Pediatric Qualification Package: CYP2C8 Ontogeny

Version	1.3-OSP12.0
Qualification Plan Release	https://github.com/Open-Systems-Pharmacology/Pediatric_Qualification_Package_CYP2C8_Ontogeny/releases/tag/v1.3
OSP Version	12.0
Qualification Framework Version	3.3

This qualification report is filed at:

https://github.com/Open-Systems-Pharmacology/OSP-Qualification-Reports

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1 Introduction to Pediatric Translation

The presented qualification report evaluates the predictive performance of the OSP suite to predict cytochrome P450 2C8 (CYP2C8)-mediated drug clearance in children.

Therefore, PBPK models of specific *in vivo* probe substances covering children aged below 6 months up to adolescents were built and evaluated. All models are whole-body PBPK models, allowing for pediatric translation in organs expressing CYP2C8. The qualification report demonstrates the level of confidence of the OSP suite with regard to reliable PBPK predictions of age-related CYP2C8-mediated drug clearance during model-informed drug development. The presented PBPK models as well as the respective qualification plan and qualification report are provided open-source and transparently documented (https://github.com/Open-Systems-Pharmacology/Pediatric_Qualification_Package_CYP2C8_Ontogeny).

Translation of Adult PBPK to Children

Using a developed and validated (adult) PBPK model for an *in vivo* probe substance, a pediatric PBPK model can be established for children at different ages by translating physiology, clearance processes (as parameterized in the adult model) and age-dependent protein binding including the variability therein.[Maharaj 2013]

The PBPK models are developed with clinical data of healthy adult subjects obtained from the literature, covering available dosing ranges for e.g. intravenous as well as oral administration, to capture both systemic clearance as well gut-wall metabolic clearance processes. For orally administered drugs, the same formulations that are used in children should ideally be included in the model for adults. Plasma concentrations following multiple-dose application, mass balance information and other clinical measurements need to be included for model development, if available. During model translation from adults to children for a specific substance, uncertainties in data-quality caused by impact of disease or the target study population, inaccurate in vitro assay-techniques regarding mass balance, as well as study differences may cause not being able to adequately predict the PK in children for all reported studies.

Prediction performance of the PBPK model for these probe substances in children are then shown by means of e.g. predicted versus observed area under the plasma concentration (AUC)-ratio plots, of which the results support an adequate prediction of the ontogeny function for the application of PBPK model translation of adult PBPK to children.

For qualification purpose, during the translation of adult PBPK to children the following assumptions and considerations were made:

- when translating an adult model to children, it was assumed that the metabolism and excretion pathways are qualitatively the same in children and in adults.
- no further changes to input parameters other than those for the physiology and protein binding. All other parameters (e.g. lipophilicity, intestinal permeability, solubility) were kept unchanged.

Anthropometric and Physiological Information

Regarding the age-dependencies of the relevant anthropometric (height, weight) and physiological parameters (e.g. blood flows, organ volumes, binding protein concentrations, hematocrit, cardiac output) in children was gathered from the literature and has been previously published. [Edginton 2006] The information was incorporated into PK-Sim® and was used as default values for the simulations in children.

The CYP2C8 ontogeny function is reported by Upreti et al. [Upreti 2015] and was integrated into PK-Sim. The ontogeny of CYP2C8 reaches 15% of adult activity at birth, peaks at 260% of adult activity around the age of 14 months and reaches adult activity by the age of 5 to 6 years. The applied ontogeny and variability of other active processes that are integrated into PK-Sim® for translation to children, are described in the publicly available ‘PK-Sim® Ontogeny Database Version 7.3' [Ontogeny Database] or otherwise referenced for the specific process.

Qualification of CYP2C8 enzyme ontogeny

To qualify the OSP suite for the pediatric translation of the pharmacokinetics of new drugs that are metabolized by CYP2C8, the following probe substance was included:

- Montelukast [Montelukast-Model]

The adult PBPK model report and the corresponding PK-Sim project file are filed at: https://github.com/Open-Systems-Pharmacology/OSP-PBPK-Model-Library/

2 Pediatric translation qualification

Evaluation of Pediatric translation

All pediatric translations are pure retrospective predictions, no pediatric pharmacokinetic studies were used to inform model parameters. All parameters necessary to model the pediatric populations, such as demographics (age, weight, height), as well as dosing formulation information were taken from the respective pediatrics studies from literature in order to evaluate their predictive performance.

