

## Introduction

The “first dose in children” in paediatric studies are usually determined mainly by two approaches:

- A physiological Based PK approach (PBPK)
- A compartmental approach using allometric scaling and maturation function

A comparison of these two methods has already been performed [1]. The aim of this work was to provide another example with a drug 80 % metabolized via CYP3A4 and for about 20 % renally eliminated by glomerular renal filtration (GFR). A study performed in paediatric population with this drug is currently undergoing.

## Methods

### Data and study design

Four children age classes were defined:

- 20 children in age-subset [6-12[ months received 0.02 mg/kg twice daily during 14 days
- 20 children in age subset [1-3[ years received 0.05 mg/kg twice daily during 14 days
- 20 children in age subset [3-18[ years:
  - with weight < 40 kg received 0.05 mg/kg twice daily during 14 days
  - with weight ≥ 40 kg received 2.5 mg twice daily during 14 days

### PBPK model

A PBPK model with ADAM absorption model, full PBPK model for distribution (Rodgers et al. method) and elimination mediated by CYP3A4 metabolism and kidneys was previously developed in adult within SimCyp®. This model was judged to be adequate to predict PK in the paediatric population for both parent and metabolite.

10 simulations of 20 subjects for each age class were performed.

### Population PK model

An adult semi-physiologic joint population PK model for the drug X and its active metabolite was scaled to children. 3- and 2- compartment models were used to described parent and metabolite dispositions, respectively. To account for first pass effect by CYP3A4, liver compartments were also included into the model, making the link between the 2 submodels (Figure 1). Weight effects were fixed to the allometric values of 0.75 and 1 on clearances and volumes of distribution, respectively [2]. In addition, for the youngest age classes, a hill-type maturation function was added on first pass effect and intrinsic clearances to reflect CYP3A4 maturation [3] and on renal clearances to reflect GFR maturation [4].

