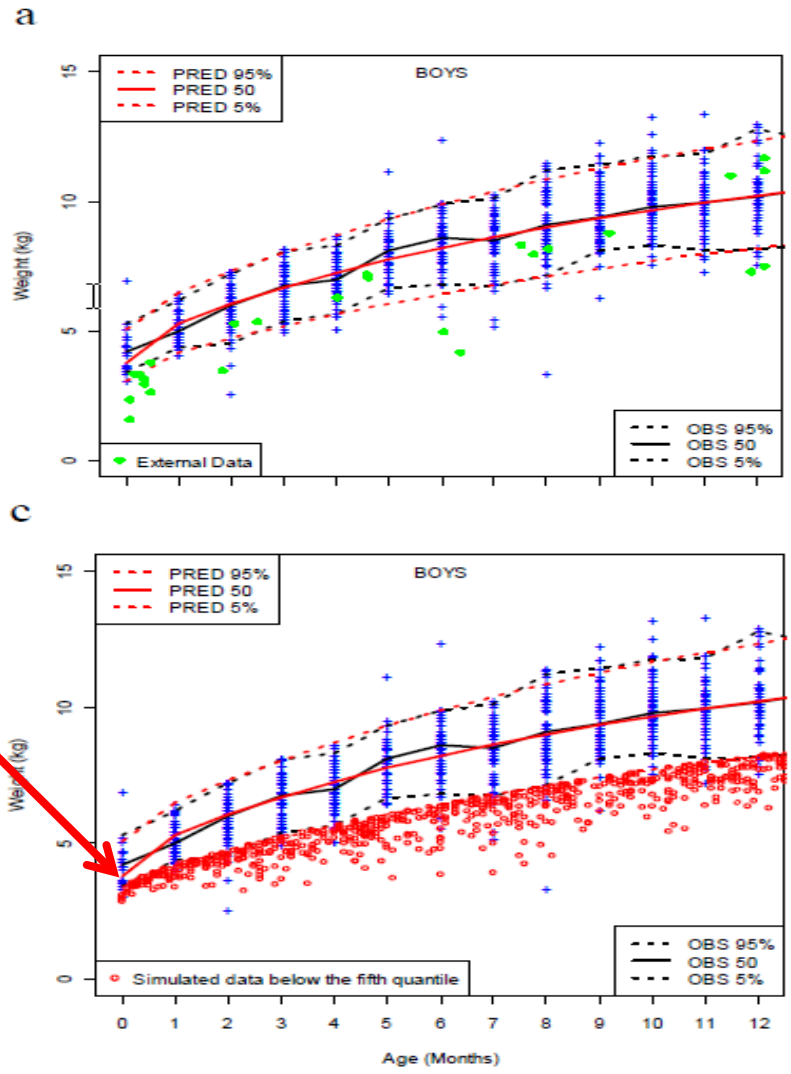




Vinks AA et al. Clin Pharmacol Ther. 2015; 98:298-308.