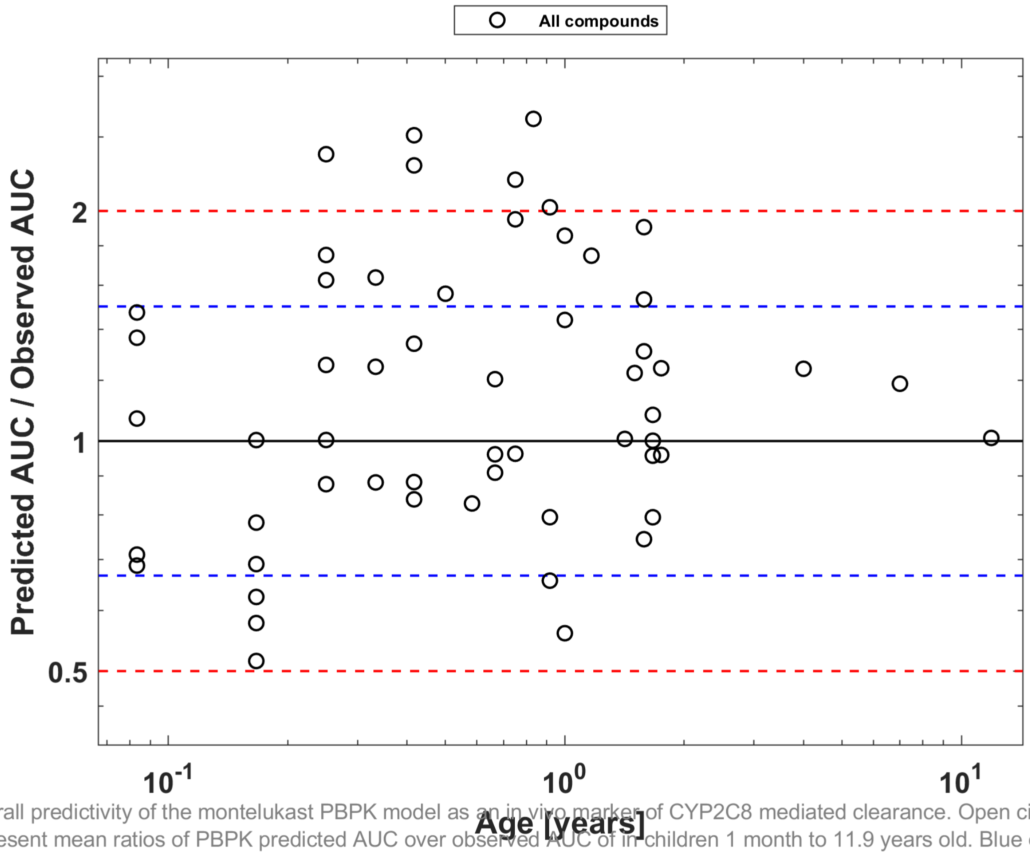
The models were evaluated by ratio plots of area under the plasma concentration-time curve (AUC), or clearance (CL) values resulting from our predictions to the values observed during clinical studies, and by comparison of concentration-time profiles if available. As a quantitative measure of the descriptive and predictive performance of each model, the geometric mean fold error was calculated according to Eq. 1:

Eq. 1: $GMFE=10^{\left(\sum\left|\log_{10}\left(\frac{\text{pred PK parameter}}{\text{obs PK parameter}}\right)\right|/n\right)}$

with GMFE = geometric mean fold error of all AUC or CL predictions of the respective model, pred PK parameter = predicted AUC or CL, obs PK parameter = observed AUC or CL, and n = number of observed values.

