Project Title

Model-informed drug development and precision dosing in neonates and infants (MONI)

Narrative summary (Character limit: 700)

Paediatric clinical studies often face limitations. One of the biggest challenges in the younger paediatric group (i.e., neonates, infants and toddlers) is defining a safe and effective dose. Thus, sampling size, growth and maturation are crucial aspects to consider when modeling and simulation tools are used to estimate key parameters that guide dose selection. Diverse strategies are reported; however, no clear approach defines paediatric doses. To achieve this, different methodologies will be investigated and compared in this project concerning their applicability in the context of paediatric trials.

Scientific abstract (Character limit: 1,600) *(provide a structured abstract using the following sub-headings: Background; Objective; Study Design; Participants; Primary and Secondary Outcome Measure (s) and Statistical Analysis)*

Background: During first-in-child studies, allometric and maturation functions are applied to scale drug clearance across the paediatric age range; a key aspect to characterize dose-exposure-response and establish dose selection. Factors altering reliability have been explored; however, clear strategies need to be investigated.

Objective: To validate the a priori guidance of paediatric decision tables to extrapolate clearance across age subgroups and drug characteristics while integrating study design scenarios to improve accuracy and precision of clearance estimation.

Study Design: Pharmacometric analysis and simulation studies.

Participants: Paediatric population from zero to two years, undergoing intravenous and/or oral administration of drugs subject to phase I metabolic processes, substrate to transporters, hepatically and/or renally excreted.

Main Outcome Measure (s): Accuracy and precision of clearance prediction, defined as a normalized root mean squared error <30% and a relative standard error <20%.

Statistical Analysis: Bias and precision between the reference and predicted clearance will be assessed by calculation of the relative and absolute relative estimation errors. The parameter uncertainty will be evaluated by non-parametric bootstrap, log-likelihood profile-sampling important resampling, and standard error analysis. Finally, a stochastic simulation-estimation approach will be performed to ensure optimality of design factors in the clearance prediction.

Brief Project Background and Statement of Project Significance

Clinical studies in paediatric drug development often face limitations, such as a small number of patients, restricted sample size, limited blood volumes and ethical implications. These challenges are particularly pronounced in younger paediatric groups (i.e. neonates, infants and toddlers). As a result, to inform treatment regimens, the definition of paediatric doses is typically based on extrapolated knowledge from a reference population (e.g., older children or adults). In this context, clearance is an essential pharmacokinetic parameter in determining dose adjustments required to achieve a similar exposure in adults and children. However, the physiological alterations leading to changes in drug elimination from birth to adulthood complicate the definition of an adequate dose for different paediatric age groups.

Modeling and simulation approaches are valuable tools to characterize drug pharmacokinetics. Available knowledge on e.g. alterations in body size with age can be incorporated into the models. However, accounting only for body size is insufficient in children below two years of age; therefore, additional developmental changes need to be considered. To address this, maturation functions are incorporated to characterize the developmental changes in drug-specific elimination pathways (e.g. specific enzymes).

Furthermore, the estimating appropriate sample sizes for paediatric studies (patient numbers as well as samples per patient) investigating the drug characteristics in the paediatric population is crucial. Sample size definition should focus on the precise estimation of key parameters defining paediatric dose selection.

Different combinations of scaling methods, maturation functions and strategies on sample size selection are reported in literature; however, there are currently no clear strategies to define paediatric doses. To achieve this, diverse strategies available to describe clearance will be investigated with respect to their applicability in the context of first-in-child dosing in paediatric trials. This pharmacometric analyses and simulation studies will be conducted at the University of Bonn and the Federal Institute for Drugs and Medical Devices (BfArM), Bonn, Germany, from July 2025 to September 2026 (*Figure 1, file attachment no. 1*).