Generating Realistic Covariates

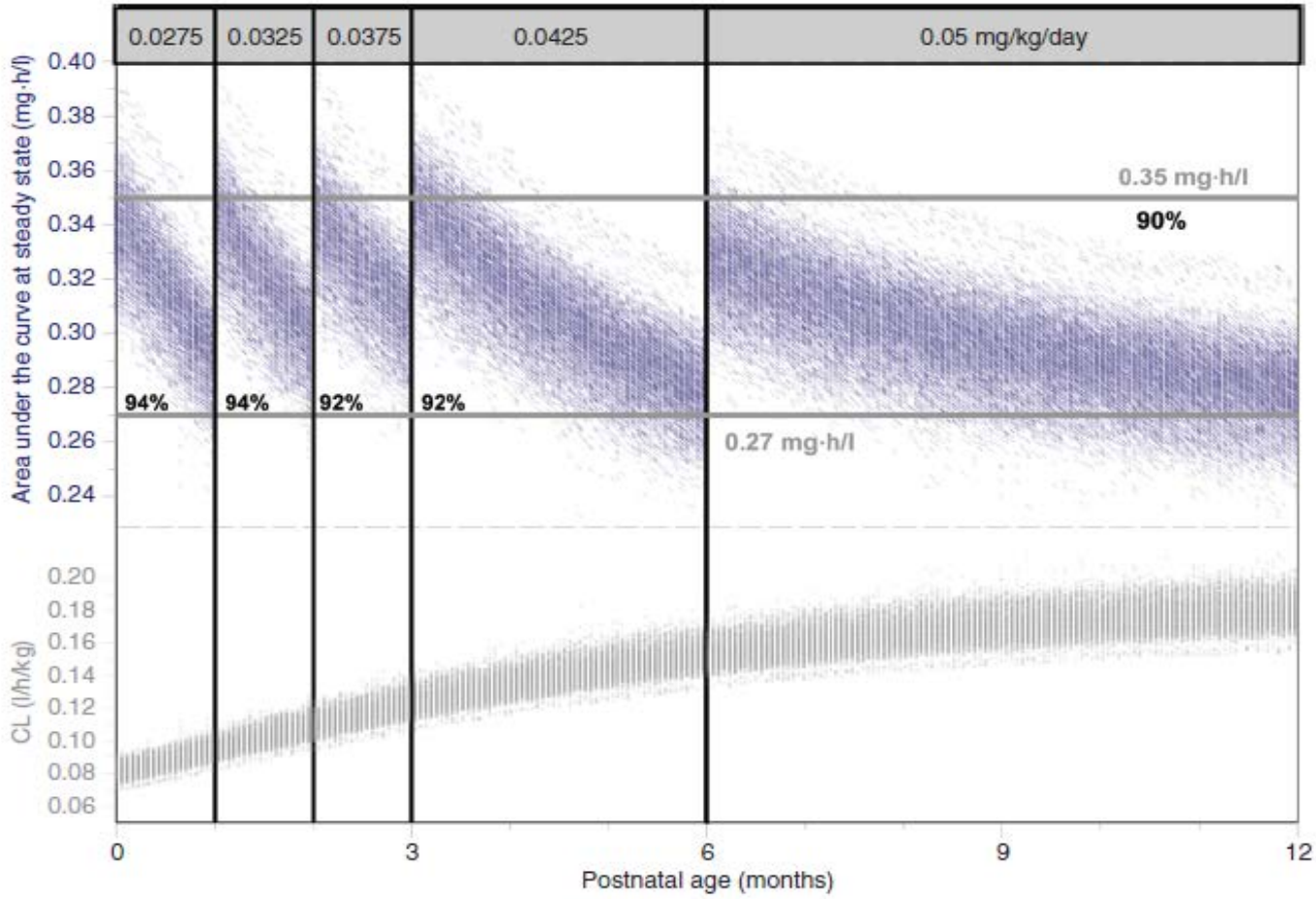
- Short bowel syndrome patients have body weights below the 5th percentile of their respective age groups
- Check with data from our short bowel syndrome patients
- Specific modeling technique (GAMLSS) was used to simulate age-matched body weights values below the 5th percentile



GAMLSS: Generalized Additive Models for Location, Scale and Shape

Clinical Trial Simulation - results

Teduglutide dosing strategy to achieve optimal target attainment



- Percentages of patients with steady-state teduglutide exposure within the targeted window of efficacy
- Dose reductions of 55, 65, 75, and 85% in the 0–1-, 1–2-, 2–3-, and 3–6-month age groups, *vs.* the optimal dosing regimen in the 6–12-month age group.

Mouksassi S, et al. Clin. Pharmacol. Ther. 2009, 86:667-71

Informative PK/PD Study Design

How many patients?

- Required number of patients for statistically robust estimation of PK/PD relationship(s)
- Precision criteria to derive sample size for pediatric PK studies

How many samples per patient?