The ratios of predicted over observed mean AUC or CL values from all compound were also plotted across all age groups in the figure below. As illustrated, most of the prediction were within the 0.5 to 2.0 range (2-fold error).

In the next sections the demographics as well as the evaluation results of the predictive performance of the specific compound PBPK models in children can be found.



Overall predictivity of the montelukast PBPK model as an in vivo marker of CYP2C8 mediated clearance. Open circles represent mean ratios of PBPK predicted AUC over observed AUC of in children 1 month to 11.9 years old. Blue dashed lines and red dotted lines represent the 1.5-fold and 2-fold error, respectively.

GMFE (AUC) = 1.403890

AUC	Number	Ratio [%]
Points total	56	-
Points within 1.5 fold	36	64.2857
Points within 2-fold	50	89.2857

Study ID	Age [y]	BodyWeight [kg]	Predicted AUC [ng*h/ml]	Observed AUC [ng*h/ml]	Pred/Obs AUC Ratio
Kearns 2008	0.083333	4.0417	20846.5762	30336.98	0.68717
Kearns 2008	0.083333	4.0417	20846.5762	29350.14	0.71027
Kearns 2008	0.083333	4.0417	20846.5762	19481.8	1.0701
Kearns 2008	0.083333	4.0417	20846.5762	15271.04	1.3651
Kearns 2008	0.083333	4.0417	20846.5762	14152.63	1.473
Kearns 2008	0.16667	4.5833	10046.0396	19490.31	0.51544
Kearns 2008	0.16667	4.5833	10046.0396	17384.8	0.57786
Kearns 2008	0.16667	4.5833	10046.0396	16069.03	0.62518
Kearns 2008	0.16667	4.5833	10046.0396	14555.88	0.69017
Kearns 2008	0.16667	4.5833	10046.0396	12845.36	0.78208
Kearns 2008	0.16667	4.5833	10046.0396	10016.44	1.003
Kearns 2008	0.25	5.125	8802.0416	10024.69	0.87804
Kearns 2008	0.25	5.125	8802.0416	8774.445	1.0031
Kearns 2008	0.25	5.125	8802.0416	6998.658	1.2577
Kearns 2008	0.25	5.125	8802.0416	5419.723	1.6241
Kearns 2008	0.25	5.125	8802.0416	5024.989	1.7517
Kearns 2008	0.25	5.125	8802.0416	3709.209	2.373
Kearns 2008	0.33333	5.6667	8681.5686	9835.066	0.88272
Kearns 2008	0.33333	5.6667	8681.5686	6941.125	1.2507
Kearns 2008	0.41667	6.2083	8698.7093	10369.89	0.83884
Kearns 2008	0.41667	6.2083	8698.7093	9843.322	0.88372
Kearns 2008	0.41667	6.2083	8698.7093	6488.084	1.3407

Study ID	Age [y]	BodyWeight [kg]	Predicted AUC [ng*h/ml]	Observed AUC [ng*h/ml]	Pred/Obs AUC Ratio
Kearns 2008	0.41667	6.2083	8698.7093	3791.252	2.2944
Kearns 2008	0.41667	6.2083	8698.7093	3462.049	2.5126
Kearns 2008	0.5	6.75	9614.0968	6167.911	1.5587
Kearns 2008	0.58333	7.2917	9805.1413	11833.5	0.82859
Kearns 2008	0.66667	7.8333	9987.5036	10986.76	0.90905
Kearns 2008	0.66667	7.8333	9987.5036	10394.92	0.96081
Kearns 2008	0.66667	7.8333	9987.5036	8289.154	1.2049
Kearns 2008	0.75	8.375	10137.9117	10534.24	0.96238
Kearns 2008	0.75	8.375	10137.9117	4612.969	2.1977
Kearns 2008	0.83333	8.9167	10286.7318	3897.288	2.6395
Kearns 2008	0.91667	9.4583	10426.5538	15879.4	0.65661
Kearns 2008	0.91667	9.4583	10426.5538	13116.26	0.79493
Kearns 2008	0.91667	9.4583	10426.5538	5155.535	2.0224
Kearns 2008	1	10	10563.8727	18848.16	0.56047
Kearns 2008	1	10	10563.8727	7334.827	1.4402
Kearns 2008	1	10	10563.8727	5690.103	1.8565
Kearns 2008	1.1667	10.375	10779.5171	6167.137	1.7479
Kearns 2008	1.4167	10.9375	11130.8847	11060.03	1.0064
Kearns 2008	1.5833	11.3125	11324.8699	15221.25	0.74402
Kearns 2008	1.5833	11.3125	11324.8699	8642.352	1.3104
Kearns 2008	1.5833	11.3125	11324.8699	7392.36	1.532
Kearns 2008	1.5833	11.3125	11324.8699	5945.002	1.9049

