# Prediction of Enfuvertide Concentration-Time Profile in a Paediatric Population after Parenteral Administration Using a Physiologically Based Pharmacokinetic Model

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**Introduction** Enfuvirtide has been shown to have comparable efficacy and long-term safety in adult and paediatric patients with human immunodeficiency virus -1. Physiologically based pharmacokinetic (PBPK) models integrate both the drug characteristics and the physiology (systems parameters), along with their variability within a population, when predicting drug PK. Pediatric PBPK models also account for the age-dependent changes in these parameters and can be applied to predict drug kinetics in children.

**Objectives** The objective of this study is to use the PBPK approach to predict enfuvertide plasma concentration profiles in children using Paediatric Simcyp Simulator V15R1.

**Materials and Methods** An enfuvertide compound file has been built for healthy volunteers adult population [1] (see also figure 1). Full PBPK model for other proteins was used to describe the distribution phase, while elimination was described using Renal Filtration and Partition Ratio models. The '% degradation of net filtrate' was set to 100%. Additional systemic clearance of 0.724 l/h was calculated from the CLiv of 1.4 L/hr. No ontogeny was assumed for the additional clearance, while renal clearance is scaled at different ages through the renal blood flow and glomerular filtration rate.

The paediatric populations in Simcyp simulator V15R1 was selected from population library. Two paediatric studies reported enfuvertide PK in children (Soy et al., 2003 and Zhang et al., 2007). In Soy's study, a total of 12 subjects (4 in each case) aged 4-12 years received a single dose of either 15, 30, or 60 mg/m$^2$ enfuvertide subcutaneously. After 24 hr similar doses were given as iv bolus. The trial setting were replicated in the simulator by simulating bolus and first order subcutaneous input separately and in each case 10 trials of 10 individuals were used. In Zhang's study, enfuvertide was given at a dose of 2.0 mg/kg subcutaneously, twice daily to 43 children (20 Female) aged 5–16 years. These trial settings were mimicked in Simcyp using 10 trials of 43 individuals and simulated for 5 days to reach steady state.

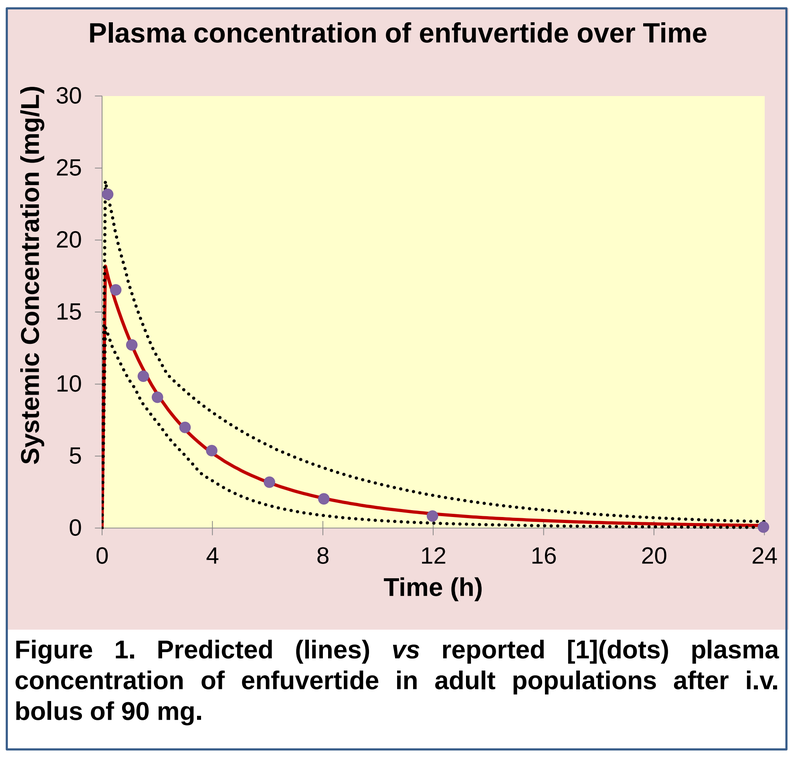


**Figure 1. Predicted (lines) *vs* reported [1](dots) plasma concentration of enfuvertide in adult populations after i.v. bolus of 90 mg.**