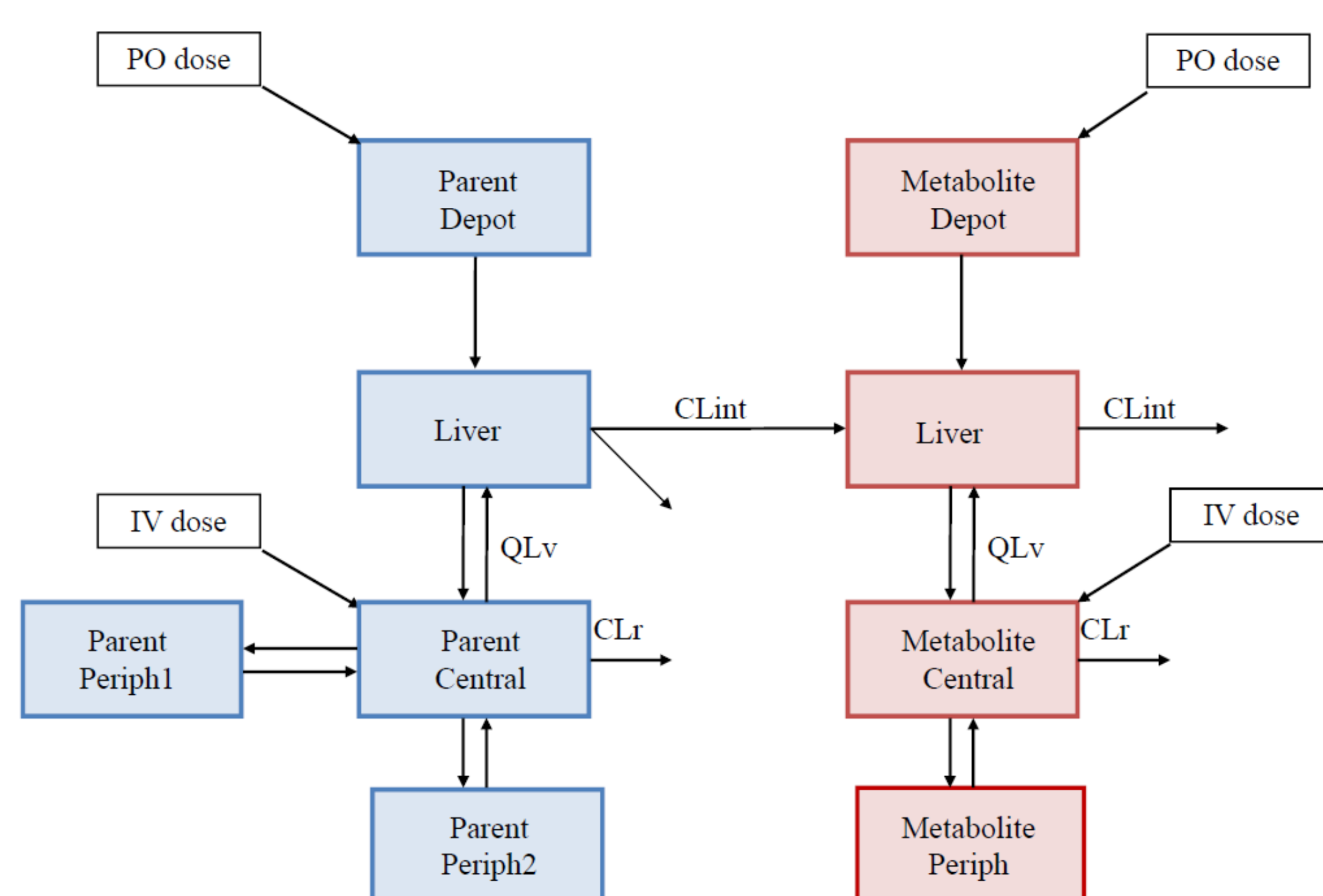


Fig.1: Population PK for parent and metabolite

### Approach Comparison

Concentration time profiles of the 200 children per age class predicted with SimCyp were simulated using the pop PK model with NONMEM 7 and were compared graphically.

## Results

### Simulated PK profiles using the population PK model scaled to children

Except for the first age class, the same magnitude of concentrations was predicted for both parent and metabolite (Figure 2) between the age classes.