Study ID	Age [y]	BodyWeight [kg]	Predicted AUC [ng*h/ml]	Observed AUC [ng*h/ml]	Pred/Obs AUC Ratio
Kearns 2008	1.6667	11.5	11424.4347	14374.25	0.79478
Kearns 2008	1.6667	11.5	11424.4347	11940.31	0.9568
Kearns 2008	1.6667	11.5	11424.4347	11414	1.0009
Kearns 2008	1.6667	11.5	11424.4347	10558.23	1.082
Kearns 2008	1.75	11.6875	11520.1486	12013.84	0.95891
Kearns 2008	1.75	11.6875	11520.1486	9250.706	1.2453
Friesen 2004	11.9	40.55	4428.2714	4387.2	1.0094
Knorr 1999	7	26	3480.9747	2929	1.1885
Knorr 2001	4	17	3382.7551	2721	1.2432
Knorr 2006	0.33333	6.8	5964.2673	3644.3	1.6366
Miyoga 2004	1.5	9	4454.6433	3629.2	1.2274
Miyoga 2004	0.75	9	4819.0816	2470.9	1.9503

2.1 Montelukast PK Ratio tables and Figures

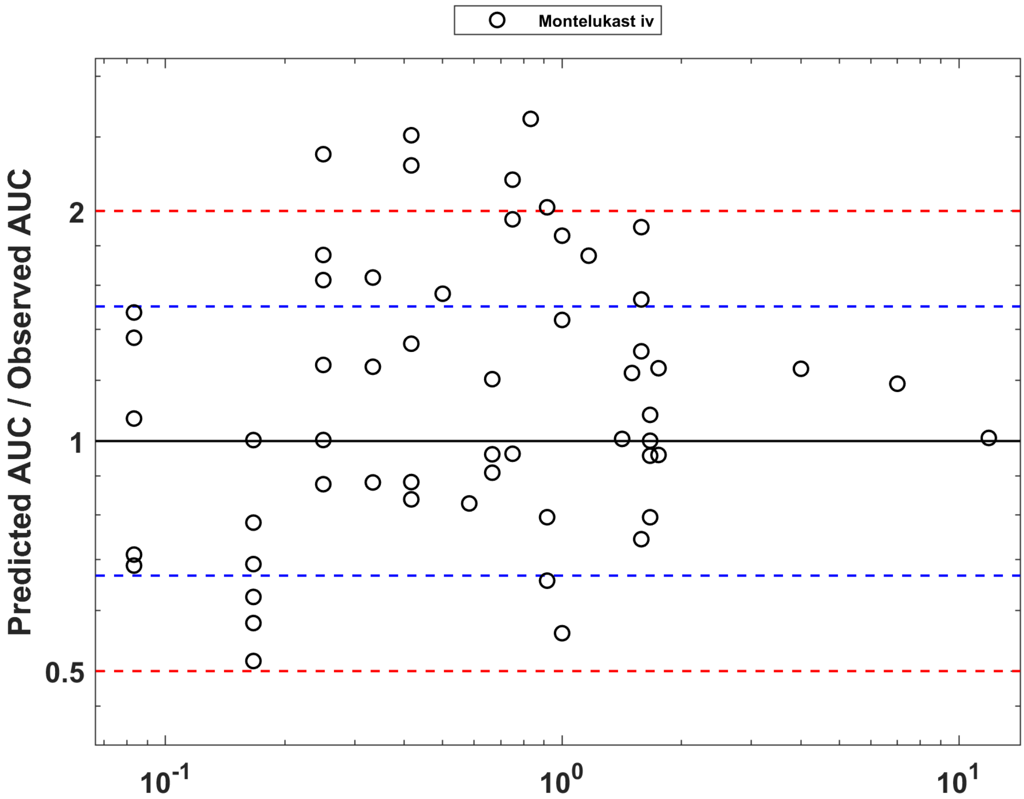
Montelukast model

Montelukast PBPK predictions in children were evaluated using pharmacokinetic (PK) data reported in the following studies:

- Knorr B, Holland S, Rogers JD, Nguyen HH, Reiss TF. Montelukast adult (10-mg film-coated tablet) and pediatric (5-mg chewable tablet) dose selections. J Allergy Clin Immunol. 2000 Sep;106(3 Suppl):S171-8.[Knorr 2000]
- Friesen CA, Kearns GL, Andre L, Neustrom M, Roberts CC, Abdel-Rahman SM. Clinical efficacy and pharmacokinetics of montelukast in dyspeptic children with duodenal eosinophilia. J Pediatr Gastroenterol Nutr. 2004 Mar;38(3):343-51. [Friesen 2004]
- Kearns GL, Lu S, Maganti L, Li XS, Migoya E, Ahmed T, Knorr B, Reiss TF. Pharmacokinetics and safety of montelukast oral granules in children 1 to 3 months of age with bronchiolitis. J Clin Pharmacol. 2008 Apr;48(4):502-11. doi: 10.1177/0091270008314251. Epub 2008 Feb 22. [Kearns 2008]