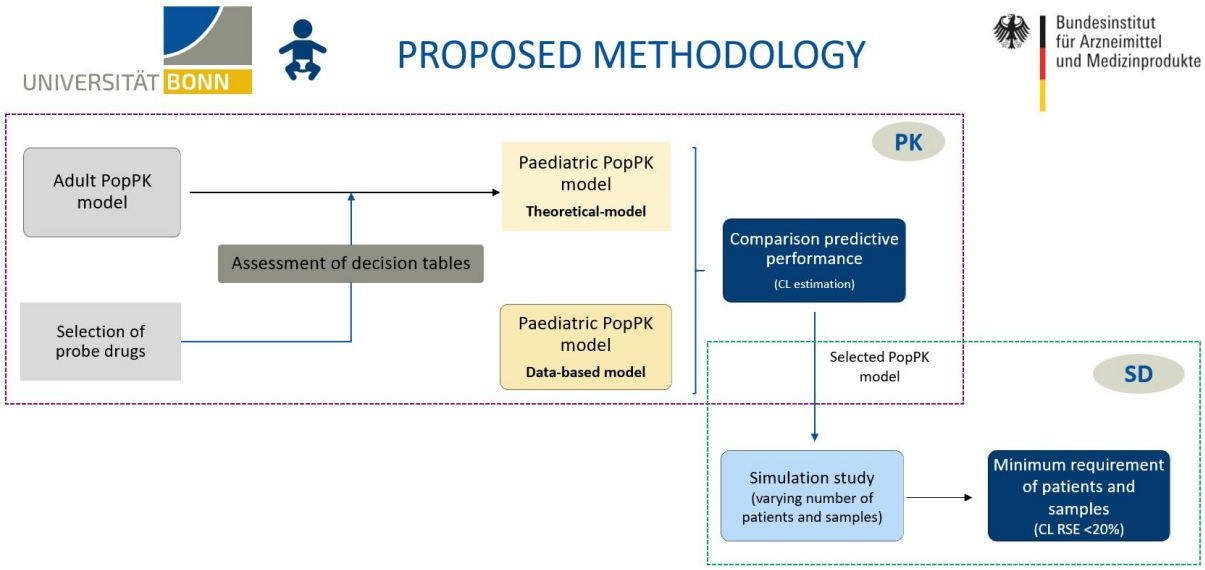

Figure 1. Model-informed drug development and precision dosing in neonates and infants (MONI): Drug-specific workflow
PK: Pharmacokinetic; SD: Study design Part

This pharmacometric analysis and simulation study will be based on an established adult model in which scaling functions, such as linear or allometric scaling (using a fixed exponent of 0.75) and maturation functions, will be incorporated in depending on the drug's pharmacokinetic properties and the paediatric age range, as suggested by the decision tables proposed by van Rongen et al. (2022) (*Figure 2, file attachment no. 2)*. Afterwards, precision and bias of the clearance estimation (data-based model) and prediction (theoretical model) will be compared to determine whether using the decision tables leads to an accurate and precise estimation of relevant pharmacokinetic parameters. In a second step, an additional analysis with the data-based model will be performed via stochastic simulation-estimation (SSE), assessing diverse design properties, such as the number of patients per cohort and sampling schedules in clinical trial scenarios to identify a minimum viable design to provide an accurate and precise estimation of clearance.

Study selection criteria were based on:

- Drugs with diverse pharmacokinetic properties (i.e., renally or hepatically cleared, different extraction ratios, differing fractions unbound of the drug, and substrate to transporters)
- Availability of ontogeny data for the enzymes/transporters involved in the metabolism of the pre-selected drugs.

For each requested clinical study, the same inclusion/exclusion criteria are applied

Specific aims of the Project (Provide description of the aims, including the study objectives and the specific hypothesis)

Based on extensive experience in paediatric studies, Van Rongen et al. (2022) have developed a useful approach for clearance prediction in paediatric patients and provided an a priori guidance in form of decision tables based on specific drug characteristics and patient's age (pp.17-19). The aim of our analyses is to validate the a priori guidance of their decision tables to extrapolate clearance across age-subgroups and drug characteristics (renal/hepatic elimination, fraction unbound, extraction ratio, and involvement of enzymes or transporters) while integrating study design scenarios to improve accuracy and precision of clearance estimation.

The specific objectives are:

1. Validate the scaling methods and maturation functions obtained from literature (van Rongen et al., 2022) to scale clearance in paediatric patients under two years and compare the predictive performance between the different clearance estimation methods in terms of accuracy and precision.
2. Assessment of optimal design scenarios related to number of patients per cohort number of samples and sampling schedule, to ensure a precise clearance estimation.

Hypothesis evaluated: The a priori incorporation of specific scaling methods and maturation functions adapted to paediatric age ranges and supported by optimal design scenarios, can improve the precision of clearance estimation in model-based approaches for children under two years when integrated into paediatric trials.

What is your Study Design?

- Individual trial analysis
- Meta-analysis (analysis of multiple trials together
- Methodological research
- Other

What is the purpose of the analysis being proposed? Please select all that apply:

- New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations
- New research question to examine treatment safety
- Confirm or validate previously conducted research on treatment effectiveness
- Confirm or validate previously conducted research on treatment safety
- Preliminary research to be used as part of a grant proposal
- Summary level data meta-analysis

- Meta-analysis using only data from the YODA Project
- Meta-Analysis using data from the YODA Project and other data sources
- Participant- level data meta-analysis
- Meta-analysis using only data from the YODA Project
- Meta-analysis using data from the YODA Project and other data sources
- Develop or refine statistical methods
- Research on clinical trial methods
- Research on comparison group
- Research on clinical prediction or risk prediction
- Other

Please justify: Modelling and simulation, statistical methods, support clinical trial design

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study (*list the explicit inclusion and exclusion criteria (i.e.: demographic/clinical characteristics) that will be applied to the patients in each trial to define your study sample)*

The proposed study will rely on data requested from the YODA Project, external providers in the Vivli Platform: The National Institute of Child Health and Human Development (NICHD), and BioMarin Pharmaceutical

For each requested clinical study, the same inclusion/exclusion criteria are applied:

Inclusion criteria: Paediatric population from zero to two years, receiving intravenous and/ or oral administration of drugs with the following scenarios:

a) Metabolized by phase I metabolism via CYP450 (bosentan, clindamycin, fluticasone propionate, methadone, sildenafil).

b) Renally excreted via tubular secretion and or glomerular filtration (ampicillin. cefepime, fluconazole, levofloxacin, meropenem, topiramate, vosoritide).

c) Substrate to transporters (ampicillin, cefepime, fluticasone, lamotrigine, methadone, meropenem, rifampin, sildenafil)

Exclusion criteria: Patients under treatment with biological drugs (e.g., adalimumab, abatacept) and renal replacement patients.