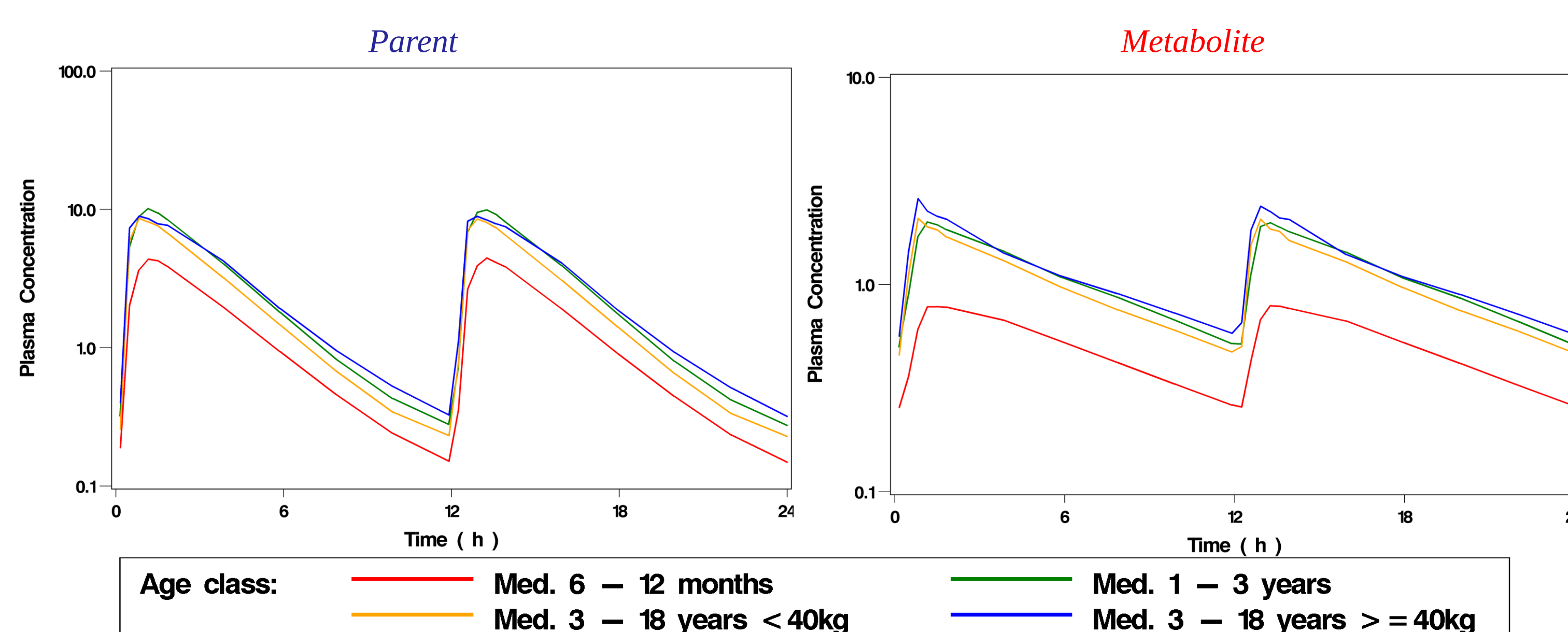


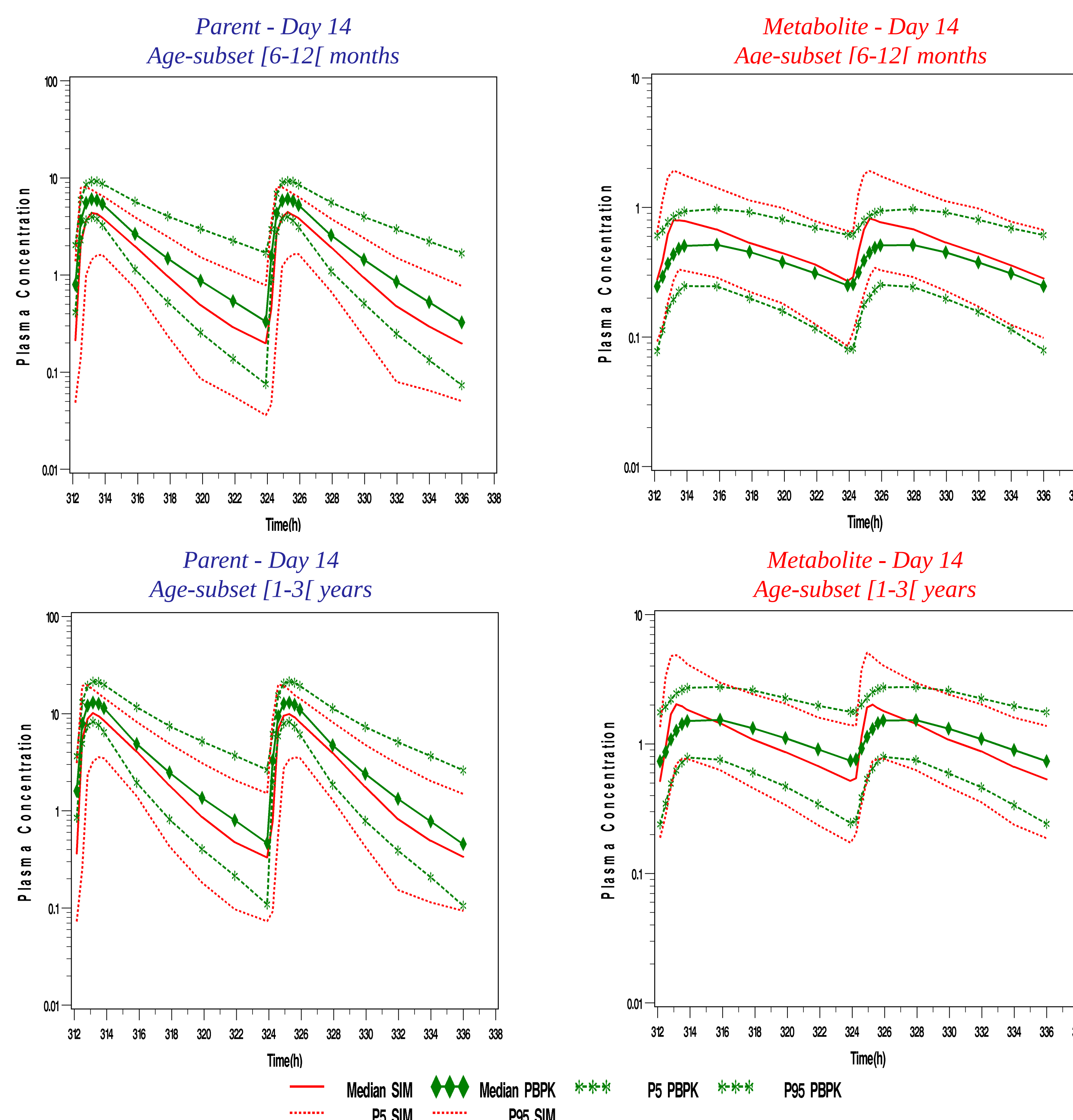
Fig.2: Simulated plasma concentration profiles (by age class)