- Knorr B, Nguyen HH, Kearns GL, Villaran C, Boza ML, Reiss TF, Rogers JD, Zhang J, Larson P, Spielberg S. Montelukast dose selection in children ages 2 to 5 years: comparison of population pharmacokinetics between children and adults. J Clin Pharmacol. 2001 Jun;41(6):612-9. [Knorr 2001]

- Knorr B, Larson P, Nguyen HH, Holland S, Reiss TF, Chervinsky P, Blake K, van Nispen CH, Noonan G, Freeman A, Haesen R, Michiels N, Rogers JD, Amin RD, Zhao J, Xu X, Seidenberg BC, Gertz BJ, Spielberg S. Montelukast dose selection in 6- to 14-year-olds: comparison of single-dose pharmacokinetics in children and adults. J Clin Pharmacol. 1999 Aug;39(8):786-93. [Knorr 1999]
- Knorr B, Maganti L, Ramakrishnan R, Tozzi CA, Migoya E, Kearns G. Pharmacokinetics and safety of montelukast in children aged 3 to 6 months. J Clin Pharmacol. 2006 Jun;46(6):620-7. [Knorr 2006]
- Migoya E1, Kearns GL, Hartford A, Zhao J, van Adelsberg J, Tozzi CA, Knorr B, Deutsch P. Pharmacokinetics of montelukast in asthmatic patients 6 to 24 months old. J Clin Pharmacol. 2004 May;44(5):487-94. [Migoya 2004]

The pediatric PBPK model predicted the clearance values of montelukast observed in pediatric studies reasonably across all available age groups, ranging from 1 month to 11.9 years old. The ratios of mean predicted over observed area under the observed plasma concentrations (AUC) are illustrated in the table below as well as in the predicted versus observed AUC ratio plot, showing that most predictions in children were within 2-fold error of observed values.



Overall predictivity of the montelukast PBPK model. Open circles represent mean ratios of PBPK predicted AUC over observed AUC of montelukast in children 1 month to 11.9 years old. Blue dashed lines and red dotted lines represent the 1.5-fold and 2-fold error, respectively.