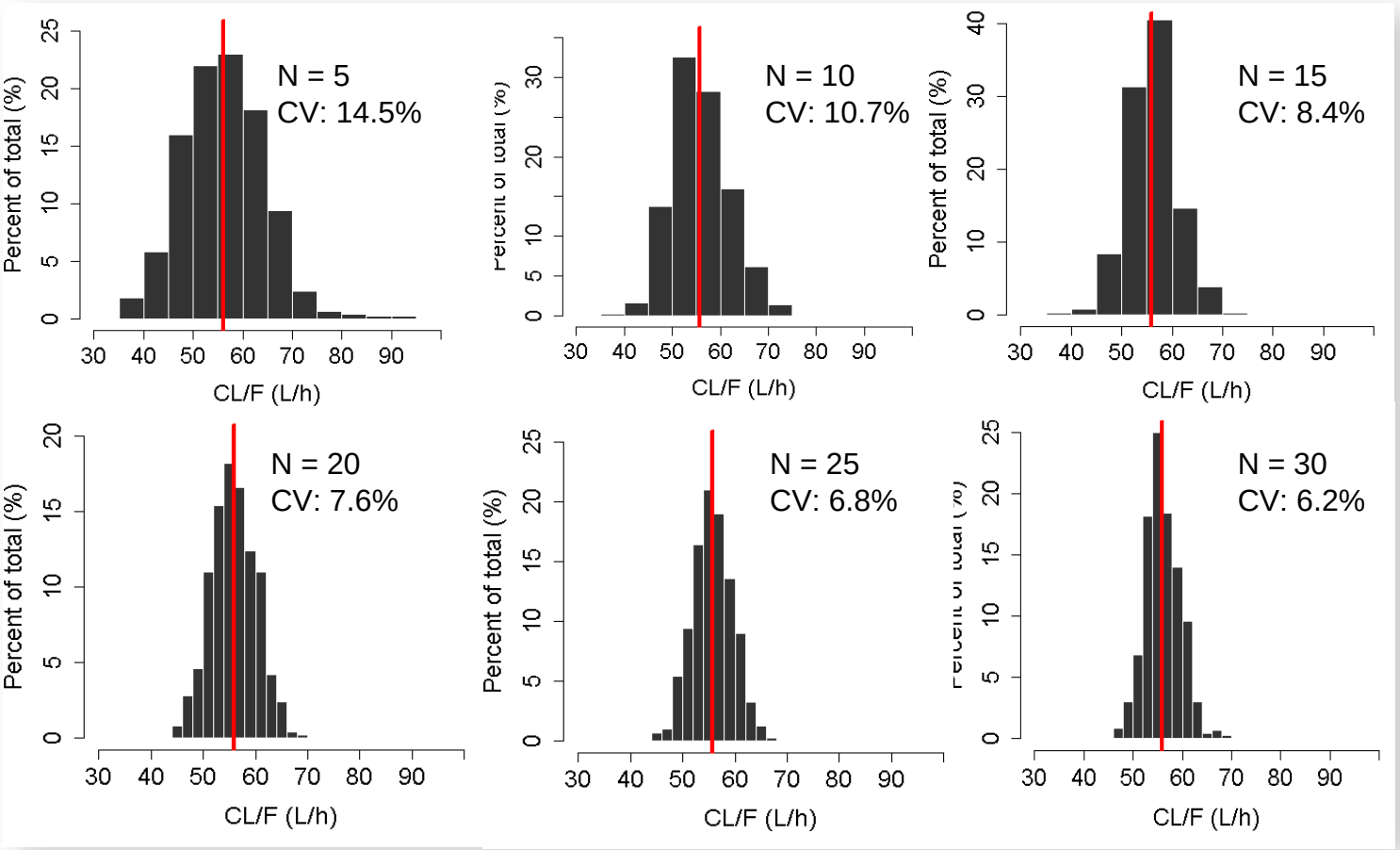
- Precision criteria and simulations

Best times to sample

- Optimal sampling times

D'Argenio DZ. Optimal sampling times for pharmacokinetic experiments. J Pharmacokinet Biopharm 1981;9(6):739-56.
Vinks et al. Antimicrob Agents Chemother. 1996;40(5):1091-7. **Wang et al. J Clin Pharmacol 2012 ; Salem et al . J Clin Pharmacol. 2013.**