### Comparison between the physiological and the compartmental approach

For the parent drug, the concentrations predicted by SimCyp (green) were slightly higher than the simulated concentration time profiles (red) obtained by compartmental population approach, especially for the youngest age class (6-12 months). It was more obvious regarding the absorption phase.

For the metabolite, the two approaches predicted the same magnitude of concentrations.

Overall, the inter-individual variability was slightly higher with the compartmental approach.



## Conclusions - Perspectives

Maturation functions were incorporated in the pop PK model. However, the part of the parent drug eliminated by renal pathway was little so the adding of maturation function on renal clearances didn't impact the simulation profiles (graphs not shown).

The approaches were compared and showed slightly higher predictions especially in the absorption phase for the parent drug. This differences were more pronounced with the youngest age class. Clinical PK data in children will be available by the end of the year and compared to the two sets of prediction.

[1] Strougo A, Eissing T, Yassen A, Willmann S, Danhof M, Freijer J. First dose in children: physiological insights into pharmacokinetic scaling approaches and their implications in paediatric drug development. *J Pharmacokinetic Pharmacodyn.* 2012 Apr;39(2):195-203. doi: 10.1007/s10928-012-9241-9. Epub 2012 Feb 5. PubMed PMID: 22311388; PubMed Central PMCID: PMC3306781.

[2] Anderson BJ, Holford NH. Mechanistic basis of using body size and maturation to predict clearance in humans. *Drug Metab Pharmacokinet.* 2009;24(1):25-36. Review. PubMed PMID: 19252334.

[3] Johnson TN, Rostami-Hodjegan A, Tucker GT. Prediction of the clearance of eleven drugs and associated variability in neonates, infants and children. *Clin Pharmacokinet.* 2006;45(9):931-56. PubMed PMID: 16928154.

[4] 1: Rhodin MM, Anderson BJ, Peters AM, Coulthard MG, Wilkins B, Cole M, Chatelut E, Grubb A, Veal GJ, Keir MJ, Holford NH. Human renal function maturation: a quantitative description using weight and postmenstrual age. *Pediatr Nephrol.* 2009 Jan;24(1):67-76. doi: 10.1007/s00467-008-0997-5. Epub 2008 Oct 10. PubMed PMID: 18846389.