**Results and Discussion** The model couples the age-dependent system parameters in the paediatric population together with the biologic PBPK algorithms and drug properties within the paediatric simulator to predict adequately the reported concentration time profile for enfuvertide in paediatric patients at different doses level (Fig. 2). The model seems to over-predict enfuvertide plasma concentrations during the distribution phase after the highest bolus dose, however the concentration profiles after the subcutaneous highest dose were predicted adequately. The issue with the bolus dose was also mentioned in the original population PK study (Soy et al., 2003).

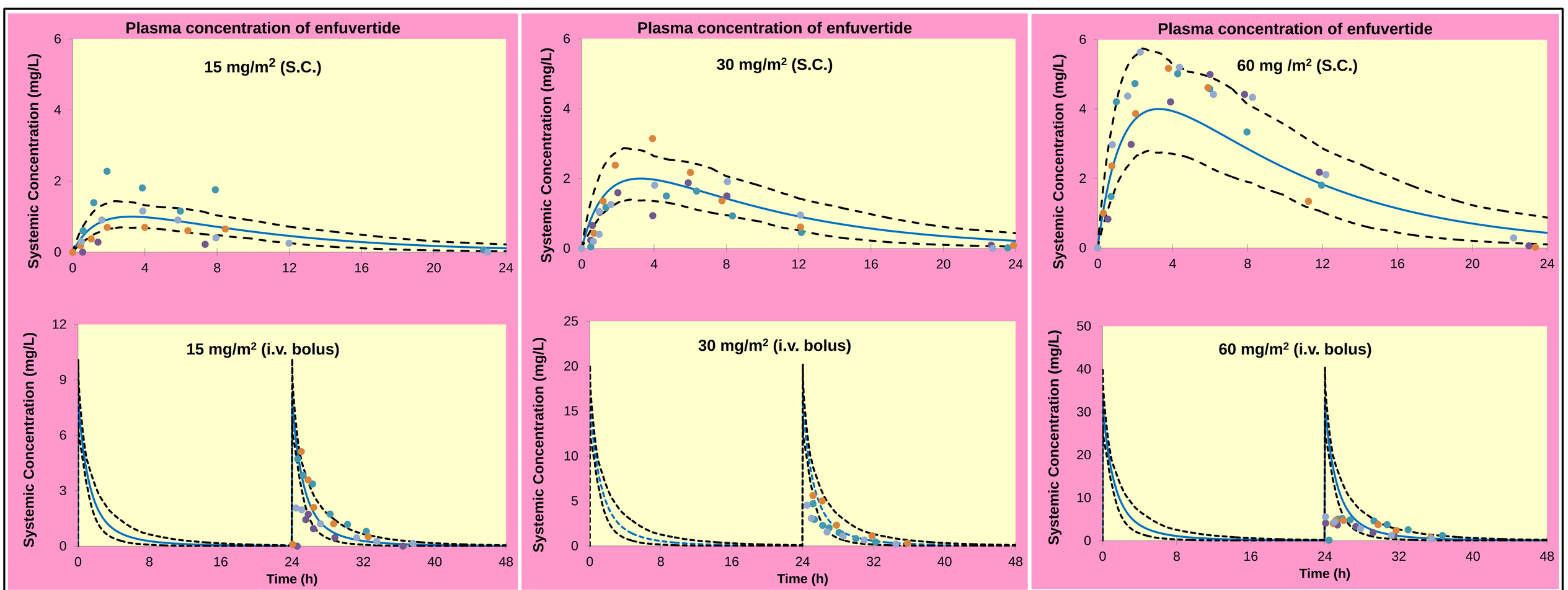


**Figure 2. Predicted (lines) plasma concentration profiles of enfuvertide in paediatric populations (4-12 years ) after i.v. bolus and subcutaneous doses of 15, 30 and 60 mg/m$^2$. Reported concentrations [2] are shown as dots from four subjects. Dotted lines represent the simulated 5th and 95th percentiles.**