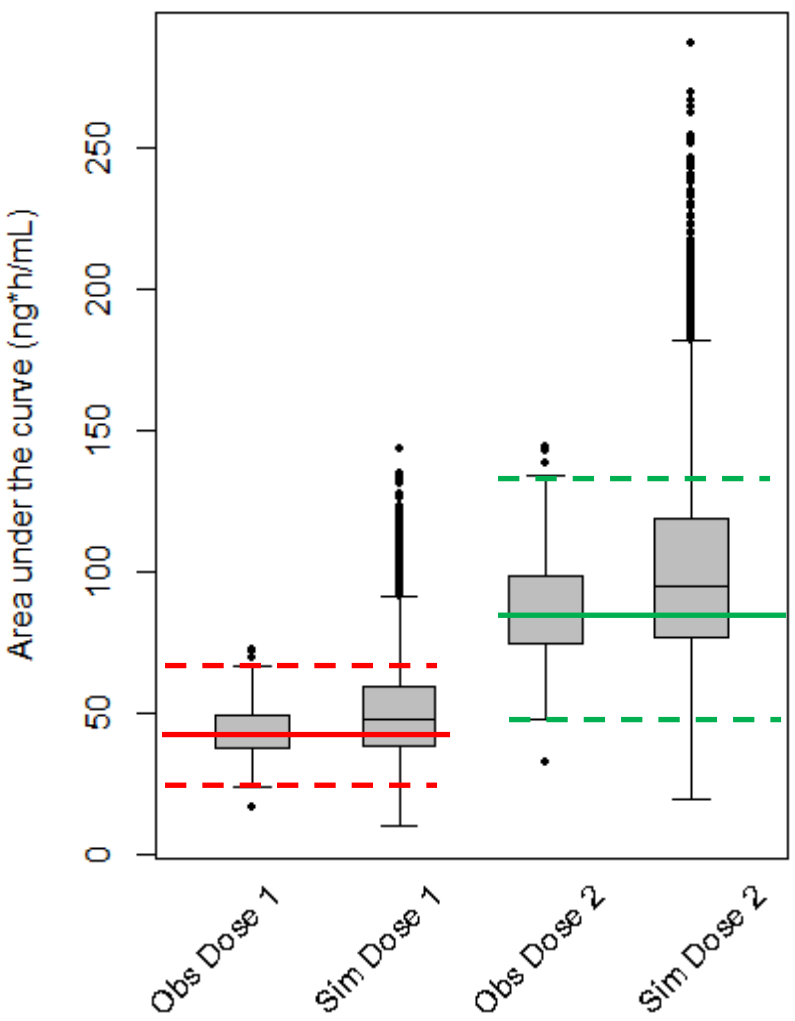
Effect of number of subjects on clearance estimates