It is planned to evaluate diverse scenarios with drugs that may differ significantly from each other. Thus, it is not intended to combine any of the requested datasets. Instead, we plan to analyze each study/platform separately, as indicated in this SAP. Table 1 (*file attachment no. 3*) provides additional information on the characteristics of the pre-selected drugs.

1. Characteristics of pre-selected drugs

Table 1A. Characteristics of drugs requested from Vivli and other data-sharing platforms

	Ampicillin	***Bosentan***	***Cefepime***	***Clindamycin***	***Fluconazole***	***Fluticasone***	***Lamotrigine***
Reason for paediatric application	Administered as standard of care in the NICus by their caregiver	Pulmonary arterial hypertension (PAH)	Critically ill patients with extracorporeal membrane oxygenation (ECMO)	Intra-abdominal infections	Prophylaxis for prevention of candidiasis	Persistent asthma	Epilepsy
Therapeutic window (paediatric)	% fT>MIC	50-200 ng/mL	40%fT> MIC	fC_{50SS} > MIC	$AUC2_{4h}$/MIC >50		2,06 – 8,43 mg/L
Publication available							
PBPK model	Simcyp*	Simcyp*	PK-Sim*	PK-Sim*	PK-Sim**// Simcyp**	No PBPK in paediatrics	GastroPlus*
PopPK model	√ [a-b]	-	√ [a-b]	√ [a]	√ [a-b]	√ [b]	√ [b]
Other	-	NCA	-	-	-	-	NCA
Decision tables Van Rongen et al.							
Protein binding (%)	20	98	16-20	60-94[c]	12	99	55
fu adults	0,8	0,02	0,8-0,84	0,06-0,4	0,88	-	0,45
ER adults	<0.3	0.44	<0.3	<0.3	<0.3	<0.3	<0.3
P-gP	-	-	Substrate	Substrate	-	Substrate	-
SLC	-	-	-	-	-	Inhibitor	-
OATs	Substrate	-	-	-	-		-
Excretion	90% renal	Hepatic metabolism	85% renal		80% renal		94% renal
CYP450-							

2A6	-	-	-	-	-		-
2E1	-	-	-	-	-		-
2C9	-	Substrate	-	-	-		-
2B6	-	-	-	-	-		-
2D6	-	-	Substrate	-	-		-
3A4	-	Substrate	-	Substrate	Inhibitor	Inhibitor	-
1A2	-	-	-	-	-	-	-
2C9	-	-	-	-	Inhibitor	-	-
2D6	-	-	-	-	-	-	-
2C19	-	-	-	-	Inhibitor	-	-

[a]Publication available based on paediatric population; [b] Publication available on adults with same disease status; [c] Binding primarily to alpha-1-acid glycoprotein; [*] Publication available on indicated platform; [**] Template available in PBPK platform; NCA: noncompartmental analysis

AUC24h: Area under the curve at 24 hours; ER: Extraction rate; fC_{50SS} > MIC: *Unbound steady-state concentration at half the dosing interval greater than the minimum inhibitory concentration; fT>MIC: Time in which free concentration exceeds the minimum inhibitory concentration; fu: Fraction unbound of drug; MIC: Minimum inhibitory concentration; OATs: Organic anion transporters; NCA: Non-compartmental analysis; NICUs: Neonatal intensive care unit; PBPK: Physiological based pharmacokinetics; P-gp: Multidrug-resistance protein 1; PopPK: Population pharmacokinetics model; SLC: Solute carrier transporter.*

Table 1B. Characteristics of drugs requested from Vivli and other data-sharing platforms

	Levofloxacin	***Lorazepam***	***Mebendazole***	***Meropenem***	***Methadone***	***Metronidazole***	***Rifampin***
Reason for paediatric application	Community-acquired pneumonia	Epileptic status	Helminth infections	Suspected or complicated intraabdominal infections	Administration as standard of care by their caregiver	Suspected or complicated intraabdominal infections	Critically ill patients
Therapeutic window	AUC24h/MIC>80	50-100 ng/mL	AUC24h/MIC >50	40% fT>MIC	400 – 600 ng/mL	AUC24h/MIC > 70	8-24 ug/mL
Publication available							
PBPK model	PK-Sim*	PK-Sim*// Simcyp*		PK-Sim*	PK-Sim**	Simcyp*	PK-Sim**// Simcyp**
PopPK model	√ [a-b]	√ [a]		√ [a-b]	√ [b]	√ [a-b]	√ [a-b]
Other	-	-		-	-	-	-
Decision tables Van Rongen et al.							
Protein binding (%)	24-38	85	90-95	2	85-90[a]	<20	90
fu adults	0,62-0,76	0,15	0,05-0,1	0,98	0,1-0,15	> 0,8	0,1
ER adults	<0.3	0.05	>0.6	<0.3	0.089	<0.3	<0.3
P-gP	Inhibitor	Substrate	Inhibitor	-	Substrate	-	Inhibitor
OATs	-	-	-	Low affinity	-	-	Inhibitor
Excretion	87% renal	88% renal – 7% feces		80% renal		60-80% renal	Primarily hepatic
CYP450-							
2A6	Inhibitor	-	-	-	-	-	Inducer