Likewise, PK parameters and their variability from the 2 mg/kg multiple dose simulations are in very good agreement with reported parameters from Zhang et al., 2007 (Table 1). Unfortunately, in the original study the concentration profile was not reported. The simulated profile for the dosage regimen is given in Fig 3.

| Parameter | Predicted (Simcyp V15R1) | | Reported (Zhang et al., 2007) | |
|---|---|---|---|---|
| | $AUC_{12hr}$ (µg/mL.h) | $C_{min,\ 47.9hr}$ (µg/mL) | $AUC_{12hr}$ (µg/mL.h) | $C_{min}$ (µg/mL) |
| Mean±SD **(CV%)** | 56.2 ±18.6 (33%) | 2.8 ± 1.3 (45%) | 51.3 ± 16.1 (31%) | 2.69 ± 1.1 (41%) |

**Table 1. Predicted vs reported [3] PK parameters for enfuvertide in paediatric population aged 5-16 years**

The paediatric age-dependent system parameters coupled with a biologic PBPK model is able to predict enfuvertide pharmacokinetics in children.

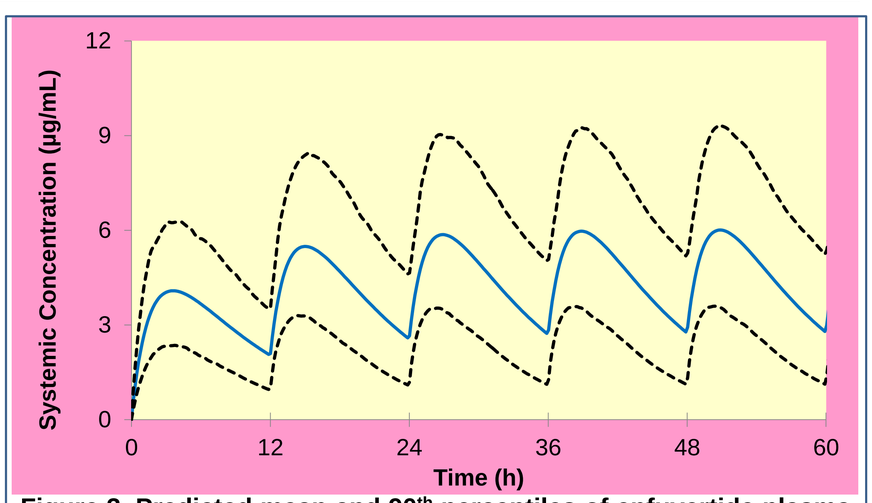


**Figure 3. Predicted mean and 90$^{th}$ percentiles of enfuvertide plasma concentration profiles in paediatric patients aged 5 -16 years after 2 mg/kg BID subcutaneous doses.**

**References** [1] Gardner I et al (2014) A semi-mechanistic model to predict renal clearance of therapeutic proteins linked to a whole body PBPK model. AAPS Conference. San Diego, USA, May 19-21, 2014
[2] Soy D et al (2003) Population pharmacokinetics of enfuvirtide in pediatric patients with human immunodeficiency virus: searching for exposure-response relationships. Clin Pharmacol Ther. 2003 Dec;74(6):569-80.
[3] Zhang X et al., (2007) Population pharmacokinetics of enfuvirtide in HIV-1-infected pediatric patients over 48 weeks of treatment. J Clin Pharmacol. 2007 Apr;47(4):510-7.