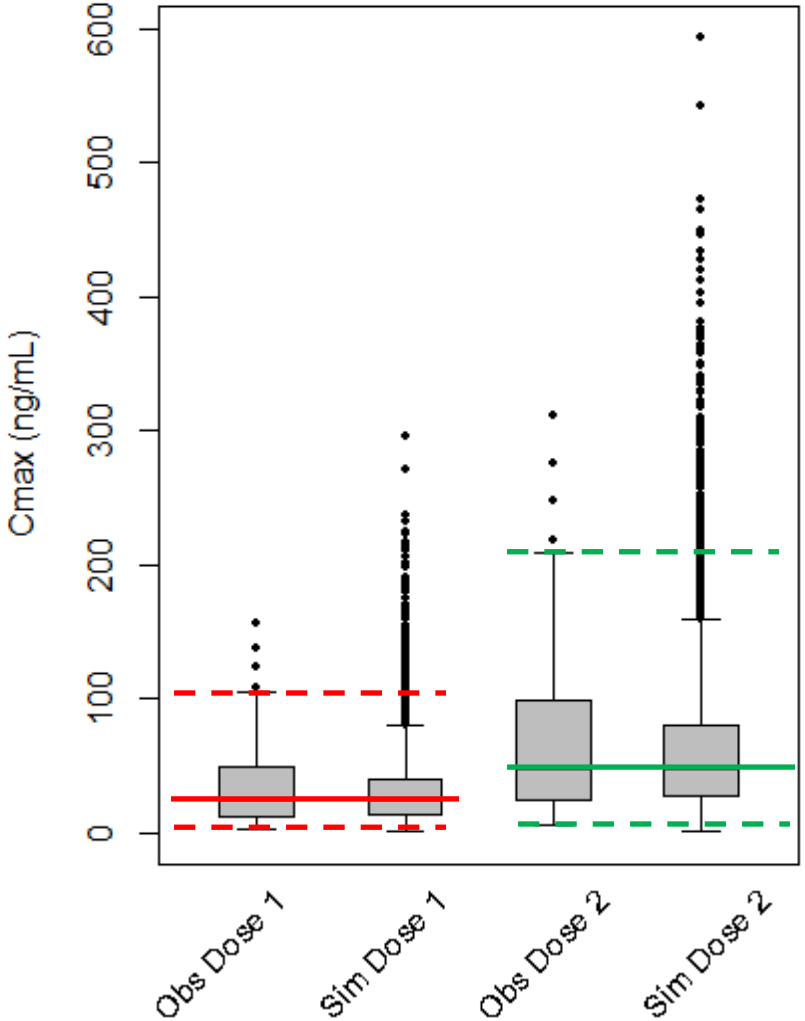


- 500 replicates with n=5, 10, 15, 20, 25 & 30 subjects were simulated
- Mean CL/F was calculated as the arithmetic mean of empirical Bayesian estimates of individual CL/F per trial

Vinks AA et al. M&S to define the right dose for children. Clin Pharmacol Ther. 2015; 98:298-308.

Simulation of drug exposure at different dose levels





Obs, observed in adult studies; Sim, predicted exposure in children and adolescents

Vinks AA et al. M&S to define the right dose for children. Clin Pharmacol Ther. 2015; 98:298-308.

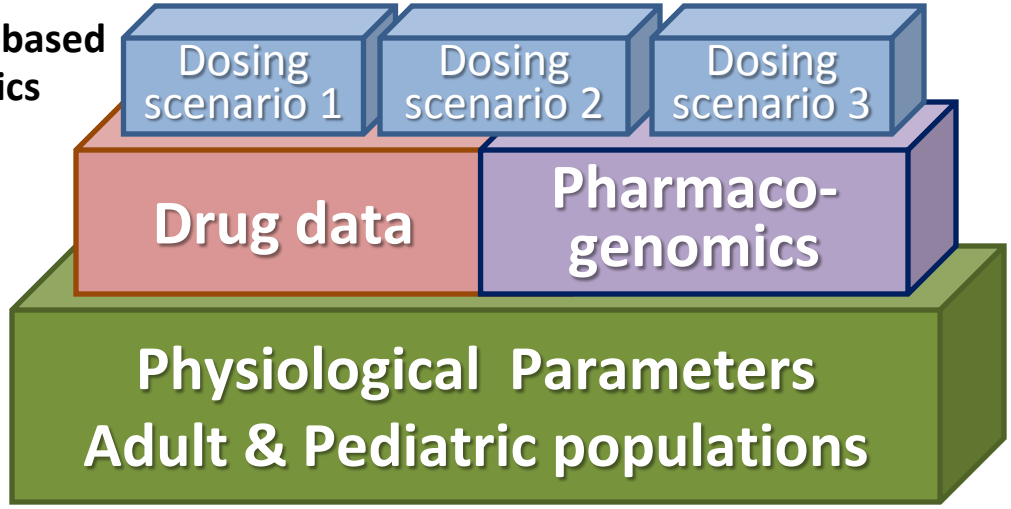
Clinical data

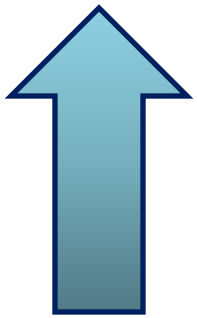
Empirical approaches
Population PK-PD & covariate exploration

Top-down

Age appropriate Models & Algorithms

Mechanistic approaches
***In vitro-in vivo* extrapolation (IVIVE) & Physiologically-based pharmacokinetics (PBPK)**





Bottom-up

Vinks AA et al. M&S to define the right dose for children. Clin Pharmacol Ther. 2015; 98:298-308.