2E1	-	-	-	-	-	-	Inducer
2C9	-	-	-	-	Substrate	-	-
2B6	-	-	-	-	Substrate	-	Inducer
2D6	-	-	-	-	Substrate	-	-
3A4	-	Substrate	-	Substrate	Substrate	-	Inducer
1A2	-	Inhibitor	Inhibitor	-	Inhibitor	-	Inducer
2C9	-	-	-	-	-	-	-
2D6	-	-	-	-	Inhibitor	-	-
2C19	-	Inhibitor	-	-	-	-	Inducer

[a]Publication available based on paediatric population; [b] Publication available on adults with same disease status; [c] Binding primarily to alpha-1-acid glycoprotein; [*] Publication available on indicated platform; [**] Template available in PBPK platform; NCA: noncompartmental analysis

AUC24h: Area under the curve at 24 hours; ER: Extraction rate; fT>MIC: Time in which free concentration exceeds the minimum inhibitory concentration; fu: Fraction unbound of drug; MIC: Minimum inhibitory concentration; OATs: Organic anion transporters; PBPK: Physiological based pharmacokinetics; P-gp: Multidrug-resistance protein 1; PopPK: Population pharmacokinetics model; SLC: Solute carrier transporter.

Table 1C. Characteristics of drugs requested from Vivli and other data-sharing platforms

	Sildenafil	***Ticarcillin***	***Topiramate***	***Vosoritide***
Reason for paediatric application	Treatment in premature infants with Pulmonary Hypertension	Staphylococcal infection in term and premature infants	Partial onset seizures	Achondroplasia
Therapeutic window (paediatric)	20-50 ng/mL	40% fT>MIC	5-20 ug/mL	<15 µg/Kg
Publication available				
PBPK model	PK-Sim*	Minimal PBPK	No PBPK model info available	No PBPK model info available
PopPK model	√ [a-b]	√ [a-]	√ [b]	√ [a-b]
Other	-	-	*****Randomized study	**-**
Decision tables Van Rongen et al.				
Protein binding (%)	96	45	9-17	NA
fu adults	0,04	0,55	0,83-0,91	NA
ER adults	>0.6	<0.3	0.3	<0.3
P-gP	Substrate	Substrate	-	NA
OATs	-	Substrate	-	-
Excretion	80% excreted in feces	*80-90% renally excreted*	80% renal excreted	*Renal excretion*
CYP450-				
2A6	-	**-**	-	-
2E1	-	**-**	-	-
2C9	*Inhibitor*	**-**	-	-
2B6	-	**-**	-	-

2D6	*Substrate*	-	-	-
3A4	*Substrate*	-	Inducer	-
1A2	-	-	-	-
2C9	-	-	-	-
2D6	-	-	-	-
2C19	-	-	Weak Inhibitor	-

[a]Publication available based on paediatric population; [b] Publication available on adults with same disease status; [c] Binding primarily to alpha-1-acid glycoprotein; [*] Publication available on indicated platform; [**] Template available in PBPK platform; NCA: noncompartmental analysis

AUC24h: Area under the curve at 24 hours; ER: Extraction rate; fT>MIC: Time in which free concentration exceeds the minimum inhibitory concentration; fu: Fraction unbound of drug; MIC: Minimum inhibitory concentration; OATs: Organic anion transporters; PBPK: Physiological based pharmacokinetics; P-gp: Multidrug-resistance protein 1; PopPK: Population pharmacokinetics model; SLC: Solute carrier transporter.

Primary and Secondary Outcome Measure (s) and how they will be categorized/ defined for your study.

This project focuses on methodological approaches, i.e. pharmacometric and simulation analysis of concentration data. The project is divided into two parts, a pharmacokinetic part (PK) and a study design part (SD). The primary and secondary outcomes were defined accordingly.

1. Pharmacokinetic part:

Primary outcome measure: Accuracy and precision of estimating individual clearance.

Secondary outcome measures: Accuracy and precision of estimating additional individual pharmacokinetic parameters (e.g., volume of distribution).

2. Study design part:

Primary outcome measure: Minimum number of patients and samples per patient required to obtain sufficiently precise estimates of clearance.

Secondary outcome measures: Minimum number of patients and samples per patient required to obtain sufficiently precise estimates of additional pharmacokinetic parameters (e.g., volume of distribution).

Main Predictor / Independent variable and how it will be categorized/defined for your study

The independent variables relevant to our study are sample collection time (expressed in time units), and patient-specific factors: weight, creatinine clearance, PMA, and age categorized according to the International Council for Harmonisation for Technical Requirements (ICH) into preterm newborn infants, term newborn infants (0-27 days), and infants and toddlers (28 days to 23 months). In addition, the dependent variable for this study is the drug plasma concentration (expressed in mass per volume units).

Other variables of interest (optional):

Drug data: dose, dose interval, administration rate, infusion rate, sampling schedule.

Modeling file types: Control stream of the final model .mod and .csv files (if available).

Clinical and anthropometric data: height

Pathological data (if applicable): mechanical ventilation, concomitant treatment, sepsis, etc.