GMFE (AUC) = 1.403890

AUC	Number	Ratio [%]
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Points within 2-fold	50	89.2857

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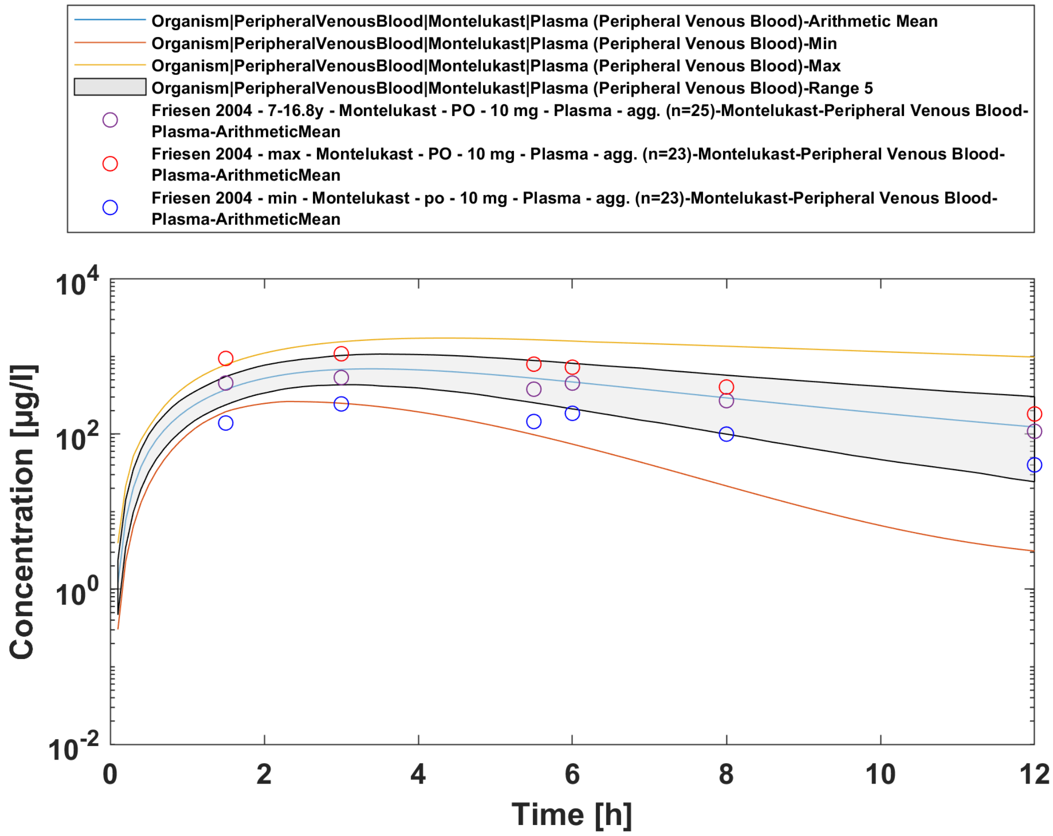
Miyoga 2004	1.5	9	4454.6433	3629.2	1.2274
Miyoga 2004	0.75	9	4819.0816	2470.9	1.9503