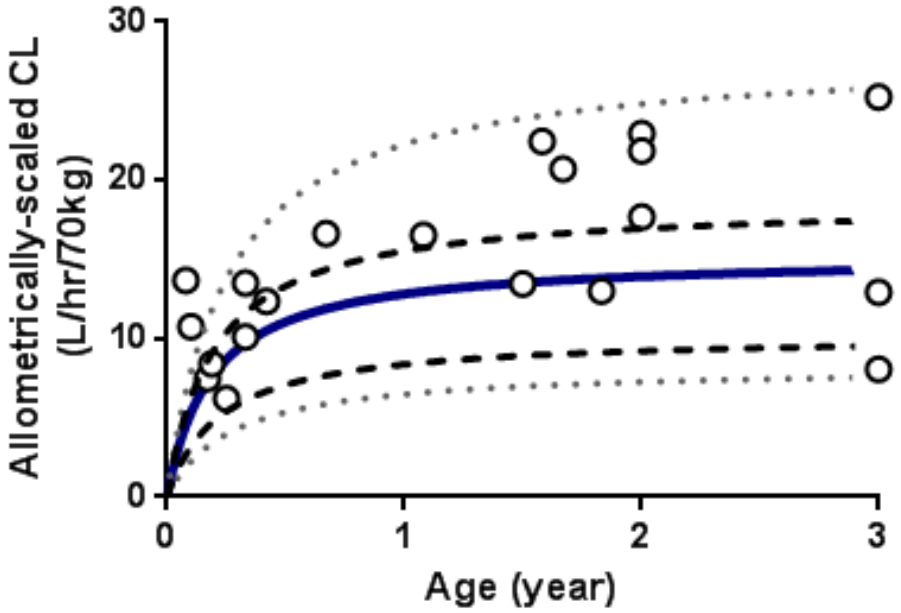
Pediatric Phase 1/2 studies - *Implementation of Pharmacometrics*

- Study of the mTOR Inhibitor Sirolimus in Neurofibromatosis Type-1 Related Plexiform Neurofibromas
- Pilot study of sirolimus plus multiagent chemotherapy for relapsed/refractory acute lymphoblastic leukemia/lymphoma
- **Assessing Efficacy and Safety of the mTOR Inhibitor Sirolimus in the Treatment of Complicated Vascular Anomalies – patients 0-18 years of age**

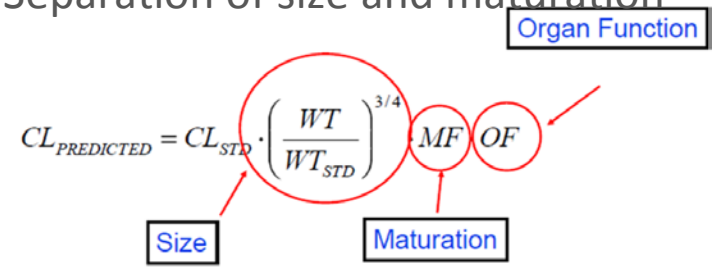
Weiss et al. Neuro-oncology. 2015 Apr;17(4):596-603; Weiss et al. Pediatric blood & cancer. 2014 Jun;61(6):982-6.
Adams et al. Pediatrics 2015. Efficacy and Safety of Sirolimus in the Treatment of Complicated Vascular Anomalies.

Maturation of drug clearance
- PBPK Simulations *vs.* Clinical observations -

Allometrically scaled Clearance *vs.* Age



Separation of size and maturation



- Individual clinical observations (N=21, 0 to 3 years-old patients)
- Median PBPK predicted profile
- 25 to 75 percentiles
- 5 to 95 percentiles

Emoto C, Fukuda T, Vinks AA et al. Development of a PBPK model for Sirolimus: Applying Principles of Growth and Maturation in Neonates and Infants. CPT: Pharmacometrics Syst Pharmacol. 2015 Feb;4(2):e17.