Statistical Analysis Plan (SAP)

The paediatric clinical data was selected based on the characteristics of the included population (from zero to two years) and the types of drugs studied (pharmacokinetic properties, i.e., renally or hepatically cleared, extraction ratios, fraction unbound of the drug, substrate to transporters and availability of ontogeny data for the enzymes participating in the drug metabolism).

The proposed study will rely on data requested from Vivli and external providers from the YODA Project and BioMarin Pharmaceutical. As mentioned before, it is planned to evaluate diverse scenarios with drugs that may differ significantly from each other. Thus, it is not intended to combine any of the requested datasets. Instead, we plan to analyze each study/platform separately, as indicated in this SAP.

The population data includes all paediatric patients under two years of age for whom pharmacokinetic information is available. Missing data are anticipated in the following scenarios: (a) missing dependent variable (drug plasma concentration); (b) missing dependent variable due to concentrations below the limit of quantification; (c) missing covariates (e.g., age, weight, PMA, creatinine clearance) or (d) missing time points. Multiple imputation methods based on the missing-at-random (MAR) assumption will be applied if needed to address these problems.

The descriptive analysis will consider the demographic and clinical characteristics of the study population. For continuous variables (e.g., age, weight, PMA, clearance), measures of central tendency and range, such as mean, median, and standard deviation, will be used. For categorical covariates (e.g., sex, comorbidities, race, etc.), frequency and proportion will be analysed.

After the exploratory analysis, a nonlinear mixed-effects model (NLME) will be developed to extrapolate an adult to a paediatric model using the scaling methods and maturation functions, resulting in a theoretical-model. Moreover, to evaluate the accuracy of clearance predictions, comparing the predicted clearance (theoretical model) with the reference clearance (data-based model) values (assuming log-normal distribution), using two key metrics to evaluate the bias and precision of the predictive performance: (i) RER and (ii) rBias, respectively. Moreover, parameter uncertainty is going to be evaluated by non-parametric bootstrap (n=1000 simulations) and commonly used methods (i.e., log-likelihood profiling – sampling importance resampling (LLP-SIR), and standard error).

To assess the impact of different design options on clearance prediction, we will develop a parametric bootstrap analysis, also known as SSE. Datasets are going to be simulated based on

the data-based model, using the final parameter estimates and the study design. First, we will perform a pilot evaluation to examine the impact of the number of SSE replications on parameter estimation (number of simulations K=100, 500, 1000), including an evaluation of the SSE scenarios convergence. Then, parameters will be re-estimated (e.g., K=1000) by exploring diverse design scenarios modifying the N patients per cohort and sampling schedules in clinical trial scenarios (minimal N per cohort =3 and sampling points = 2; with a desired precision to target the 95% confidence intervals within an initial interval of 70-141% of the geometric mean estimate of clearance for each designed group with a 80% power. Finally, a comparison of the clearance values initially used for each simulation from the data-based model will be performed by RER, rBias, and to determine the most adequate design factor, the NRMSE is going to be calculated considering acceptable a cut-off value of <30% and a precise clearance estimate (CL_{RSE} <20%) in the different clinical scenarios.

Software Used

- Phython
- R
- RStudio
- STATA
- Open Office
- I am not analysing participant-level data/plan to use another secure data sharing platform

Software additional information:

As our project will focus on Pharmacometric analyses and simulation studies, we asked to the YODA-Project team and request to Vivli Center for global clinical research the inclusion of the following software into their safety environment platform:

1. NONMEM software v.7.5.1 (Icon Development Solutions, Dublin, Ireland)
2. Pearl-speaks-NONMEM v.5.3.1
3. Pirana Certara USA, Inc., Overlook Center v.23.1.2

Project Timeline (*including anticipated project start date, analysis completion date, date manuscript drafted and first submitted for publication, and date results reported back to the YODA Project*)

- It was estimated by Vivli Center for global clinical research data, an average of 5.4 months considering the approval process, signing the DUA, and uploading the data; therefore, the target analysis was modified accordingly:

- **Anticipated Project Start Date:** November 2025 (or when data received)
- **Analysis Completion Date:** June 2027 (this estimate reflects general results from all the databases requested to additional providers; while data will be analyzed independently, coordination of timelines across providers approvals is considered).
- **Manuscript draft and first submitted for publications:** Three months after competition of analysis the initial manuscript will be completed and submitted to a peer-reviewed journal for publication consideration (considering the data use agreement from the YODA Project)

  Results report to the YODA Project: Within 30 days of acceptance for publication, in accordance with the YODA Project data agreement and reporting requirements.

Dissemination Plan:

The results of these analyses will be submitted as abstracts and presented at international meetings, e.g. of the Population Approach Group in Europe (PAGE), the American Society for Clinical Pharmacology and Therapeutics (ASCPT), the Iberoamerican Pharmacometric Network (RedIF), and the American Association of Pharmaceutical Scientists (AAPS). In addition, it is planned to submit the research findings to peer-reviewed journals targeted at the scientific community, such as Clinical Pharmacokinetics, CPT: Pharmacometrics & Systems Pharmacology, and European Journal of Paediatrics.

