Background
There is a growing use of biologic drugs in paediatrics, but less is known about the ontogeny of their associated distribution and elimination pathways compared to small molecules [1]. Doses of therapeutic proteins in children are mainly estimated by allometry, which can lead to overdosing in these patients [2, 3]. The PBPK approach can offer a possibility to predict dose and disposition of biologics in a paediatric population if age-dependent system parameters are accounted for.

Objectives
To predict the disposition of erythropoietin in children using the Simcyp Paediatric Simulator.

Methods
The full PBPK model for other proteins was used to simulate erythropoietin distribution. It contains 13 organs, which are connected via the arterial and venous blood stream. Lymph flow from all organs except for bone and spleen is collected in a central lymph compartment and is circulated back to the venous blood stream. Each organ is further divided into vascular space, interstitial space and intracellular space. The Paediatric Simulator accounts for the age-dependency in the tissue volumes and flows to and from these organs, including vascular and endothelial volumes. Interstitial volume is calculated from the tissue volume, the age-dependent fraction of extracellular water and vascular volume according to the following equation:

\[ V_{interstitial}(L) = (V_{tissue} \times f_{ECW}) - (V_{vascular} \times (1 - HCT)) \]

where HCT is haematocrit. The lymph volume is a function of body weight. As there were no published values for lymph flow in the literature, it was scaled allometrically as shown below:

\[ \text{Lymph flow rate} [L/h] = 0.287 \times \left( \frac{\text{BW}_{adult}}{\text{BW}_{child}} \right)^{0.75} \]

All other parameters such as pore size and numbers of pores in a certain area are the same as in the adult model.

The compound file for erythropoietin was developed in adults by using a molecular weight of 30,400 g/mol and a clearance of 9.0 mL/min/kg. The model was verified using adult data from Salmonson et al. (1990), in which 6 healthy adult men received 50 U/kg of erythropoietin i.v. [4]. The model was then used to explore the exposure to the adult dose in paediatrics and also to replicate available studies in children at the received doses. Wu et al. (2012) administered different doses of erythropoietin i.v. to one day old neonates [3] and Braun et al. (1993) gave a dose of 4,000 U/m² to children aged 7-20 years [2].

Result
The model was able to predict the data in adults reasonably well (Fig. 1A). Simulations for the same dose (50 U/kg i.v.) in paediatrics aged 1 day, 6 years, 13 years and 18 years are given in Fig. 1B. Adolescents and adults have a perfect overlay, whereas neonates have a much higher plasma concentration.

Discussion
The disposition of erythropoietin was predicted reasonable well by using the Simcyp Paediatric Simulator in the entire paediatric age range from one day old neonates to adolescents after administration of different doses. The model could be used to predict dose and disposition for other therapeutic proteins in paediatrics.

References