Abstract for the 21st International Workshop on Vascular Anomalies (ISSVA 2016) April 26-29, 2016, Buenos Aires, Argentina

Title: Developmental Pharmacokinetics of Sirolimus: implications for dosing in neonates and infants with vascular anomalies

Authors: Tomoyuki Mizuno, PhD, Chie Emoto, PhD, Tsuyoshi Fukuda, PhD, Paula Mobberley-Schuman, Adrienne Hammill MD PhD, Denise M. Adams, MD, Alexander A. Vinks, PharmD, PhD

Purpose: We recently reported sirolimus to be efficacious and well tolerated in patients with complicated vascular anomalies. Nevertheless dosing information for this pediatric population is very limited, especially for neonates and infants. The purpose of this study was to characterize the developmental trajectory of sirolimus clearance in very young patients using data from our pharmacokinetically guided clinical trial. In addition, we developed an age-appropriate dosing algorithm to facilitate achievement of the appropriate sirolimus target concentrations.

Methods: A total of 316 sirolimus pre-dose concentrations were obtained from 24 patients aged 3 weeks to 4 years participating in a concentration-controlled sirolimus Phase 2 study in children with complicated vascular anomalies. Sirolimus pharmacokinetic (PK) parameters were calculated using Bayesian estimation with a recently published population PK model (MW/Pharm, Mediware, Czech Republic). Allometrically scaled sirolimus clearance was modeled as a function of age using a sigmoidal E_{max} model (NONMEM 7.2, ICON, USA). Using the developmental PK model, sirolimus doses required to reach a trough target concentration of 10-15 ng/mL were simulated across the different age groups from 0-24 months.

Results: Allometrically scaled sirolimus clearance increased with age up to 24 months. The non-linear relationship between age and allometrically scaled clearance was well described by the sigmoidal E_{max} model. Based on the developmental PK model, predicted sirolimus maintenance doses were estimated as 0.4, 0.6, 0.9, 1.3 and 1.6 mg/m^2 every 12 hours for the 1, 3, 6, 12 and 24 months age groups, respectively.

Conclusion: This study quantitatively described the relationship between sirolimus clearance and age in neonates and infants. An age-appropriate dosing algorithm was developed that will facilitate sirolimus target concentration attainment. This algorithm in combination with therapeutic drug monitoring will allow precision dosing in very young children receiving sirolimus treatment for complicated vascular anomalies.