Bibliography

van Rongen, A., Krekels, E. H., Calvier, E. A et al., (2022). An update on the use of allometric and other scaling methods to scale drug clearance in children: towards decision tables. Expert Opinion on Drug Metabolism & Toxicology, 18(2), 99-113.

Owen, J. S., & Fiedler-Kelly, J. (2014). Introduction to population pharmacokinetic/ pharmacodynamic analysis with nonlinear mixed effects models. John Wiley & Sons.

Supplementary information

2. Decision tables from van Rongen et al., 2022

Table 1. Decision table for pediatric scaling methods for renally cleared drugs through glomerular filtration (GF) and active tubular secretion (ATS) for typical children of different ages.

	1 day[1]	1 month[1]	6 months	1 year	2 years	5 years	15 years
GF of drugs binding to albumin	*If $f_{u,adults}$ > 0.34* PBPK	LinearBW	AS0.75	**AS0.75**	**AS0.75**	**AS0.75**	AS0.75
	If $f_{u,adults}$ ≤0.34 LinearBW		**LinearBW**	LinearBW	LinearBW	LinearBW	LinearBW
GF of drugs binding to AAG	*If $f_{u,adults}$ < 0.23 OR $f_{u,adults}$ > 0.78* PBPK	*If $f_{u,adults}$ ≤0.45* AS0.75	*All $f_{u,adults}$ values* AS0.75	*All $f_{u,adults}$ values* **AS0.75**	*All $f_{u,adults}$ values* **AS0.75**	**AS0.75**	AS0.75
	If $f_{u,adults}$ 0.23-0.78 LinearBW	*If $f_{u,adults}$ ≥ 0.34* LinearBW	*If $f_{u,adults}$ ≥ 0.34* LinearBW	*If $f_{u,adults}$ ≥ 0.34* LinearBW	*If $f_{u,adults}$ ≥ 0.34* LinearBW	LinearBW	LinearBW
ATS	OCT2	OCT2					
	OAT1	OAT1	OAT1				
	OAT3	OAT3	OAT3	OAT3			
	Pgp	Pgp					

For GF results are split by plasma protein that the drug is binding to; albumin or AAG. When the table refers to two scaling options; **bold font indicates systematically most (reasonably) accurate scaling method**, regular font indicates systematically less accurate, but still (reasonably) accurate scaling option. Both scaling options with regular font indicates both scaling methods perform equally well. In some cases a scaling method can only be applied for drugs with specific properties (depicted in *italic font*).

For active tubular secretion (ATS); green color indicates scaling based on GF only is accurate and ATS does not need to be taken into account for accurate pediatric renal clearance scaling. Pink color indicates for which transporters, transporter maturation needs to be taken into account to achieve accurate scaling.

AAG = α_1-acid glycoprotein; AS0.75 = fixed allometric scaling with an exponent of 0.75; ATS = active tubular secretion; $f_{u,adults}$ = drug fraction unbound in adults; GF = glomerular filtration; linearBW = linear bodyweight-based scaling; OAT = organic anion transporter; OCT = organic cation transporter; PBPK = physiologically-based pharmacokinetic modeling; Pgp = P-glycoprotein

[1]The decision table applies to term neonates only.

Figure 2A. Reprinted from van Rongen et al., 2022; *Expert opinion on drug metabolism & toxicology*; https://doi.org/10.1080/17425255.2021.2027907

2. Decision tables from van Rongen et al., 2022

Table 2. Decision table for pediatric scaling methods for hepatically cleared drugs binding to *albumin* for typical children of different ages.

	1 day [1,2,3]	1 month[1,3]	6 months	1 year	2 years	5 years	15 years
100% enzyme maturation	AS0.75[2]	**AS0.75**	AS0.75	AS0.75	**AS0.75**	**AS0.75**	AS0.75
	LinearBW[2,4]	LinearBW	LinearBW	LinearBW	LinearBW	LinearBW	LinearBW
Highest % enzyme maturation[5]	AS0.75[3]	**AS0.75[3]**	**AS0.75**	**AS0.75**	**AS0.75**	**AS0.75**	AS0.75
	LinearBW[3,4]	LinearBW[3]	LinearBW	LinearBW[4]	LinearBW[4]	LinearBW[4]	LinearBW
Lowest % enzyme maturation[5]	*If low + IM* ER_{adults} AS0.75×MF_{PBPK}	*If low + IM* ER_{adults} AS0.75×MF_{PBPK}	*If low + IM* ER_{adults} AS0.75×MF_{PBPK} BEPC[6]	*If low + IM* ER_{adults} AS0.75×MF_{PBPK} BEPC[6]	LinearBW[7]	AS0.75[7]	AS0.75
	If high ER_{adults} PBPK	*If high* ER_{adults} PBPK	*If high* ER_{adults} PBPK	*If high* ER_{adults} PBPK		**LinearBW[7]**	LinearBW

AS0.75 and linearBW are considered first, only when these scaling methods are not accurate, other methods are considered.

Results are split by enzyme maturation (100% of adult values, highest and lowest reported enzyme maturation value for each age according to Table 4). When the table refers to two scaling options; **bold font indicates systematically most (reasonably) accurate scaling method**, regular font indicates systematically less accurate, but still (reasonably) accurate scaling option. Both scaling options with regular font indicates both scaling methods perform equally well. In some cases a scaling method can only be applied for drugs with specific properties (depicted in *italic font*).