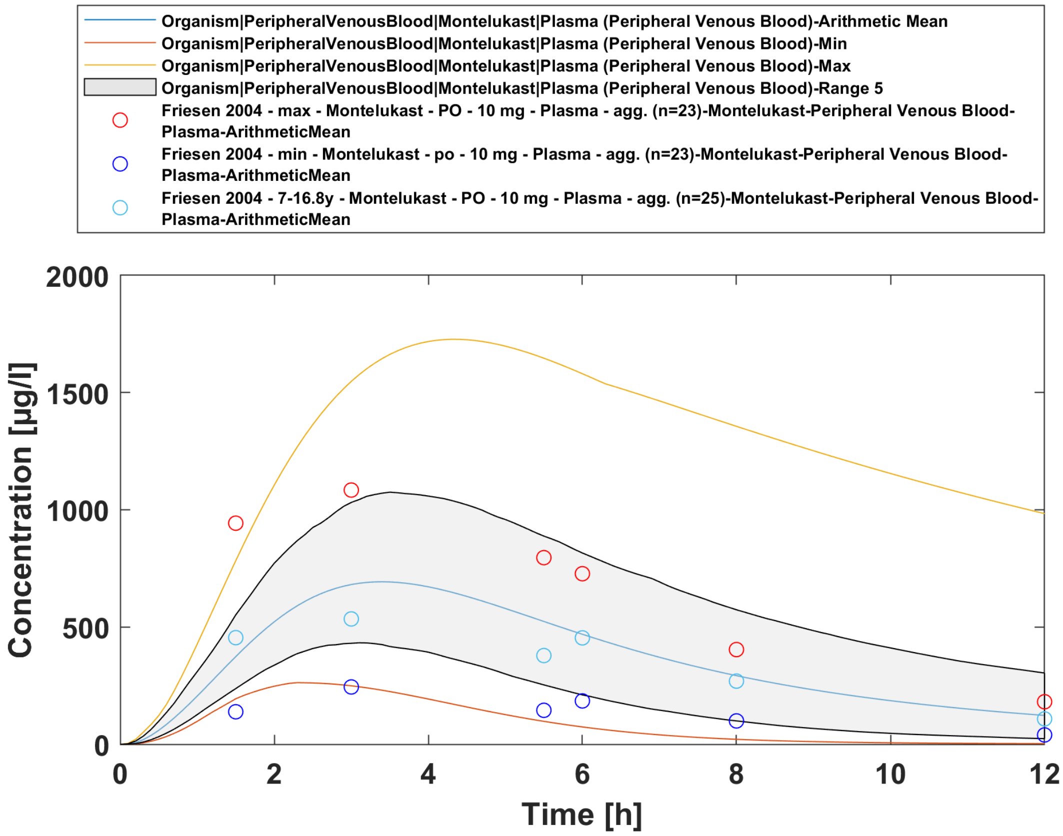
2.2 Montelukast Concentration-Time profiles in Children

Concentration-Time Profiles

Predicted versus observed plasma concentration-time profiles are listed below. Only simulations where observed data was available for comparison are shown. Depending if the observed data were individual data or aggregated data, individual predictions or population predictions including variability are shown, respectively.



Time Profile Analysis



Time Profile Analysis 1

3 References

Edginton 2006 Edginton AN, Schmitt W, Willmann S. Development and evaluation of a generic physiologically based pharmacokinetic model for children. Clin Pharmacokinet. 2006;45(10):1013-34.

Friesen 2004 Friesen CA, Kearns GL, Andre L, Neustrom M, Roberts CC, Abdel-Rahman SM. Clinical efficacy and pharmacokinetics of montelukast in dyspeptic children with duodenal eosinophilia. J Pediatr Gastroenterol Nutr. 2004 Mar;38(3):343-51.

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Maharaj 2013 Maharaj AR, Barrett JS, Edginton AN. A workflow example of PBPK modeling to support pediatric research and development: case study with lorazepam. The AAPS journal. 2013;15(2): 455-464.

Migoya 2004 Migoya E1, Kearns GL, Hartford A, Zhao J, van Adelsberg J, Tozzi CA, Knorr B, Deutsch P. Pharmacokinetics of montelukast in asthmatic patients 6 to 24 months old. J Clin Pharmacol. 2004 May;44(5):487-94.

Montelukast-Model Montelukast-Model, Whole-body PBPK model of Montelukast. (https://github.com/Open-Systems-Pharmacology/Montelukast-Model)

Ontogeny Database OSPSuite.Documentation/PK-Sim Ontogeny Database Version 7.3.pdf (https://github.com/Open-Systems-Pharmacology/OSPSuite.Documentation/blob/38cf71b384cfc25cfa0ce4d2f3addfd32757e13b/PK-Sim%20Ontogeny%20Database%20Version%207.3.pdf)

Upreti 2015 Upreti VV, Wahlstrom JL. Meta-analysis of hepatic cytochrome P450 ontogeny to underwrite the prediction of pediatric pharmacokinetics using physiologically based pharmacokinetic modeling. J Clin Pharmacol. 2016 Mar;56(3):266-83. doi: 10.1002/jcph.585. Epub 2015 Oct 9.