Target Controlled Drug Management

Participating Centers

Patient visit
Data & sample collection
UPS shipment
Web/email notification

Centralized
LC-MS/MS
Bio-Analysis

Confirmation
Dose change

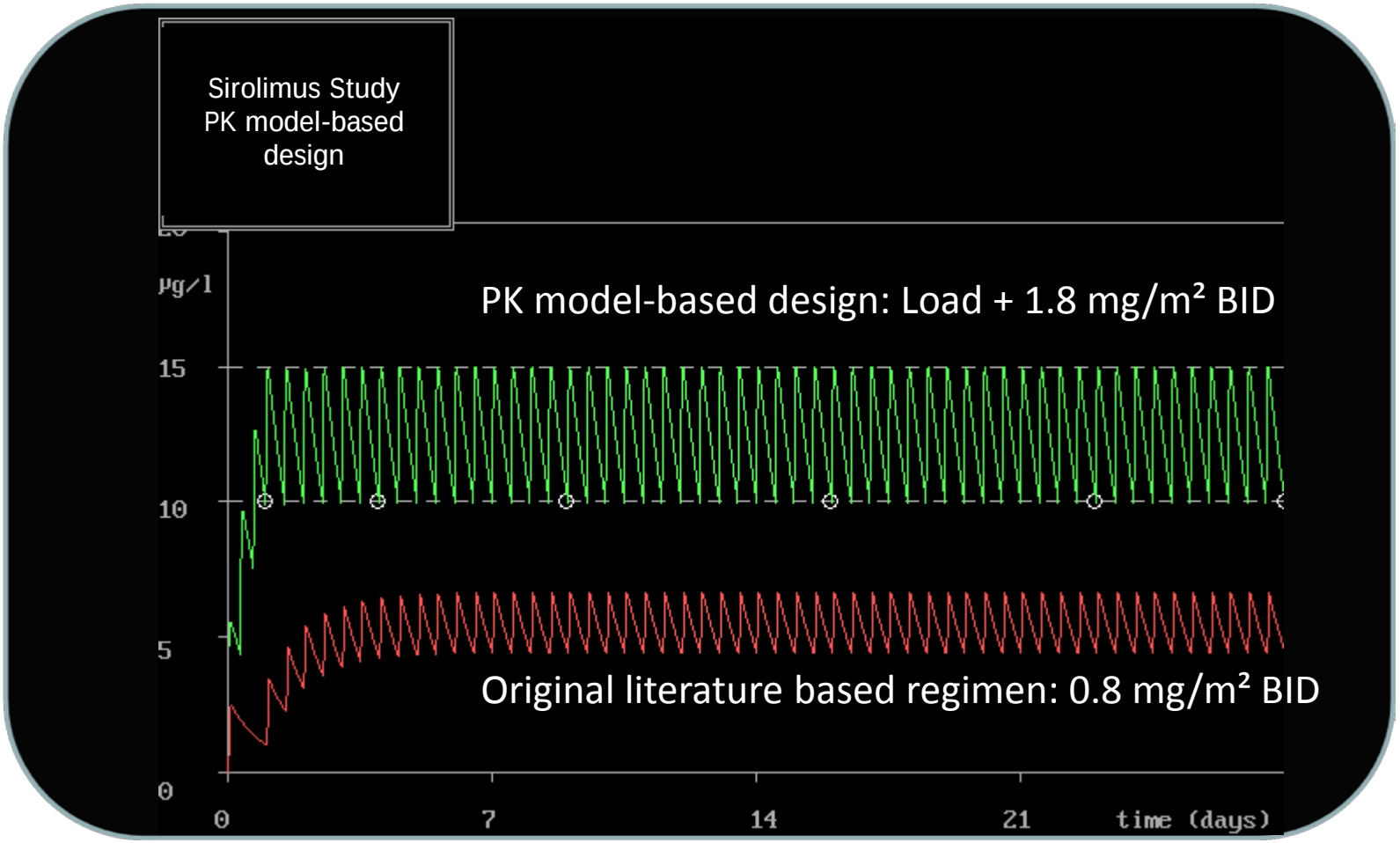
Bayesian estimation
Dosing recommendation
Uploaded to web portal
Email notification

Results reported
via Web portal
Email notification

http://clinicaltrials.gov/ct2/show/NCT00634270

Pharmacokinetically Guided Dosing of Sirolimus

Pilot study in refractory acute lymphoblastic leukemia/lymphoma



PK model-based prediction for a 8y old, 29.8 Kg male patient (BSA 1.0 m^2).
Loading dose: 5.4 mg, administered as 1.8mg q8h on day 1; maintenance dose of 1.8 mg BID.
Predicted concentrations (open circles) per protocol on days 1, 4, 9, 16, 23, and 28.
Pre-dose trough target 10-12 ng/mL; range 10-15 ng/mL (dotted lines)

Concluding remarks

- Modeling and simulation are powerful tools for the design of informative PK/PD studies in neonates, infants and children
- With relative sparse data, and application of literature information it is possible to make (initial) informed decisions on pediatric study design
- Implementation of D-optimal design will increase information content and improve the cost-effectiveness of studies
- PBPK (and PD) will improve our understanding of important ontogeny effects and help identify those studies that have to be performed to support pediatric drug development
- Model-based dosing (Bayesian estimator) is the way forward in concentration controlled trials in pediatric drug development and clinical precision dosing in children

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Downtown Cincinnati view across Ohio river from Northern Kentucky