AS0.75 = fixed allometric scaling with an exponent of 0.75; BEPC = between-drug extrapolation of pathway-specific pediatric covariate functions [15]; ER_{adults} = extraction ratio in adults; IM = intermediate; linearBW = linear bodyweight-based scaling; MF_{PBPK} = maturation function obtained from PBPK model expressing isoenzyme maturation as percentage of adult values of isoenzyme abundance according to Table 4; PBPK = physiologically-based pharmacokinetic modeling

[1]The decision table applies to term neonates only.

[2]For term neonates of 1 day 100% enzyme maturation is only applicable to SULT1A1, other enzyme maturation values are low (see Table 4), therefore for 1 day old neonates mostly the lowest % enzyme maturation is applicable.

[3]For term neonates of 1 day and 1 month; no isoenzymes with an isoenzyme activity higher than 100% (SULT1A1) exist, so highest enzyme maturation is equal to 100% enzyme maturation.

[4]For drugs with low ER (≤ 0.3) few drugs have a PE% that is slightly higher than 50% (max 60%).

[5]The lowest and highest values for every age are: 10% and 100% at 1 day and 1 month, 21% and 122% at 6 months, 13% and 153% at 1 year, 18% and 159% at 2 years, 32% and 152% at 5 years, and 79% and 125% at 15 years (see Table 4 for reference).

[6]BEPC is possible from model drugs with low ER to drugs with low and intermediate (0.3–0.7) ER. And for model drugs with intermediate ER to test drugs with low and intermediate ER.

[7]Exception for drugs mainly metabolized by UGT2B7; for 2-5-year-old children the same scaling methods as 1 year should be used (AS0.75×MF_{PBPK}, BEPC or PBPK), because of very low UBT2B7 enzyme maturation at these ages.

Figure 2B. Reprinted from van Rongen et al., 2022; *Expert opinion on drug metabolism & toxicology*; https://doi.org/10.1080/17425255.2021.2027907

2. Decision tables from van Rongen et al., 2022

Table 3. Decision table for pediatric scaling methods for hepatically cleared drugs binding *a_1-acid glycoprotein* for typical children of different ages.

	1 day[1,2,3]	1 month[1,3]	6 months	1 year	2 years	5 years	15 years
100% enzyme maturation	PBPK[2]	*If high + IM ER_{adults}* AS0.75	AS0.75	AS0.75	**AS0.75**	**AS0.75**	AS0.75
		If low ER_{adults} AS0.75×MF_{PBPK} BEPC			LinearBW[4]	LinearBW	LinearBW
Highest % enzyme maturation[5]	PBPK[3]	*If high + IM ER_{adults}* AS0.75[3]	*If high + IM ER_{adults}* AS0.75	*If high + IM ER_{adults}* AS0.75	*If high + IM ER_{adults}* AS0.75	AS0.75	AS0.75
		If low ER_{adults} AS0.75×MF_{PBPK}[3] BEPC[3]	*If low ER_{adults}* AS0.75×MF_{PBPK} BEPC	*If low ER_{adults}* AS0.75×MF_{PBPK} BEPC	*If low ER_{adults}* AS0.75×MF_{PBPK} BEPC		LinearBW
Lowest % enzyme maturation[5]	PBPK	*If low + IM ER_{adults}* AS0.75×MF_{PBPK}	*If low + IM ER_{adults}* AS0.75×MF_{PBPK}	*If low + IM ER_{adults}* AS0.75×MF_{PBPK}	LinearBW[6]	**AS0.75[6]**	AS0.75
		If high ER_{adults} PBPK	*If high ER_{adults}* PBPK	*If high ER_{adults}* PBPK		LinearBW[6]	LinearBW

AS0.75 and linearBW are considered first, only when these scaling methods are not accurate, other methods are considered.

Results are split by enzyme maturation (100% of adult values, highest and lowest reported enzyme maturation value for each age according to Table 4). When the table refers to two scaling options; **bold font indicates systematically most (reasonably) accurate scaling method**, regular font indicates systematically less accurate, but still (reasonably) accurate scaling option. Both scaling options with regular font indicates both scaling methods perform equally well. In some cases a scaling method can only be applied for drugs with specific properties (depicted in *italic font*).

AS0.75 = fixed allometric scaling with an exponent of 0.75; BEPC = between-drug extrapolation of pathway-specific pediatric covariate functions [15]; ER_{adults} = extraction ratio in adults; IM = intermediate; linearBW = linear bodyweight-based scaling; MF_{PBPK} = maturation function obtained from PBPK model expressing isoenzyme maturation as percentage of adult values of isoenzyme abundance according to Table 4; PBPK = physiologically-based pharmacokinetic modeling

[1]The decision table applies to term neonates only.

[2]For term neonates of 1 day 100% enzyme maturation is only applicable to SULT1A1, other enzyme maturation values are low (see Table 4), therefore for 1 day old neonates mostly the lowest % enzyme maturation is applicable.[3] For term neonates of 1 day and 1 month; no isoenzymes with an isoenzyme activity higher than 100% (SULT1A1) exist, so highest enzyme maturation is equal to 100% enzyme maturation.

[4]For drugs with low ER (≤ 0.3) few drugs have a PE% that is slightly higher than 50% (max 60%).

[5]The lowest and highest values for every age are: 10% and 100% at 1 day and 1 month, 21% and 122% at 6 months, 13% and 153% at 1 year, 18% and 159% at 2 years, 32% and 152% at 5 years, and 79% and 125% at 15 years (see Table 4 for reference).

[6]Exception for drugs mainly metabolized by UGT2B7; for 2-5-year-old children the same scaling methods as 1 year should be used (AS0.75×MF_{PBPK} or PBPK), because of very low UBT2B7 enzyme maturation at these ages.

Figure 2C. Reprinted from van Rongen et al., 2022; *Expert opinion on drug metabolism & toxicology*; https://doi.org/10.1080/17425255.2021.2027907

3. Vivli Listed and Provisioned Studies by External Providers

Table 2. Studies requested from Vivli and other data-sharing platforms

Vivli listed and provisioned studies	Sponsor Protocol ID	URL to request data	Title	Data Contributor name	Data requested from
	10.57982/84p7-c722	https://dash.nichd.nih.gov/study/20222	Ampicillin	National Institute of Child Health and Human Development (NICHD)	Vivli
	10.57982/ra7e-8508	https://dash.nichd.nih.gov/study/416147	Cefepime	National Institute of Child Health and Human Development (NICHD)	Vivli
	10.57982/m14h-jc69	https://dash.nichd.nih.gov/study/412574	Clindamycin	National Institute of Child Health and Human Development (NICHD)	Vivli
	10.57982/xcc3-4r53	https://dash.nichd.nih.gov/study/19812	Fluconazole	National Institute of Child Health and Human Development (NICHD)	Vivli

	AsthmaNet 004	https://biolincc.nhlbi.nih.gov/studies/asthmanet_infant/	Fluticasone propionate	BioLINCC (a data-sharing platform funded by the National Institutes of Health)	Vivli
	LAM20007	https://www.gsk-studyregister.com/en/trial-details/?id=LAM20007	Lamotrigine	GlaxoSmithKline	Vivli
	10.57982/857e-cw34	https://dash.nichd.nih.gov/study/18573	Lorazepam	National Institute of Child Health and Human Development (NICHD)	Vivli
	10.57982/pjzj-g135	https://dash.nichd.nih.gov/study/2091	Meropenem	National Institute of Child Health and Human Development (NICHD)	Vivli
	10.57982/v50x-0b95	https://dash.nichd.nih.gov/study/424635	Metronidazole	National Institute of Child Health and Human Development (NICHD)	Vivli
	10.57982/b7mw-dt09	https://dash.nichd.nih.gov/study/20477	Methadone	National Institute of Child Health and Human	Vivli

				Development (NICHD)	
	10.57982/kg6t-av39	https://dash.nichd.nih.gov/study/226673	Rifampin	National Institute of Child Health and Human Development (NICHD)	Vivli
	10.57982/xgt1-0q90	https://dash.nichd.nih.gov/study/228953	Sildenafil	National Institute of Child Health and Human Development (NICHD)	Vivli
	10.57982/69rh-3166	https://dash.nichd.nih.gov/study/228768	Ticarcillin	National Institute of Child Health and Human Development (NICHD)	Vivli
Vivli Listed Studies Provisioned by External Providers	**AC-052-374**	https://yoda.yale.edu/clinical-trial/nct01338415-a-prospective-multicenter-open-label-extension-of-future-3-to-assess-the-safety-tolerability-and-efficacy-of-the-pediatric-formulation-of-bosentan-two-versus-three-times-a-day-in-chil/	Bosentan	Johnson & Johnson	YODA Project/Vivli
	CR002392	https://yoda.yale.edu/clinical-trial/nct00034736-a-multicenter-randomized-open-label-comparative-study-to-compare-the-efficacy-and-safety-of-	Levofloxacin	Johnson & Johnson	YODA Project/Vivli

		levofloxacin-and-standard-of-care-therapy-in-the-treatment-of-children-with-community-acqui/			
	CR100933	https://yoda.yale.edu/clinical-trial/nct02034162-a-double-blind-randomized-multi-center-parallel-group-placebo-controlled-study-to-evaluate-the-efficacy-and-safety-of-a-single-dose-of-a-500-mg-chewable-tablet-of-mebendazole-in-the/	Mebendazole	Johnson & Johnson	YODA Project/Vivli
	CR002233	https://yoda.yale.edu/clinical-trial/nct00113815-a-randomized-double-blind-placebo-controlled-fixed-dose-ranging-study-to-assess-the-safety-tolerability-and-efficacy-of-topiramate-oral-liquid-and-sprinkle-formulations-as-an-adjunc/	Topiramate	Johnson & Johnson	YODA Project/Vivli
Studies, Data, or Tools not available on Vivli	NCT03583697	Unique Protocol ID: 111-206 Official Title: A Phase 2 Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of BMN 111 in Infants and Young Children With Achondroplasia, Age 0 to < 60 Months	Vosoritide	BioMarin BioPharmaceutical	BioMarin BioPharmaceutical